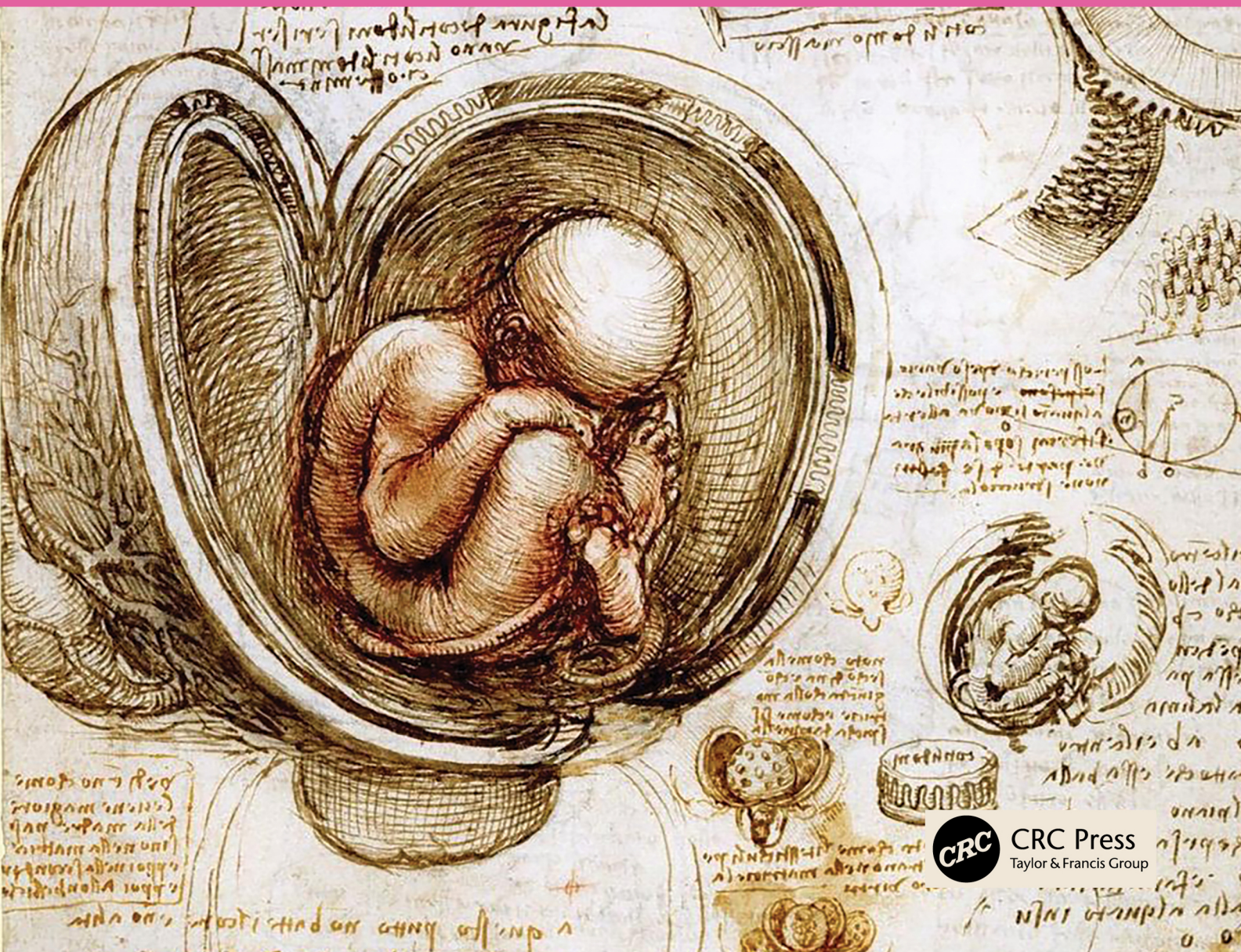
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MATERNAL-FETAL
MEDICINE

Obstetric Evidence Based Guidelines

Fourth Edition

Edited by

Vincenzo Berghella



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OBSTETRIC EVIDENCE BASED GUIDELINES

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OBSTETRIC EVIDENCE BASED GUIDELINES

FOURTH EDITION

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I dedicate this fourth edition to my father Andrea Berghella, who passed away at 87 in January 2019. He was and remains my professional inspiration and guiding light. The bright light of his lighthouse, to use a metaphor, keeps on shining inside my mind and heart and leading me onwards and upwards.

To Federica, Andrea, Pietro, Mamma, Anna, and Michele, for giving me the serenity, love, and strength at home now, then, and in the future to fulfill my dreams and spend my talents as best as possible

To all those who loved the prior editions

To the health of mothers and babies

And, as I often toast – To the next generation!

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INTRODUCTION

Welcome to the fourth edition of our evidence-based books on obstetrics and maternal-fetal medicine! I am indebted for your support! I can't believe how much praise we have received for these companion volumes. Your words of encouragement have kept me and all the wonderful collaborators going on strong for 15 years! It has been extremely worthwhile and fulfilling. You are making me happy! In return, I hope we are helping you and your patients toward ever better evidence-based care of pregnant women and their babies, and therefore better outcomes. Indeed, most maternal and perinatal morbidities and mortalities throughout the world are improving.

To me, pregnancy has always been the most fascinating and exciting area of interest, as care involves not one, but at least two persons—the mother and the fetus—and leads to the miracle of a new life. I was a third-year medical student when, during a lecture, a resident said: "I went into obstetrics because this is the easiest medical field. Pregnancy is a physiologic process, and there isn't much to know. It is simple." I knew from my "classical" background that "obstetrics" means to "stand by, stay near," and that indeed pregnancy used to receive no medical support at all. After more than 31 years of practicing obstetrics, I now know that although physiologic and at times simple, obstetrics and maternal-fetal medicine can be the most complex of the medical fields: pregnancy is based on a different physiology than for nonpregnant women, can include any medical disease, require surgery, etc. It is not so simple. In fact, ignorance can kill, in this case with the health of the woman and her baby both at risk. Too often, I have gone to a lecture, journal club, rounds, or other didactic event to hear presented only one or a few articles regarding the subject, without the presenter reviewing the pertinent best review of the total literature and data. It is increasingly difficult to read and acquire knowledge of all that is published, even just in obstetrics, with over 3,000 scientific manuscripts published monthly on this subject. Some residents or even authorities would state at times that "there is no evidence" on a topic. We indeed used to be the field with the worst use of randomized trials [1]. As the best way to find something is to look for it, my coauthors and I searched for the best evidence. On careful investigation, indeed there are data on almost everything we do in obstetrics, especially on our interventions. Indeed, our field is now the pioneer for numbers of meta-analysis and extension of work for evidence-based reviews [2]. Obstetricians are now blessed with lots of data and should make the best use of it.

The goals of this book are to summarize the best evidence available in the obstetrics and maternal-fetal medicine literature and make the results of randomized controlled trials (RCTs) and meta-analyses of RCTs easily accessible to guide clinical care. The intent is to bridge the gap between knowledge (the evidence) and its easy application. To reach these goals, we reviewed all trials on effectiveness of interventions in obstetrics. Millions of pregnant women have participated in thousands of properly conducted RCTs. The efforts and sacrifice of mothers and their fetuses for science should be recognized at least by the physicians' awareness and understanding of these studies. Some of the trials have been summarized in over 600 Cochrane reviews, with hundreds of other meta-analyses also published in obstetrical topics (Table I.1). All the Cochrane reviews, as well as other meta-analyses and trials in obstetrics and maternal-fetal medicine, were reviewed and referenced. The material presented in single trials or meta-analyses is too detailed to be readily translated to advice for the busy clinician who needs to make dozens of clinical decisions a day. Even the Cochrane Library, the undisputed leader for evidence-based medicine efforts, has been criticized for its lack of flexibility and relevance in failing to be more easily understandable and clinically readily usable [3]. It is the gap between research and clinicians that needed to be filled, making sure that proven interventions are clearly highlighted, and are included in today's care. Just as all pilots fly planes under similar rules to maximize safety, all obstetricians should manage all aspects of pregnancy with similar, evidenced-based rules. Indeed, only interventions that have been proven to provide benefit should be used routinely. On the other hand, *primum non nocere*: interventions that have clearly been shown to be not helpful or indeed harmful to mother and/or baby should be avoided. Another aim of the book is to make sure the pregnant woman and her unborn child are not marginalized by the medical community. In most circumstances, medical disorders of pregnant women can be treated as in nonpregnant adults. Moreover, there are several effective interventions for preventing or treating specific pregnancy disorders.

Evidence-based medicine is the concept of treating patients according to the best available evidence. While George Bernard Shaw said: "I have my own opinion, do not confuse me with the facts," this can be a deadly approach, especially in medicine, and compromise two or more lives at the same time in obstetrics and maternal-fetal medicine. What should be the basis for our interventions in medicine? Meta-analyses provide a comprehensive summary of the best research data available. As such, they provide the best guidance for "effective" clinical care [4]. It is unscientific and unethical to practice medicine, teach, or conduct research without first knowing all that has already been proven [4]. In the absence of trials or meta-analyses, lower level evidence is reviewed. This book aims at providing a current systematic review of all the best evidence, so that current practice and education, as well as future research, can be based on the full story from the best-conducted research, not just the latest data or someone's opinion (Table I.2).

These evidence-based guidelines cannot be used as a "cookbook," or a document dictating the best care. The knowledge from the best evidence presented in the guidelines needs to be integrated with other knowledge gained from clinical judgment, individual patient circumstances, and patient preferences to lead to the best medical practice. These are guidelines, not rules. Even the best scientific studies are not always perfectly related to any given individual, and clinical judgment must still be applied to allow the best "particularization" of the best knowledge for the individual, unique patient. Evidence-based medicine informs clinical judgment, but does not substitute it. It is important to understand though that greater clinical experience by the physician actually correlates with inferior quality of care if not integrated with knowledge of the best evidence [5]. The appropriate treatment is given in only 50% of visits to general physicians [5].

TABLE I.1: Obstetric Evidence

- Over 600 current Cochrane reviews
- Hundreds of other current meta-analyses
- Thousands of RCTs
- Millions of pregnant women randomized

TABLE I.2: Goals of This Book

- Improve the health of women and their children
- "Make it easy to do it right"
- Implement the best clinical care based on science (evidence), not opinion
- Education
- Develop lectures
- Decrease disease, use of detrimental interventions, and therefore costs
- Reduce medicolegal risks

TABLE I.3: This Book Is For

- Obstetricians
- Midwives
- Family medicine and others (practicing obstetrics)
- Residents
- Nurses
- Medical students
- Maternal-fetal medicine attendings
- Maternal-fetal medicine fellows
- Other consultants on pregnancy
- Lay persons who want to know "the evidence"
- Politicians responsible for health care

At times, limitations in resources may also limit the applicability of the guidelines, but should not limit the physician's knowledge.

Guidelines and clinical pathways based on evidence not only point to the right management but also can decrease medicolegal risk [6]. We aimed for brevity and clarity. Suggested management of the healthy or sick mother and child is stated as straightforwardly as possible for everyone to easily understand and implement (Table I.3). If you find the Cochrane reviews, scientific manuscripts, and other publications difficult to "translate" into care of your patients, this book is for you. We wanted to prevent information overload.

On the other hand, "everything should be made as simple as possible, but not simpler" (Albert Einstein). Key management points are highlighted at the beginning of each guideline and in bold in the text. The chapters are divided in two volumes, one on obstetrics and one on maternal-fetal medicine; cross-references to chapters in *Maternal-Fetal Evidence Based Guidelines* have been noted in the text where applicable. Please contact me (vincenzo.berghella@jefferson.edu) for any comments, criticisms, corrections, missing evidence, etc.

I have the most fun discovering the best ways to alleviate discomfort and disease. The search for the best evidence for these guidelines has been a wonderful, stimulating journey. Keeping up with evidence-based medicine is exciting. The most rewarding part, as a teacher, is the dissemination of knowledge. I hope, truly, that this effort will be helpful to you, too.

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HOW TO "READ" THIS BOOK

The knowledge from randomized controlled trials (RCTs) and meta-analyses of RCTs is summarized and easily available for clinical implementation. Key management points are highlighted at the beginning of each guideline, and in bold in the text. Relative risks and 95% confidence intervals from studies are quoted sparingly. Instead, the straight recommendation for care is made if one intervention is superior to the other, with the percent improvement often quoted to assess the degree of benefit. If there is insufficient evidence to compare to interventions or managements, this is clearly stated.

References: Cochrane reviews with 0 RCT are not referenced, and instead of referencing a meta-analysis with only one RCT, the actual RCT is usually referenced. RCTs that are already included in meta-analyses are not referenced, both for brevity and because they can be easily accessed by reviewing the meta-analysis. If new RCTs are not included in a meta-analysis, they are obviously referenced. Each reference was reviewed and evaluated for quality according to a modified method as outlined by the U.S. Preventive Services Task Force (http://www.ahrq.gov):

I Evidence obtained from at least one properly designed randomized controlled trial.

II-1 Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments could also be regarded as this type of evidence.

III (Review) Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

These levels are quoted after each reference. For RCTs and meta-analyses, the number of subjects studied is stated and, sometimes, more details are provided to aid the reader to understand the study better.

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LIST OF ABBREVIATIONS

Ab	antibody
AC	abdominal circumference
ACA	anticardiolipin antibody
ACOG	American College of Obstetricians and Gynecologists
ACS	acute chest syndrome
ADR	autosomic dysreflexia
AF	amniotic fluid
AFI	amniotic fluid index
AFP	alpha-fetoprotein
AFV	amniotic fluid volume
Ag	antigen
AIDS	acquired immune deficiency syndrome
ALT	alanine aminotransferase
ANA	antinuclear antibodies
aPT	activated prothrombin time
APS	antiphospholipid syndrome
aPTT	activated partial thromboplastin time
AROM	artificial rupture of membranes
ART	assisted reproductive technologies
ARV	antiretroviral therapy
ASA	aspirin
ASD	atrial septal defect
AST	aspartate aminotransferase
AT III	antithrombin III
AZT	zidovudine
bid	"bis in die," i.e., twice per day
BPD	biparietal diameter
BPD	bronchopulmonary dysplasia
BPP	biophysical profile
BPS	biophysical profile score
BMI	body mass index
BP	blood pressure
CAP	community-acquired pneumonia
CBC	complete blood count
CCB	calcium channel blocker
CDC	Centers for Disease Control and Prevention
CF	cystic fibrosis
CHD	congenital heart defect
CL	cervical length
CMV	cytomegalovirus
CNS	central nervous system
COX	cyclooxygenase
CRL	crown–rump length
CSE	combined spinal epidural
CSF	cerebrospinal fluid
CT	computerized tomography
CVS	chorionic villus sampling
DES	diethylstilbestrol
DIC	disseminated intravascular coagulation
DM	diabetes mellitus
DNA	deoxyribonucleic acid
DRVVT	dilute Russell's viper venom time
DV	ductus venosus
DVP	deepest vertical pocket
DVT	deep vein thrombosis
ECV	external cephalic version
EDC	estimated date of confinement
EDD	estimated date of delivery
EKG	(synonym of EDC) electrocardiogram
FBS	fetal blood sampling
FDA	Food and Drug Administration
FFN	fetal fibronectin
FGR	fetal growth restriction
FHR	fetal heart rate
FISH	fluorescent in situ hybridization
FLM	fetal lung maturity
FOB	father of baby
FPR	false-positive rate
FTS	first-trimester screening
FVL	factor V Leiden
g	grams
GA	gestational age
GBS	group B streptococcus
GDM	gestational diabetes mellitus
GI	gastrointestinal
HAART	highly active antiretroviral therapy
HAV	hepatitis A virus
HBV	hepatitis B virus
HBsAg	hepatitis B surface antigen
HCG	human chorionic gonadotropin
Hct	hematocrit
HCV	hepatitis C virus
HG	hyperemesis gravidarum
Hgb	hemoglobin
HIE	hypoxic-ischemic encephalopathy
HIV	human immunodeficiency virus
HR	heart rate
HSV	herpes simplex virus
HTN	hypertension
ICU	intensive care unit
IUGR	intrauterine growth restriction (synonym of FGR)
IV	intravenous
IVH	intraventricular hemorrhage
L&D	labor and delivery floor
LA	lupus anticoagulant
Lab	laboratory
LFT	liver function tests
LMP	last menstrual period
LBW	low birth weight (infants)
LMW	low molecular weight
LMWH	low-molecular-weight heparin
LR	likelihood ratio
MAS	meconium aspiration syndrome
MCA	middle cerebral artery
MCV	mean corpuscular volume
MOM	multiple of the median
MRI	magnetic resonance imaging
MTHFR	methylenetetrahydrofolate reductase
MVP	maximum vertical pocket
NA	not available
NAIT	neonatal alloimmune thrombocytopenia
NEC	necrotizing enterocolitis
NIH	National Institutes of Health
NIH	nonimmune hydrops
NRFS	nonreassuring fetal status
NRFHR	nonreassuring fetal heart rate

NRFHT	nonreassuring fetal heart testing
NSAID	nonsteroidal antiinflammatory drug
NT	nuchal translucency
NTD	neural tube defect
NST	nonstress test
n/v	nausea and/or vomiting
OR	operating room
ORA	oxytocin receptor agonist
PC	protein C
PCR	polymerase chain reaction
PE	pulmonary embolus
PFT	pulmonary function tests
PGM	prothrombin gene mutation
PID	pelvic inflammatory disease
PL	pregnancy loss
PNC	prenatal care
po	"per os," i.e., by mouth
PPH	postpartum hemorrhage
PRCD	planned repeat cesarean delivery
PS	protein S
PT	prothrombin time
PTB	preterm birth
PTT	partial thromboplastin time
PPROM	preterm prelabor rupture of membranes
pRBC	packed red blood cells
PROM	prelabor rupture of membranes
PSV	peak systolic velocity
PTL	preterm labor
PTU	propylthiouracil
PUBS	percutaneous umbilical blood sampling
PVH	periventricular hemorrhage
qd	once a day
qid	four times per day
qhs	before bedtime
QS	quadruple screen
RBC	red blood cell
RCT	randomized controlled study
RDS	respiratory distress syndrome
RNA	ribonucleic acid
ROM	rupture of membranes
RPR	rapid plasma regain
RR	respiratory rate
Rx	treatment
SAB	spontaneous abortion
SC	subcutaneous
SCI	spinal cord injury
SDP	single deepest pocket
SIDS	sudden infant death syndrome
SLE	systemic lupus erythematosus
SPTB	spontaneous preterm birth
STD	sexually transmitted diseases (synonym of STI)
STI	sexually transmitted infections
STS	second-trimester screening
TB	tuberculosis
TG	*Toxoplasma gondii*
tid	three times per day
TOL	trial of labor
TRAP	twin reversal arterial perfusion
TRH	thyrotropin-releasing hormone
TSH	thyroid-stimulating hormone
TSI	thyroid-stimulating immune globulins
TTTS	twin–twin transfusion syndrome
TVU	transvaginal ultrasound
UA	umbilical artery
UFH	unfractionated heparin
U/S	(or u/s) ultrasound
VBAC	vaginal birth after caesarean
VDRL	venereal disease research laboratory
VSD	ventricular septal defect
VTE	venous thromboembolism
WHO	World Health Organization

1

PRECONCEPTION CARE

Johanna Quist-Nelson

Key points

- Preconception care is a set of **interventions that aim to identify and modify biomedical, behavioral, and social risks to a patient's health or pregnancy outcome through prevention and management. The foundation of preconception care is prevention.**
- **Preconception care should occur any time any health care provider sees a reproductive-age patient** (e.g., 15- to 44 years old).
- **Personal and family history, physical exam, laboratory screening, reproductive plan, nutrition, supplements, weight, exercise, vaccinations, and injury prevention** should be reviewed in all reproductive-age patients.
- **Folic acid 400 µg/day,** as well as proper diet and exercise, should be encouraged starting at least one month before conception, so anytime a pregnancy is possible.
- Regarding **vaccinations,** patients should receive the **influenza** vaccine if planning pregnancy during flu season; the **rubella** and **varicella** vaccines if there is no evidence of immunity to these viruses; and **tetanus/diphtheria/pertussis as well as COVID** vaccines if lacking adult vaccination.
- **Specific interventions** to reduce morbidity and mortality for both the woman and her baby should be offered to those identified with chronic diseases or exposed to teratogens or illicit substances.

History

Preconception care has ancient origins. Plutarch (46–120 CE) wrote that the ancient Spartans "[…] ordered the maidens to exercise […], to the end that the fruit they conceived might […] take firmer root and find better growth" [1].

Definition

Preconception care is a **set of interventions that aim to identify and modify biomedical, behavioral, and social risks to a patient's health or pregnancy outcome through prevention and management** [2, 3]. This care has also been called pre-pregnancy, interpregnancy care, or periconceptional medicine [4].

Aim and effectiveness

The foundation of preconception care is prevention. Prevention of disease is the most effective form of medicine, and health care should shift from the delivery of procedure-based acute care to the provision of counseling-based preventive care [5, 6]. For example, the two leading causes of death in the first year of life—birth defects and disorders caused by preterm birth (PTB)—can be significantly reduced by preconception care. **Randomized controlled trials have corroborated that patients are likely to incorporate change in modifiable health behaviors in response to preconception counseling** [7]. General practitioner–initiated preconception counseling not only can decrease adverse pregnancy outcomes but also reduces anxiety in reproductive-age patients [8].

Timing and target population

The time that people should start caring for a pregnancy is before conception. **Preconception care should occur any time any health care provider sees a reproductive-age patient.** A reproductive-age patient is usually defined as one between **15 and 44 years** of age, but occasionally even younger or older patients contemplate, or at least are at risk of, pregnancy. One should engage any individual who plans or considers pregnancy in counseling, including lesbian, gay, bisexual, transgender, questioning, intersex, asexual, and ally (LGBTQIAA) individuals [9].

The first prenatal visit is "months too late!" [10]. It often happens after first-trimester exposure to a potential teratogen has already occurred. There are about 1 billion reproductive-age patients worldwide. In the United States, as an example, approximately half of pregnancies are planned [11]. As patients get pregnant later in life, disease prevalence and medication exposure increase. Approximately 80% of reproductive-age U.S. patients have dental disease, 66% are obese or overweight, 55% drink alcohol, 11% continue to smoke during pregnancy, 9% have diabetes, 6% have asthma, 3% have hypertension, and 3% have cardiac disease [2]. The incidences of many of these conditions among pregnant patients are on the rise.

While some beneficial interventions could be started as soon as a pregnancy is diagnosed, this is unrealistic. Many of the preventive measures take time—often months—such as quitting smoking, losing weight, folic acid supplementation, and stabilization of medical conditions with effective and safe medications.

Opportunities for preconception care

By the age of 25, about 50% of U.S. patients have had at least one birth. The highest fertility rate occurs in 25- to 30 years old patients. By the age of 44, >85% have given birth at least once. About 84% of reproductive-age patients, when asked, answer that they had a health care visit within the prior year [6]. Therefore, **universal preconception care can be achieved if health care providers make it a priority and plan for it at every opportunity** (Table 1.1). The approach should be **"every reproductive-age patient, every time"** [6]. **Every reproductive-age patient should be asked at every health care encounter: "Are you considering pregnancy?" and "Could you possibly become pregnant?"** Increased awareness of preconception care can be accomplished through improving health resources, public outreach, and advertising. Despite its great effectiveness, not all health care plans cover preconception care. **A preconception visit (or often more**

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TABLE 1.1: Visits That Are Opportunities for Preconception Care

- Adolescent (first gynecological exam)
- Any visit to a doctor during reproductive years (15- to 44 years old)
- College—Graduate school health
- Family planning, contraception prescribing, and counseling
- Annual ob-gyn
- Postpartum
- Pregnancy test (especially if negative)
- Health maintenance
- Medical work
- Emergency visit
- Fertility

than one) should be standard primary care, as stated by the Centers for Disease Control and Prevention [2]. It should be as routine as prenatal care, as should the screening and interventions associated with it. A clear political will to drive the funding and insurance coverage for preconception care is required.

Therefore, providers of all specialties should be aware of the evidence-based recommendations (Tables 1.1–1.8). Organizations representing family and internal medicine, obstetrics and gynecology, nurse midwifery, nursing, public health, diabetes, neurology, cardiology, and many other associations have supported recommendations for preconception care. Unfortunately, practitioners seldom implement them [12], even though it is an opportunity to optimize the health of the patient independent of whether she is planning pregnancy [6]. Only one out of six obstetrician-gynecologists (ob-gyns) or family physicians provides preconception care to the majority of patients for whom they provide prenatal care [13].

Preconception care may often need to be **multidisciplinary care.** Prior to pregnancy, a patient can have numerous different medical problems affecting different specialties, and her care should occur in close collaboration between the different fields involved. **Maternal physiology is different from nonpregnant adult physiology**. An entire field, **maternal-fetal medicine**, is dedicated to the care of pregnancies with maternal or fetal problems, and these specialists are particularly adept at directing best practices for preconception counseling. Preconception care occurs best if all practitioners, including primary and specialty care, either directly implement or appropriately refer for implementation of effective preconception screening and intervention. The worse scenario is the belief that a positive pregnancy test is a good reason to "stop all medicines," thereby stopping disease

TABLE 1.2: Topics to Be Reviewed in Preconception Care

Screening for Risk Assessment

- Personal and family history, physical exam, and laboratory screening

Preventive Health

- Reproductive plan
- Nutrition, supplements, weight, and exercise
- Vaccinations/infections
- Injury prevention

Specific Individual Issues/"Exposures"

- Chronic diseases
- Medications (teratogens)
- Substance use disorder/environmental hazards and toxins

Source: Modified from Refs. [2, 14].

TABLE 1.3: Preconception Screening Assessment for All Reproductive-Age Patients (15–44 Years Old)

History

- Reason for visit
- Health status: obstetrical, gynecological, medical, surgical, and family history
- Use of prescription, over-the-counter, complementary, and alternative medicines
- Allergies (to medications or other)
- Tobacco, alcohol, other drug use
- Work-related exposures
- Dietary/nutrition assessment
- Physical activity
- Urinary and fecal incontinence

Physical Examination

- Height, weight, body mass index (BMI)
- Blood pressure
- Head
- Neck: adenopathy and thyroid
- Breasts
- Heart, lungs
- Abdomen
- Pelvic examination
- Skin

Laboratory Testing

- Rubella titer[a]
- Varicella titer[a]
- Human immunodeficiency virus (HIV) testing[b]
- Cervical cytology[c]
- Hepatitis C antibody[d]
- Chlamydia testing (if aged 25 years or younger and sexually active)

Evaluation and Counseling

Sexuality and Reproductive Planning

- High-risk behaviors
- Discussion of a reproductive health plan
- Contraceptive options for prevention of unwanted pregnancy, including emergency contraception
- Genetic counseling

Sexually Transmitted Diseases

- Partner selection
- Barrier protection

- Sexual function

Fitness and Nutrition

- Dietary/nutrition assessment
- Exercise program
- Folic acid supplementation (0.4 mg/day)
- Calcium intake

Psychosocial Evaluation

- History of abuse/neglect/violence (physical, sexual, and emotional)
- Sexual practices
- Lifestyle/stress
- Sleep disorders
- Home and work (including satisfaction and environmental hazards)
- Interpersonal/family relationships; social support
- Depression (suicide)
- Criminality
- Education

TABLE 1.3 (Continued): Preconception Screening Assessment for All Reproductive-Age Patients (15–44 Years Old)

Language and culture
Health insurance status, coverage, access, public programs
Cardiovascular Risk Factors
Family history
Hypertension
Dyslipidemia
Obesity
Diabetes mellitus
Health/Risk Behaviors
Hygiene (including dental)
Injury prevention
• Safety belts and helmets
• Occupational hazards
• Recreational hazards
• Firearms
• Hearing
• Exercise and sports involvement
Breast self-examination
Vaccinations
See Table 1.5

Source: Modified from Refs. [1, 14, 16].

[a] Unless documented immunity.

[b] HIV screening should be offered as routine to all patients of reproductive age, under an "opt-out" policy. Physicians should be aware of and follow their states'/countries' HIV screening requirements.

[c] Annually beginning no later than age 21 years; every 2–3 years after three consecutive negative test results if age 30 years or older with no history of cervical intraepithelial neoplasia 2 or 3, immunosuppression, HIV infection, or diethylstilbestrol exposure in utero.

[d] Most adults need to be screened only once. Persons with continued risk for hepatitis C virus (HCV) infection should be screened periodically [45].

treatment. Prevent panic: get patients ready for a healthy pregnancy before contraception is stopped.

Content of preconception care

Topics pertinent to optimizing preconception health and therefore future maternal and perinatal outcome should be discussed. Topics to be discussed in preconception care are listed in Table 1.2 [2, 14]. Further research is needed to determine the best content of preconception care and the most effective way to implement it [15, 16].

Universal screening and related interventions

History, exam, and laboratory screen

Suggested preconception screening assessment is shown in Table 1.3 [14, 17]. A **questionnaire should be completed ahead of time**, either on paper or online, to review this extensive list. A standardized form improves the completeness of preconception screening, which necessitates time and commitment [18]. This standardized preconception form should be integrated into the permanent record of all reproductive-age patients. In a randomized trial, patients assigned to be screened with a preconception risk survey were found to have an average of nine risk factors, supporting the facts that even low-risk patients may benefit from preconception screening [15].

History should be detailed, especially when pertinent positives are detected. **Prior inpatient and outpatient medical records should be reviewed**. Patients should be empowered with easy access to their records (best if electronic) to facilitate multispecialty care coordination. Personal prenatal medical record access has been associated with increased maternal control, satisfaction

TABLE 1.4: Preconception Laboratory Screening Depending on Risk Factors

Personal History

Age

- >35: fasting glucose

Prior Obstetrical History

- Prior birth of a newborn weighting more than 9 lb or >4,500 g (macrosomia): fasting glucose
- History of gestational diabetes mellitus: fasting glucose
- Prior unexplained fetal death: check autopsy and karyotype of fetal death; antiphospholipid antibody testing; fasting glucose
- Prior infant with congenital anomaly (if not screened in that pregnancy): fasting glucose
- Prior recurrent unexplained early pregnancy loss: antiphospholipid antibody testing; study of uterine anatomy; parental karyotype

Prior Medical History

- Metabolic syndrome/obesity; family history of lipid or coronary disorders: cholesterol/lipid profile
- Diabetes: lipid profile; hemoglobin A1c; cardiac and renal baseline function assessment; ophthalmologic exam
- Hypertension: fasting glucose; baseline cardiac, renal, and liver functions
- Multiple coronary heart disease risk factors (e.g., tobacco use, hypertension): lipid profile
- High-density lipoprotein cholesterol level ≤35 mL/dL: fasting glucose
- Triglyceride level ≥250 mg/dL: fasting glucose
- History of impaired glucose tolerance or impaired fasting glucose: fasting glucose
- Chronic use of steroids: fasting glucose
- Polycystic ovary syndrome: fasting glucose
- History of vascular disease: fasting glucose
- Marfan syndrome: echocardiogram for assessment of aortic root; eye exam for lens
- History of STD, drug use, etc.: HIV, Hep C
- Recipients of blood from donors who later tested positive for HCV infection: Hep C

(*Continued*)

TABLE 1.4 (Continued): Preconception Laboratory Screening Depending on Risk Factors

- Recipients of blood or blood-component transfusion or organ transplant before July 1992: Hep C
- Recipients of clotting factor concentrates before 1987: Hep C
- Chronic (long-term) hemodialysis: Hep C
- History of transfusion from 1978 to 1985: HIV
- Invasive cervical cancer: HIV
- HIV infection: STD screening; PPD
- Medical risk factors known to increase risk of TB if infected: PPD
- Not sure if had varicella infection in past: varicella titer

Social History

- HIV or TB contact, illicit drug use: TB testing
- History of injecting illegal drugs: Hep C; HIV; STD screening (chlamydia, gonorrhea, syphilis, etc.); PPD
- Occupational percutaneous or mucosal exposure to HCV-positive blood: Hep C
- More than one sexual partner since most recent HIV test or a sex partner with more than one sexual partner since most recent HIV test: HIV
- Seeking treatment for STDs: HIV
- History of prostitution: STD screening; HIV
- Past or present sexual partner who is HIV positive or bisexual or injects drugs: HIV
- Long-term residence or birth in an area with high prevalence of HIV infection: HIV
- Adolescents who are or ever have been sexually active: HIV
- Adolescents entering detention facilities: HIV; STD screening
- Offer to patients seeking preconception evaluation: HIV (all patients should be screened)
- History of multiple sexual partners or a sexual partner with multiple contacts: STD screening
- Sexual contact with individuals with culture-proven STD: STD screening
- History of repeated episodes of STDs: STD screening
- Attendance at clinics for STDs: STD screening
- All sexually active patients aged 25 years or younger: chlamydia
- All sexually active adolescents: gonorrhea
- Close contact with individuals known or suspected to have TB: PPD
- Born in country with high TB prevalence: PPD
- Medically underserved: PPD
- Low income: PPD
- Alcoholism: PPD
- Resident of long-term care facility (e.g., correctional institutions, mental institutions, and nursing homes and facilities): PPD
- Health professional working in high-risk health care facilities: PPD

Family History

- Family history of diabetes mellitus: fasting glucose
- Family history of diabetes; history of gestational diabetes, overweight/obese, hypertension, high-risk ethnic group (African American, Hispanic, Native American): fasting glucose every 3 years
- Family history suggestive of familial hyperlipidemia: lipid profile
- Family history of premature (age <50 years for men, age <60 years for patients) cardiovascular disease: lipid profile
- Colorectal cancer or adenomatous polyps in first-degree relative younger than 60 years or in two or more first-degree relatives of any ages; family history of familial adenomatous polyposis or hereditary nonpolyposis colon cancer: colonoscopy
- First-degree relative (i.e., mother, sister, or daughter) or multiple other relatives who have a history of premenopausal breast or breast or ovarian cancer: mammography
- Family history of Marfan syndrome: echocardiogram for assessment of aortic root; eye exam for lens
- Family history of breast cancer: mammography
- Family history of thyroid disease: TSH
- Ashkenazi Jewish testing—familial dysautonomia; Tay-Sachs; Canavan; Fanconi anemia type C; Niemann-Pick disease type A; Bloom syndrome; Gaucher disease; glycogen storage 1a; maple syrup urine disease; mucolipidosis type IV
- Ethnicity testing; consider genetic counseling

Physical Examination

- Overweight (BMI ≥ 25): fasting glucose or hemoglobin A1c
- Hypertension: fasting glucose or hemoglobin A1c

Laboratory Screening

- Persistently abnormal alanine aminotransferase levels: Hep C
- Glycosuria: fasting glucose

Source: Modified from Ref. [14].

Abbreviations: STDs, sexually transmitted diseases; HIV, human immunodeficiency virus; Hep C, hepatitis C; HCV, hepatitis C virus; PPD, purified protein derivative; TB, tuberculosis; IV, intravenous; TSH, thyroid-stimulating hormone; BMI, body mass index.

TABLE 1.5: Recommended Preconception Vaccinations

All Reproductive-Age Patients
- No recent prior COVID vaccination: **COVID**
- During flu season: **influenza**
- No evidence of immunity to rubella: **MMR**
- No evidence of immunity to varicella: **varicella**
- No adult Td vaccination in last 2 years: **tetanus/diphtheria/pertussis (Tdap)**

High-Risk Populations
- Hepatitis B nonimmune: **hepatitis B vaccine**

Age
- All girls and patients 9–26 years old: HPV
- All persons 18 years old and younger without immunity to hepatitis B infection: hepatitis B

Occupational
- Health care workers: hepatitis B, influenza, MMR, varicella
- Public safety workers who have exposure to blood in the workplace: hepatitis B
- Students in schools of medicine, dentistry, nursing, laboratory technology, and other allied health professions: hepatitis B
- Staff of institutions for the developmentally disabled: hepatitis B
- Individuals who work with HAV-infected nonhuman primates or with HAV in a research laboratory setting: hepatitis A
- Military recruits: meningococcus
- Microbiologists routinely exposed to *Neisseria meningitidis* isolates: meningococcus

Social History/Living Situation
- Individuals with more than one sexual partner in the previous 6 months: hepatitis B
- Household contacts and sexual partners of individuals with chronic hepatitis B infection: hepatitis B
- Inmates of correctional facilities: hepatitis B
- Clients of institutions for the developmentally disabled: hepatitis B
- Illegal injected drug users: hepatitis B
- Illegal drug users (injected and noninjected): hepatitis A
- Exposure to environment where pneumococcal outbreaks have occurred: pneumococcus
- Unhealthy alcohol use : pneumococcus
- Tobacco smoking: pneumococcus
- Residents of long-term care facilities: influenza, pneumococcus
- First-year college students living in dormitories: meningococcus

Travel/Immigration
- Individuals traveling to or working in countries that have high or intermediate endemicity of hepatitis A: hepatitis A
- International travelers who will be in countries with high or intermediate prevalence of chronic hepatitis B infection for more than 6 months: hepatitis B
- Travel to areas hyperendemic or epidemic for *Neisseria meningitides*: meningococcus

Pulmonary Conditions
- Chronic pulmonary disorders, including asthma: pneumococcus

Cardiac Conditions
- Chronic cardiovascular disorders (e.g., CHF, cardiomyopathies): influenza, pneumococcus

Renal Conditions
- Chronic metabolic diseases, including renal dysfunction: influenza, pneumococcus
- Nephrotic syndrome: pneumococcus
- End-stage renal disease, including those on dialysis: hepatitis B

Endocrine Conditions
- Diabetes mellitus: influenza, pneumococcus

Hematologic/Immunologic Conditions
- Prior transfusions: hepatitis A, hepatitis B
- Patients with clotting factor disorders (those who receive clotting factor concentrates): hepatitis A
- Chronic illness, such as functional asplenia (e.g., sickle cell disease) or splenectomy: pneumococcus
- Immunocompromised patients (e.g., HIV infection, hematologic or solid malignancies, chemotherapy, steroid therapy): pneumococcus
- Adults with anatomic or functional asplenia: pneumococcus, meningococcus
- Terminal complement component deficiencies: meningococcus

Infectious Conditions
- Individuals with a recently acquired or recent evaluation for STI: hepatitis B
- All clients in STD clinics: hepatitis B
- HIV: hepatitis B, influenza, pneumococcus, consider meningococcus

GI/Hepatic Conditions
- Chronic liver disease: hepatitis A, hepatitis B, pneumococcus

Neurologic Conditions
- Cerebrospinal fluid leaks: pneumococcus

Source: Modified from Ref. [14] (see also Chap. 38 in *Maternal-Fetal Evidence Based Guidelines*, Fourth Edition).

Abbreviations: MMR, measles, mumps, and rubella; HPV, human papillomavirus; HAV, hepatitis A virus; CHV, congestive heart failure; HIV, human immunodeficiency virus; STI, sexually transmitted infection; STD, sexually transmitted disease.

TABLE 1.6: Preconception Interventions for All Patients

Intervention	Prevention of
Folic acid 400 µg/day[a]	NTDs and also probably cardiac defects, facial clefts
Vaccinations	Maternal/perinatal infection[b] (Table 1.5)
Proper diet and exercise	Obesity, diabetes, hypertensive diseases, and their consequences
Injury prevention (e.g., seat belts, helmets)	Physical trauma
Screen for specific risk factors	See Table 1.7

Abbreviations: NTDs, neural tube defects; STD, sexually transmitted disease; MTHFR, methylenetetrahydrofolate reductase.

[a] Consider higher dose, especially for patients taking antiseizure medications, other drugs that might interfere with folic acid metabolism, those with homozygous MTHFR enzyme mutations, or those who are obese.

[b] By decreasing perinatal transmission, also decrease congenital defects caused by infection.

TABLE 1.7: Preconception Care for Specific Maternal Medical Disorders

Disorder	Chapter in MF Evidence Based Guidelines	Brief Preconception Recommendations	Prevention of
Hypertensive disorders	1	• Discontinue ACE inhibitors and ARB; transition to another antihypertensive • Investigation into other etiologies • Baseline creatinine • Consider retinal exam, urine protein assessment and electrocardiography in women with longstanding disease	Congenital anomalies, HTN complications, CD, FGR, placental abruption, PTB, perinatal death
Cardiac disease	2	• Any necessary or possible cardiac interventions undergone prior to pregnancy • Patients with group III lesions or dilated cardiomyopathy are advised not to conceive	Worsening maternal cardiac condition, PTB, HTN
Obesity	3	• Counseling, diet and exercise to return to normal BMI • Evaluation of fasting lipids, fasting blood sugar • Screening for thyroid disease, OSA, HTN • If coexisting HTN or DM, obtain ECG and ECHO • Education about poor perinatal outcomes in obese patients • Motivational interviewing • Those who have recently had bariatric surgery should be counseled that pregnancy is optimal after the period of rapid weight loss	Infertility, fetal NTDs, PTB, CD, HTN disorders, diabetes, VTE
Pregestational diabetes	4	• Optimize glycemic control with goal Hgb A1c <6.5% • Screen for asymptomatic bacteriuria • Consideration for retinal exams, urine proteinuria screening • Thyroid screening	Congenital anomalies, length of NICU admission, perinatal mortality and long-term health consequences in infant; miscarriage; maternal hospitalizations, maternal renal disease
Hypothyroidism	6	• Monitor TSH and FT4 to assure euthyroid state	Infertility, maternal HTN, miscarriage, preeclampsia, abruption, anemia, PTB, LBW, fetal death, possibly neurological problems in infant
Hyperthyroidism	7	• If radioiodine is required, should be completed 6–12 months before attempting conception • Emphasize minimum of 150 µg iodine daily (recommendation for all preconception patients)	Spontaneous pregnancy loss, PTB, preeclampsia, fetal death, FGR, maternal congestive heart failure, and thyroid storm; neonatal Graves' disease

TABLE 1.7 (Continued): Preconception Care for Specific Maternal Medical Disorders

Disorder	Chapter in MFM Evidence Based Guidelines	Brief Preconception Recommendations	Prevention of
Prolactinoma	8	• Treat with dopamine agonist until decreasing size of adenoma to at least <1 cm, and normal prolactin	Risk of increasing size of maternal prolactinoma, possibly causing optic nerve impairment
History of hyperemesis gravidarum	9	• Start prenatal vitamins at 3 month prior to conception	Decreases risk of recurrence of hyperemesis
Inflammatory bowel disease	11	• Plan conception when disease is in remission >6 months • Discontinue MTX 3–6 months prior to conception • Screen for B_{12}, vitamin D, and iron deficiency	Birth defects
Liver transplantation	13	• Plan pregnancy when stable on immunosuppressive regimen >1 year • Assess baseline kidney/liver function, 24-hour urine • If patient is on mycophenolic acid products, assess fetal risks and consider switching to alternative immunosuppressant	PTB, HTN, preeclampsia, FGR, GDM, graft rejection
Anemia	14	• Evaluation of etiology, assessment for iron, B_{12}, and folate deficiency • In patients of African ancestry, hemoglobin electrophoresis • Genetic consult for patients with hereditable disorder	SGA, PTB, maternal CV compromise, need for transfusion
Sickle cell disease	15	• Start on 4 mg folic acid daily to optimize hemoglobin status • Vaccinate with pneumococcal and influenza • Discontinue teratogenic medications (ACE inhibitors, iron chelators)	Birth defects, crises
von Willebrand disease	16	• Consult hematology, genetics; administer hepatitis B vaccine • Baseline labs (von Willebrand factor antigen, ristocetin cofactor activity, factor VIII, low-dose ristocetin-induced platelet aggregation, multimer assay)	Postpartum hemorrhage
Renal disease/transplant	17	• Assess baseline creatinine, 24-hour proteinuria, intravenous pyelogram • Plan pregnancy when stable on immunosuppressive regimen, with drug therapies at maintenance levels if possible • Post-transplant, await >1 year before conception	Preeclampsia
Seizures	19	• Recommend deferring conception until seizure-free on minimal medication, preferably monotherapy • Consult neurology to consider weaning medication if >2 years seizure-free • Start on folic acid 2–4 mg daily	Congenital anomalies
Spinal cord injury	20	• If cause is congenital, start on folic acid 4 mg daily and genetic counseling	Congenital anomalies
Mood disorders	21	• Counsel on the risks of discontinuing antidepressants in pregnancy • Stabilize mood on lowest effective dose prior to pregnancy • Avoid paroxetine, given risks of cardiac malformations	Cardiac malformations

(*Continued*)

TABLE 1.7 (Continued): Preconception Care for Specific Maternal Medical Disorders

Disorder	Chapter in MFM Evidence Based Guidelines	Brief Preconception Recommendations	Prevention of
Smoking	22	• Counsel regarding preventable pregnancy outcomes in patient who smoke • Encourage cessation with behavioral and educational interventions	PTB, LBW
Drug use disorder	23	• Encourage patients to postpone conception until after completing detoxification or instituting replacement therapy in the case of opioid use disorder	PTB, FGR, neonatal withdrawal, etc. (effect depends on drug)
Asthma	26	• Control of asthma with appropriate regimen through multidisciplinary care, set expectations to continue management throughout pregnancy	PTB, LBW, preeclampsia, perinatal mortality
Tuberculosis	26	• Screen high-risk patients (hx of incarceration, TB exposure, international travel or immigration) with PPD or interferon gamma-release assay and treat accordingly	Active TB
Lupus	27	• Recommend conception when disease is in remission for >6 months • Screen for HTN, renal, heart, lung, or brain disease as well as antiphospholipid and SSA/SSB antibodies • Decrease meds to lowest possible effective dose • Replace mycophenolate mofetil and with other medications	HTN, preeclampsia, PTB, fetal death, FGR, neonatal lupus
Venous thromboembolism and mechanical heart valves	30	• Screen all patients with history of VTE for thrombophilia • Perform any necessary valve replacements before pregnancy • If mechanical heart valve, consider continuing warfarin after full counseling of risks of warfarin embryopathy and under direction of cardiologist	Recurrence of venous thromboembolism
Hepatitis A	31	• Vaccinate patients who travel abroad, are at risk for contracting the disease, or are infected with chronic hepatitis B or C prior to pregnancy; vaccine also safe in pregnancy	
Hepatitis B	32	• Administer HBV vaccine to any patient who is susceptible before pregnancy • If chronically infected, screen for hepatitis A and vaccinate prior to pregnancy	Perinatal HBV transmission
Hepatitis C	33	• Screen high risk populations prior to pregnancy • Vaccinate against hepatitis A and B if nonimmune • Consider treatment preconception	Cirrhosis, HCC, HCV infant transmission
HIV	34	• Initiate or modify antiretroviral therapy avoiding teratogenic agents • CD4 count and indicated prophylaxis based on level • Screen for STIs • Advise how to optimize conception, yet minimizing risk of transmission	Perinatal HIV infection

TABLE 1.7 (Continued): Preconception Care for Specific Maternal Medical Disorders

STI testing	35, 36, 37, 38	• Screen and treat for gonorrhea, chlamydia, syphilis and trichomonas in high risk patients (e.g. <25, prior STI, multiple sexual partners, inconsistent condom use, sex work, or drug use)	Ectopic pregnancy
PKU		• Low-phenylalanine diet	PKU-related mental retardation
Intimate partner violence	24	• Counseling; Referral to appropriate agency	Physical and emotional trauma and their consequences, fetal loss
Alcohol use disorder		• Medical and behavioral therapy • Avoid all alcohol intake	Congenital anomalies, mental retardation
Supplements and over-the-counter medications		• Review and counsel: avoid excess of recommended daily allowance (RDA) (see also Chap. 2)	Congenital anomalies

Abbreviations: MF, Maternal-Fetal; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; HTN, hypertension; CD, cesarean delivery; PTB, preterm birth; LBW, low birth weight; NICU, neonatal intensive care unit; BMI, body mass index; DM, diabetes mellitus, EKG, electrocardiogram; ECHO, echocardiogram; OSA, obstructive sleep apnea; NTD, neural tube defects; VTE, venous thromboembolism; FGR, fetal growth restriction; TSH, thyroid-stimulating hormone; FT4, free thyroxine; CV, cardiovascular; MTX, methotrexate; TB, tuberculosis; PPD, purified protein derivative; SSA/SSB, Sjogren syndrome related antigen A and B; HIV, human immunodeficiency virus; STI, sexually transmitted infections; PKU, phenylketonuria.

TABLE 1.8: Teratogens

Prescribed Drugs

- Androgens and testosterone derivatives (e.g., danazol)
- Angiotensin-converting enzyme (ACE) inhibitors (e.g., enalapril, captopril) and angiotensin II receptor blockers
- Coumadin derivatives (e.g., warfarin)
- Carbamazepine
- Diethylstilbestrol
- Folic acid antagonists (methotrexate and aminopterin)
- HMG-CoA reductase inhibitors (statins)
- Lithium
- Phenytoin
- Primidone
- Streptomycin and kanamycin
- Tetracycline
- Thalidomide and leflunomide
- Trimethadione and paramethadione
- Valproic acid
- Vitamin A above RDA and its derivatives (e.g., isotretinoin, etretinate, and retinoids)

Chemicals

- Lead
- Mercury

Drugs

- Alcohol
- Cocaine

Infections

- Cytomegalovirus
- Rubella
- Syphilis
- Toxoplasmosis
- Varicella

Radiation

Source: Modified from Refs. [58, 59].

Abbreviations: HMG-CoA, 3-hydroxy-3-methyl-glutaryl-CoA reductase; RDA, recommended daily allowance.

during pregnancy, and increased availability of antenatal records during hospital attendance [19].

Prior **obstetrical and gynecological history**, including prior pregnancy complications, should be reviewed. Other reproductive issues should also be assessed: fertility, including the possibility of assisted reproductive technology needs; sexuality (in particular high-risk behaviors); contraception; partner selection; and sexual function. Several social issues need to be reviewed as well (Table 1.3).

All couples should have a basic screen for family history of **heritable genetic disorders**, with a pedigree to at least the second prior generation. Patients belonging to an ethnic group at increased risk for a recessive condition (Table 1.4) should be offered appropriate screening. All couples should be made aware of the option for **cystic fibrosis** (CF) screening and hemoglobin electrophoresis screening [20]. Patients with a specific indication for genetic testing should be referred for formal genetic counseling (see Chaps. 5 and 6).

Physical exam details are shown in Table 1.3. Pelvic exam may include cytologic and sexually transmitted infection screening for patients with certain risk factors. **Laboratory tests** are done routinely (Table 1.3) and depending on risk factors (Table 1.4) [14].

Reproductive health plan

Asking a reproductive-age woman, and therefore inducing her to think about, her reproductive health plan, should be a priority of any medical visit [21]. Such a plan should address the desire (or not) for children; the optimal number, spacing, and timing of pregnancies; contraception to achieve this plan; opportunities to improve her health and therefore a successful reproductive life; and age-related changes in fertility [21]. Having a reproductive health plan reduces unintended pregnancies, age-related infertility, and fetal exposure to teratogens [2]. Very few patients know that a **short interpregnancy interval (i.e., <6 months from the end of the last pregnancy to the next conception)** is associated with increased incidence of both small-for-gestational-age and low-birth-weight neonates [22]. Folic acid depletion may be the etiology for these increased risks [23]. Education and **contraception advice** are necessary to aim for the wished reproductive plan,

avoid unplanned pregnancies, and optimize the 18- to 24-month interpregnancy interval goal. In a nonrandomized study, preconception care decreased the number of unintended pregnancies [24].

All patients should be counseled that 2–3% of babies are born with minor (usually) or major anomalies. Screening and diagnostic options to detect aneuploidy and birth defects should be reviewed so that patients may consider their options in relation to their personal values.

Nutrition, weight, and exercise

Lifelong habits of healthy diet and regular exercise should be established preconceptionally [25]. Proper diet and exercise can prevent several complications of pregnancy, including gestational diabetes and hypertensive complications [26]. Some studies suggest a correlation between a diet high in fruits, vegetables, nuts, and legumes; less than two servings of meat weekly; and at least two servings of fish weekly (the "Mediterranean Diet") with decreased rates of infertility and PTB [27–30].

In addition to following a healthy diet, issues of food safety are important to review. All meat, seafood, and shellfish should be **thoroughly cooked.** Eating at least 12 oz of **fish** weekly is associated with several benefits, including a lower rate of PTB (see Chap. 18) [29], but patients must avoid >2 servings/week of shark, swordfish, king mackerel, some tuna, or tilefish, all of which may contain high concentrations of methyl mercury. Albacore (white) tuna has more mercury than canned light tuna [30]. Other recommendations include **eating only pasteurized eggs and dairy products and washing raw fruits and vegetables** before eating. Patients should try to obtain a minimum daily iodine intake of 150 mg/day. Education about proper hand, food, and cooking utensil hygiene is important, especially in developing countries.

Body mass index (BMI) should be calculated at least annually for reproductive-age patients [31]. For patients with a BMI that falls outside the normal range [31–36], preconception counseling regarding the patient's increased risk of complications in pregnancy is extremely important. **Formal nutritional counseling should be offered and goals set to avoid pregnancy until optimal weight is achieved.** Patients with a low BMI should be screened for eating disorders. In overweight and obese patients, **calorie and portion-size control** may be the most effective methods of sustained preconception weight loss. Unfortunately, there are no current evidence-based guidelines as to the most effective method of weight loss in the preconception period for obese and overweight patients [36]. Postpartum individual counseling on diet and physical activity increased the proportion of patients returning to pre-pregnancy weight from 30% to 50% in one randomized trial [32].

An exercise routine that can be started preconceptionally and safely continued in pregnancy may include yoga; brisk walking (including hiking and backpacking); jogging; swimming; biking; cross-country skiing; and using fitness equipment such as an elliptical trainer, treadmill, or stationary bike. Patients should be given standard advice for engaging in regular physical activity for 30–60 min/day for 5 or more days per week.

Supplements

The preconception intervention with the most evidence-based data to support its efficacy is **folic acid supplementation.** Folic acid supplementation is recommended, with a **minimum of 400 µg/day** for all patients (93% decrease in neural tube defects [NTDs]), and **4 mg/day for patients with prior children with NTDs or those on certain epileptic medications** (69% decrease in recurrent NTDs) [34].

Supplementation should **start at least 1 month before conception and continue until at least 28 days after conception (time of neural tube closure)**. Given the unpredictability of planned conception, all reproductive-age patients should be on folic acid supplementation from menarche to menopause. Patients taking antiseizure medications, such as phenytoin, carbamazepine, or barbiturates, may benefit from higher doses of folic acid. Patients with homozygous methylenetetrahydrofolate reductase (MTHFR) enzyme mutations or those who are obese may also need higher doses of folic acid supplementation. As increases in baseline serum folate level are directly proportional to a decrease in the incidence of NTDs, some experts have advocated 5 mg of folic acid per day as optimal universal supplementation [35]. Folic acid supplementation has also been associated with a decrease in the risk of congenital anomalies other than NTDs (e.g., cardiac, facial clefts) [36–38].

The overall benefits or risks of fortifying basic foods such as grains with added folate have been associated with a 140–200 µg/day increase in supplementation and a 20–50% decrease in incidence of NTDs [35]. Education with provision of printed material [35, 39], computerized counseling [40], and learner-centered nutrition education [41] all increase the awareness of the folate/NTDs association and the use of the folate supplements. These interventions may be effective in increasing the prophylactic use of additional preconception care activities.

There is insufficient evidence to justify the routine use of other supplements in reproductive-age patients, especially in the developed world, unless a nutritional deficiency has been identified. It is important to obtain a **daily intake of minimum 150 mg of iodine** and 10,000 IU of vitamin A (as beta-carotene) if deficiencies of these nutrients are identified. The use of certain supplements may be detrimental, especially if excessive amounts of lipid-soluble vitamins such as vitamin A (>10,000 IU/day) are taken, since they can be teratogenic. All supplements, including alternative and complementary medicines, should be reviewed (see also Chap. 2) [42, 43].

Maternal infection prevention and vaccines

Preconception vaccination for the prevention of fetal and maternal disease is an important preconception intervention (Table 1.5) (see also Chap. 40 in *Maternal-Fetal Evidence Based Guidelines).* **Maternal immunity to infections such as rubella and varicella** should be assessed for potential vaccination of nonimmune patients, thus eliminating their risk for congenital syndromes associated with these viruses. Vaccination with live attenuated viruses should occur at least 4 weeks prior to conception due to the theoretical risk of live virus affecting the fetus.

Annual influenza vaccination for patients and their partners contemplating pregnancy will reduce the chance of maternal prenatal infection, a time during which higher morbidity has been documented. Influenza vaccination for new mothers and other close contacts of the newborn will reduce the risk of infection for the child who is unable to receive vaccination until 6 months of age. Through this process of "cocooning," the newborn is protected from the high morbidity and mortality rates associated with influenza in the first year of life [44].

Hepatitis B vaccination should be offered to all susceptible patients of reproductive age. This is especially true in regions with intermediate and high rates of endemicity (where ≥2% of the population is hepatitis B surface antigen [HBsAg] positive). Perinatal transmission of hepatitis B results in a 90% chance of chronic infection in the newborn, which places the child at risk

for future cirrhosis and hepatocellular carcinoma. In regions of low prevalence, vaccination should be targeted to high-risk groups (Table 1.5).

Recent guidelines have recommended hepatitis C screening in all adults ≥18 years old. This can be done during preconception, as treatment for hepatitis C is currently only performed in non-pregnant individuals [45].

Tetanus vaccination should remain up-to-date in reproductive-age women, particularly in regions of the world where maternal and neonatal tetanus is prevalent [46]. This has been shown to markedly reduce the incidence of tetanus related to parturition. Due to increasing prevalence and the high morbidity and mortality rates of neonatal pertussis, vaccination (in combination with tetanus and diphtheria) is recommended for all patients and their partners of reproductive age who have not been immunized in their adult lives (since the age of 11 years) [47]. It is well documented that 75% of cases of neonatal pertussis have a family member as the index case [48].

Other vaccination recommendations based on medical, occupational, or social risks are described in Table 1.5.

Injury prevention

The second leading cause of death in reproductive-age patients is accidents. Use of **seat belts** and **helmets** should be reviewed and strongly encouraged where appropriate. Inquiry should be made regarding occupational and recreational hazards. Possession and use of firearms should be evaluated.

Universal recommendations

Preconception recommendations for all patients are listed in Table 1.6. Reproductive-age patients should be aware of these evidence-based recommendations, both through their doctors and through public awareness campaigns. Several online resources are available [49–52]. Patients and their partners should take more responsibility for their care and the future health of their offspring, and implement the health and lifestyle changes recommended.

Specific issues

History of preterm birth

There are currently no preconception recommendations for a patient with a history of preterm birth outside of the general recommendations for patients trying to conceive. Randomized controlled trials examining preconception initiation of low-dose aspirin did not demonstrate an increase in live birth rate or decrease in PTB [53, 54]. Interval antibiotic treatment with azithromycin and metronidazole between pregnancies in patients with a prior spontaneous PTB (<34 weeks) has not been associated with decreased risk of preterm delivery [55, 56].

Advanced maternal age

In recent years, there has been a trend to delay childbearing. This trend is especially prevalent in developed countries, for example, in the United States where the birth rate in 40- to 44 years old patients has increased from 5.2 births per 1,000 in 1990 to 10.4 births per 1,000 patients in 2013 [57]. It is well established that patients of advanced maternal age (AMA) are at increasing risk of poor obstetric outcomes, stillbirth, and fetal death [58–60]. Patients of extreme AMA (>45 years old) have been found to have an increased prevalence of preexisting chronic disease [61]. Although no Level I evidence exists for preconception testing in this population, it is reasonable to screen patients of extreme AMA who also have chronic hypertension, diabetes, hyperlipidemia, or heart disease with a cardiac echocardiogram.

Chronic diseases

The incidences of several medical disorders such as obesity, diabetes mellitus, and hypertension are high and on the rise in reproductive-age patients. There is literature for evidence-based recommendations on each disease or condition that can involve the reproductive-age patient and affect their reproductive health [3, 4, 17]. Full review of each is beyond the scope of this chapter (see individual chapters in *Maternal-Fetal Evidence Based Guidelines*). Some common conditions are discussed for brief preconception management review (Table 1.7).

Diabetes

Diabetes (see Chaps. 4 and 5 in *Maternal-Fetal Evidence Based Guidelines*) is associated with an increased risk of congenital anomalies, in particular cardiac defects and NTDs, if poorly controlled in the first weeks of pregnancy. The risk of congenital anomalies is related to long-term diabetic control, reflected in the level of glycosylated hemoglobin **(HgB A1c): <7% = no increased risk** (2–3% baseline); 7–9% = 15%; 9–11% = 23%; >11% = 25% [34]. **It has been estimated that euglycemia (with normal HgB A1c) during the first trimester, which can only be achieved through attentive preconception counseling, could prevent >100,000 U.S. pregnancy losses or birth defects per year** [2]. Another cost analysis reported that universal preconception care could lead to averted lifetime costs for the affected cohort of children as high as $4.3 billion [62, 63]. The benefits of preconception diabetes care have been previously demonstrated [64, 65], even in teenagers [66]. Preconception care is also essential for counseling of the patient with conditions severe enough to make a successful pregnancy extremely unlikely. The diabetic patient with either ischemic heart disease, untreated proliferative retinopathy, creatinine clearance <50 mL/min, proteinuria >2 g/24 hour, creatinine >2 mg/dL, uncontrolled hypertension, or gastropathy should be told not to get pregnant before these conditions can be improved, and counseled regarding adoption if the conditions cannot be improved [67]. The frequency of fetal/infant and maternal morbidity and mortality are reduced in diabetic patients seeking consultation in preparation for pregnancy, but unfortunately only about one-third of these patients receive such consultation [68]. The preconception consultation affords the opportunity to screen for vascular consequences of the diabetes, with **ophthalmologic, electrocardiogram (ECG), and renal evaluation via a 24-hour urine collection for total protein and creatinine clearance**, and determine ancillary pregnancy risks. Proliferative retinopathy should be treated with laser before pregnancy. **Thyroid-stimulating hormone (TSH)** should be checked, as 40% of young patients with type 1 diabetes have hypothyroidism. Of note, there is insufficient evidence to treat subclinical hypothyroidism [69].

Diabetes evaluation should emphasize the importance of tight glycemic control, with normalization of the HgB A1c to <7%. To achieve euglycemia, **diet, glucose monitoring, and exercise** are always stressed. **If euglycemia is not achieved with these means, oral hypoglycemic agents or insulins are utilized**, and their regimens should be optimized preconceptionally. Of the oral hypoglycemic agents, **Glucophage (metformin) is the preferred agent at this time** [70] and probably continued during pregnancy. The original safety data available for glyburide showed that it did not cross the placenta in appreciable amounts [71],

but recent data have shown a 70% level in umbilical blood compared to maternal blood [72]. The other oral hypoglycemic agents should not be used for preconception glycemic control, as there is no sufficient evidence for their safety and efficacy in pregnancy. **A common insulin regimen currently used by diabetologists is long-acting (e.g., glargine) and short-acting (e.g., lispro)**. This is a safe and effective regimen in pregnancy too. Patients compliant with insulin pumps should continue this regimen with the understanding of increased insulin requirements in pregnancy.

If a patient has a history of gestational diabetes, appropriate postpartum diabetes screening should be performed. Interconception counseling and lifestyle modifications may be beneficial for future pregnancies [73].

Hypertension

Hypertension (see Chap. 1 in *Maternal-Fetal Evidence Based Guidelines*) is associated with several maternal and fetal risks in pregnancy. **Serum creatinine, 24-hour urine for total protein and creatinine clearance, ECG, and ophthalmologic exam** are suggested, especially in patients with long-standing or severe hypertension. It is important to identify cardiovascular risk factors, identify any reversible causes of hypertension, and assess for target organ damage or cardiovascular disease. If hypertension is newly diagnosed and has not been evaluated previously, a medical consult may be indicated to assess for any of these factors. Secondary hypertension, target organ damage (left ventricular dysfunction, retinopathy, dyslipidemia, microvascular disease, and prior stroke), maternal age >40, previous pregnancy loss, systolic blood pressure ≥180 mmHg, or diastolic blood pressure ≥110 mmHg are associated with higher risks in pregnancy. Abnormalities should be addressed and managed appropriately. If, for example, serum creatinine is >1.4 mg/dL, the patient should be aware of increased risks in pregnancy (pregnancy loss, reduced birth weight, PTB, and accelerated deterioration of maternal renal disease). Even mild renal disease (creatinine 1.1–1.4 mg/dL) with uncontrolled hypertension is associated with 10-fold higher risk of fetal loss. Preconception prevention can be enormously effective. **Thirty minutes of exercise three times per week in all patients with hypertension and weight reduction if overweight are recommended**. Restriction of sodium intake to <2.4 g sodium daily intake recommended for essential hypertension is beneficial in nonpregnant adults. If antihypertensive medical therapy is necessary, **angiotensin-converting enzyme (ACE) inhibitors and angiotensin II (AII) receptor antagonists should be discontinued**, as they are associated with birth defects, fetal growth restriction, oligohydramnios, neonatal renal failure, and neonatal death in pregnancy. All other antihypertensive agents should be used at the lowest effective dose, and are probably safe if started preconceptionally and continued in pregnancy.

Abnormal body mass index

Obesity rates are increasing in the population and can be associated with infertility, miscarriage, and congenital anomalies, as well as other comorbid diseases. Patients should be counseled regarding the benefits of **weight reduction in the preconception period** to reduce these risks [74, 75]. If a woman has had a recent bariatric surgery, the following 12–24 months can be a time of rapid weight loss, and it is recommended that pregnancy be avoided during this time [76].

Patients who are underweight are at risk for having low-birth-weight infants and should also be counseled about attaining weight optimization before pregnancy [77].

Seizure disorders

Conception should be deferred until seizures are well controlled on the minimum effective dose of medication (see Chap. 19 in *Maternal-Fetal Evidence Based Guidelines*). **Monotherapy** is preferable. Lamotrigine has been reported to be first-line therapy for nonpregnant adults for partial seizures [78–80] and associated with a low incidence of major malformations [81], but not in all studies [82]. The best choice is the antiepileptic drug (AED) that best controls the seizures. The AEDs are usually Food and Drug Administration (FDA) category C (human risk unknown, but none proven yet) except for the **following AEDs that are known potential teratogens: carbamazepine, primidone, phenytoin, and valproate** (Table 1.8). These four AEDs should therefore be avoided, if possible, by using a different therapy beginning in the preconception period. **Patients who have been seizure-free for ≥2 years with a normal electroencephalogram (EEG) may be eligible to stop anticonvulsant therapy after consulting with a neurologist** [83].

Medications/Teratogens

Detailed discussion regarding prescribed and over-the-counter medications should occur at the preconception visit. The indication, safety, effectiveness, and necessity of each drug need to be reviewed. Often, patients and their doctors stop efficacious and necessary medications as soon as the patient finds out she is pregnant, compromising the health of both the patient and her baby. **The vast majority of prescribed medications are safe in pregnancy, even in the first trimester. Only a few drugs, chemicals, infections, or radiations are proven teratogens** (Table 1.8) [84, 85]. These should be avoided, except in rare circumstances (e.g., the patient with mechanical cardiac valves who accepts the teratogenic risk of warfarin). This medication counseling is often a crucial part of preconception care and can save and ameliorate significantly the health of a future offspring. Great resources exist on the Web for up-to-date teratologic information [86–88].

Substance use disorder/Environmental hazards/Toxins

Tobacco use during pregnancy is associated with increased risks of several complications (see Chap. 22 in *Maternal-Fetal Evidence Based Guidelines*). The benefits of smoking cessation are tremendous: prevention of 10% of perinatal deaths, 35% of low-birth-weight births, and 15% of preterm deliveries [89]. Smoking only one to five cigarettes per day is associated with a 55% higher incidence of low-birth weight compared to nonsmokers. Reproductive-age patients should be informed of other smoking-related diseases, such as ischemic heart disease, cancer, lung diseases, pneumonia, stroke, and congestive heart failure. Patients at greatest risk for smoking are those <25 years old with less than a high school education. Smoking makes a major contribution to disparities in mortality [90]. Smoking cessation programs are associated with a 6% increase in smoking cessation and decrease in incidences of low-birth weight by 19% and PTB by 16% [91]. **Support and reward techniques** to help quit smoking are one of the best forms of evidence-based medicine, supported by over 20 high-quality randomized trials. The "5 As" for screening and interventions to prevent smoking in pregnancy are **Ask, Advise, Assess, Assist, and Arrange** [71]. **Counseling with behavioral and educational interventions is associated with the highest cessation rates. If necessary, most pharmacotherapies are effective preconception**, but contraindicated or with uncertain

safety and efficacy during pregnancy. Nicotine replacement therapy (e.g., patch, gum, and bupropion) is safe and effective in reproductive-age patients, but there is insufficient evidence for recommending them in pregnant smokers. Nicotine replacement therapy is associated with known adverse fetal effects, and nicotine is detected in breast milk. Possibly the best prevention of the adverse effects of smoking on pregnancy is achieved by avoiding sale of tobacco to young people, prohibition of smoking in public places, increase in tobacco taxation, workplace smoking cessation programs, and banning of tobacco sponsorship of sporting and cultural events.

Numerous recreational drug exposures have adverse pregnancy effects (see Chap. 23 in *Maternal-Fetal Evidence Based Guidelines*). This list is extensive and includes, but is not limited to, common recreational drugs such as alcohol, cannabinoids, cocaine, heroin, and methamphetamines. Patients with substance use disorder are disproportionately overrepresented among patients with unplanned pregnancies, and thus discussing birth control methods and approaches to a planned pregnancy is important.

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2

PRENATAL CARE

Gabriele Saccone and Kerri Sendek

Key points

- **Prenatal care is of benefit to pregnant women, especially those with modifiable risk factors**.
- **Most women should be offered midwife-led models of care**. Continuity of care by midwives has been associated with improved patient satisfaction.
- **Group prenatal care should be promoted**, as it has been associated with a reduction in preterm birth, greater satisfaction, and higher breastfeeding initiation.
- Prenatal care usually consists of 7–12 visits per pregnancy, with a first visit soon after the pregnancy test is positive and in time to establish the location and number of embryo(s), usually at around 6–8 weeks, then at 11–14 weeks for aneuploidy screening, followed by visits about every 4 weeks approximately at 16, 20, 24, and 28 weeks, about every 2 weeks from 34 to 36 weeks, and weekly until delivery. **In settings with limited resources** where the number of visits is already low, **reduced-visit programs of antenatal care (<5) are associated with an increase in perinatal mortality**.
- **Early ultrasonography** should be used to determine the estimated date of delivery if there is any uncertainty regarding the last menstrual period.
- **Regular exercise is beneficial to overall maternal fitness and sense of well-being**, as well as associated with prevention of excessive weight gain and prevention of preterm birth and gestational diabetes.
- **Sexual activity** in pregnancy is associated with **better outcomes**.
- **Balanced nutrition and protein supplementation** is associated with modest increases in maternal weight gain and in mean birth weight and **reduction in risk of small-for-gestational-age, stillbirth, and neonatal death**. High-protein and isocaloric protein supplementation should be avoided, as they are associated with increased risk of small for gestational age (SGA).
- **Suggested weight gain** in pregnancy is shown in **Figure 2.1**. Women who are **underweight** are at increased risk for low birth weight and **preterm birth** and have better outcomes with a higher total weight gain.
- **Folic acid supplementation is recommended for neural tube defect (NTD) prevention**, with **400 µg/day for most women** and 4 mg/day for women with prior children with NTD or women taking certain medications that rapidly metabolize folate. **All reproductive-age women should be on folic acid supplementation**.
- **Women should be allowed to carry their record**.
- Immunity to **rubella, varicella, hepatitis B, influenza, tetanus, and pertussis should be assessed at the first prenatal visit**. Ideally, **needed vaccinations should be provided preconceptionally. COVID vaccine is safe at any time in pregnancy, and should be recommended**. **Influenza vaccine** is recommended for pregnant women during flu season and **TDaP (tetanus, diphtheria, pertussis) vaccine** is recommended for all pregnant women, regardless of the immunity status, after 28 weeks. Partners and family members should be encouraged to be vaccinated as well.
- **Prenatal education** directed at specific objectives has been demonstrated to be effective.
- **Implementation of community-based interventional care packages** is associated with a trend for **reduction in maternal mortality** and with **significant reductions in maternal morbidity, neonatal mortality, stillbirths, and perinatal mortality**.
- **Perineal massage** with sweet almond oil for 5–10 minutes daily from 34 weeks until delivery is associated with a significantly higher chance of an intact perineum in nulliparous women.
- **Antenatal classes with training to prepare for labor and delivery** are associated with **arriving to the labor and delivery ward more often in active labor** and **less use of epidural analgesia**.
- **Identifying mothers at risk for postpartum depression assists in prevention compared to intervening on the general population**.
- **Breastfeeding is the best feeding method for most infants** and should be **strongly encouraged**. **Continued counseling and education** facilitate breastfeeding success.
- **Unsensitized RhD-negative women should be offered anti-D immunoglobulin prophylaxis** at 28–30 weeks.
- **Sweeping or "stripping" of membranes** during cervical exam at ≥37 weeks **reduces the rate of postterm delivery**.
- **Magnesium lactate or citrate chewable tablets** 5 mmol in the morning and 10 mmol in the evening for 3 weeks for women with leg cramps are associated with **significant improvement in persistent leg cramps**.
- **Water gymnastics** for 1 hour weekly starting at <19 weeks **reduces back pain** in pregnancy and allows more women to continue to work, with no adverse effects. **Both physiotherapy and acupuncture** starting <32 weeks for 10 sessions **might reduce back and pelvic pain**.
- **Exercise, increase in water intake, dietary counseling, and certain foods (e.g., prunes)** have shown relief in constipation. If these self-help measures are inadequate, the pregnant woman should then try **daily bran or wheat fiber supplements**.

Definition

Prenatal care is the care provided to pregnant women with the aim to prevent complications and decrease the incidence of perinatal and maternal morbidity and mortality [1]. This care consists

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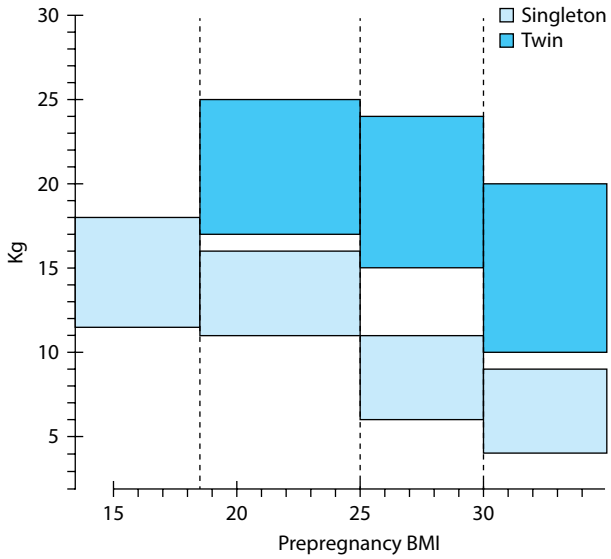


FIGURE 2.1 Institute of Medicine Recommended Total Weight Gain in Pregnancy by Prepregnancy BMI [kg (lb)]; see also Table 2.6. (Data from Ref. [58].)

of health promotion, risk assessment, and intervention linked to the risks and conditions uncovered. These activities require the cooperative and coordinated efforts of the patient, family, prenatal care providers, and other specialized providers. Prenatal care begins when conception is first considered and continues until labor begins. The objectives of prenatal care for the mother, infant, and family relate to outcomes through the first year following birth [1].

Purpose

Prenatal care developed, historically, to reduce the incidence of low-birth-weight (LBW) and preterm infants [2]. It has evolved to encompass a broader purpose: To identify pregnancies with maternal or fetal conditions associated with increased risk of morbidity, to provide interventions to prevent or treat such complications, and to provide education support and health promotion that can have lasting effects on the health of an entire family [3]. **Care should be systematic and evidence based**, and should result in informed shared decision-making between the patient and the provider.

Effectiveness

Prenatal care benefits pregnant women; however, there are no randomized controlled trials (RCTs) of prenatal care versus no prenatal care, and most studies are observational. Selection bias (women who self-select to prenatal care usually are more inclined to have better outcomes) leads to confounding bias (e.g., risk factors associated with LBW and neonatal death are also risk factors for inadequate prenatal care).

There are, however, several RCTs on the number of prenatal care visits, which indirectly demonstrate the beneficial effects of prenatal care. There is a higher incidence of perinatal mortality (relative risk [RR] 1.14, 95% confidence interval [CI] 1.00–1.31) **in programs with significantly less (<5) numbers of prenatal visits, compared to the usual 8–12**. This is particularly significant for low- and middle-income countries [4]. Also, studies demonstrate **a reduction in poor outcomes in high-risk pregnancies with enhanced prenatal care** at no added cost (see the section "Number and Timing of Visits") [4]. In addition, **women are dissatisfied with a reduced schedule of prenatal visits**, indicating a perceived benefit by women [4].

Organizational issues

Health care provider

There is no evidence that physicians need to be involved in the prenatal care of every woman experiencing an uncomplicated pregnancy. The effect of **midwife-led care** compared to physician-led care or to other provider-led care has been evaluated mostly for the whole pregnancy, including both antepartum care and care during labor and delivery (see also Chaps. 7 and 8). Therefore it is somewhat difficult to assess the effect of midwife-led care just on antepartum care. From the evidence from both antepartum and labor and delivery (L&D) care, **most low-risk women can be offered midwife-led models of care, and women should be encouraged to ask for this option. Women with substantial medical or obstetric complications should consult with a physician**. In a meta-analysis, women—the vast majority low risk—who had midwife-led models of care were **less likely to experience antenatal hospitalization** and **less likely to experience fetal loss before 24 weeks' gestation** (RR 0.79, 95% CI 0.65–0.97), although there were no statistically significant differences in fetal loss/neonatal death of at least 24 weeks (RR 1.01, 95% CI 0.67–1.53) or in fetal/neonatal death overall (RR 0.83, 95% CI 0.70–1.00) (see also Chap. 7) [5].

Group prenatal care

In a meta-analysis, educational interventions were the focus of group prenatal care. No consistent results were found, and sample sizes were very small to moderate. No data were reported concerning anxiety, breastfeeding success, or general social support. Knowledge acquisition, sense of control, factors related to infant-care competencies, and some labor and birth outcomes were measured. The largest of the included studies (n = 1275)

examined an educational and social support intervention to increase vaginal birth after cesarean delivery. This high-quality study showed similar rates of vaginal birth after cesarean delivery in "verbal" and "document" groups (RR 1.08, 95% CI 0.97–1.21) [6]. One large RCT demonstrated significant **reduction in preterm birth (PTB), greater satisfaction with care, and higher breastfeeding initiation** at no added cost for group prenatal care over standard care in a group of medically low-risk (but socially at-risk) women in an urban clinic [7]. In this study, group care included, among other interventions, continuity of care from a single provider, patient keeping copies of their records, no waiting time at visits, about 20 hours of provider/patient time, and 8–10 women in each group session. **In the developing world, participatory intervention with women's groups** is associated with **decreased maternal and neonatal mortality** in several large cluster-randomized trials [8–10]. In one of these studies, participatory care involved a female facilitator convening nine women's group meetings every month. The facilitator supported groups through an action-learning cycle in which they identified local perinatal problems and formulated strategies to address them [8]. This strategy holds great promise in decreasing maternal and perinatal deaths among the most vulnerable in our world.

Group prenatal care may even be utilized in a higher-risk population. In a non-RCT study, group prenatal care for women with gestational diabetes mellitus (GDM) was associated with decreased progression to A2 gestational diabetes and improved postpartum follow-up for appropriate diabetes screening without significantly affecting obstetrical or neonatal outcomes [11].

Group prenatal care should be promoted and further studied among more diverse populations.

Prenatal record

A formal, structured record should be used for documenting care during the pregnancy. Structured records with reminder aids help ensure that providers incorporate evidence-based guidelines into clinical practice. There is no trial comparing different records. **Women should be allowed to carry their record**. A meta-analysis of three trials showed that carrying the record is **associated with increased maternal control and satisfaction during pregnancy, increased availability of antenatal records during hospital attendance**, and with more operative deliveries. Importantly, all of the three trials included in the meta-analysis report that more women in the case notes group would prefer to hold their antenatal records in another pregnancy [12].

Number and timing of visits

There is insufficient evidence to recommend an ideal schedule of prenatal visits for all pregnant women. The most important visit to optimize pregnancy outcomes is the **preconception visit** (see Chap. 1). A visit early, soon after the pregnancy test is positive, and in time to establish location and number of embryo(s), usually around 6–8 weeks, is also desirable. For women with prior cesarean delivery in particular, this early ultrasound is important also to rule out the risk of cesarean scar pregnancy.

At this early visit, each woman should be assessed for risk factors (see Tables 1.3 and 1.4 in Chap. 1). The frequency of subsequent visits can be determined based on risk factors.

In developed countries, **prenatal care usually consists of 7–12 visits per pregnancy, with a prenatal visit ideally at 10–14 weeks for aneuploidy screening** (see Chaps. 5 and 6), **followed by visits about every 4 weeks approximately at 16, 20, 24, and 28 weeks, about every 2 weeks from 32 to 36 weeks, and then weekly until delivery** (Table 2.1). Uncomplicated multiparous women may need fewer visits than uncomplicated nulliparous ones. Individual patient needs and risk factors should be assessed at the first prenatal visit and reassessed at each appointment thereafter. **Telemedicine can be considered for some visits**. The patient should be encouraged to obtain a **home blood pressure monitor** and a **weight scale** to track important vital signs.

A small reduction in the traditional number of prenatal visits in both developed and developing countries has not been associated with adverse biological maternal or perinatal outcomes, **but women may feel less satisfied with fewer visits** [4]. **In settings with limited resources where the number of visits is already low, reduced antenatal visits (<5) are associated with an increase in perinatal mortality compared to standard care, although admission to neonatal intensive care may be reduced** [4]. **Women prefer the standard visits schedule. Where the standard number of visits is low, visits should not be reduced without close monitoring of fetal and neonatal outcomes** [4]. **In addition, women in high-resource settings were more often dissatisfied with a reduced schedule of visits (defined as eight). The schedule of visits should be determined by the purpose of the appointment. A minimum of four prenatal care visits is recommended even for low-risk women** [4].

Structure

Initial visit

Ideally, this visit should occur at around 6–8 weeks. Women should receive *written* information regarding their pregnancy care services, the proposed schedule of visits, screening tests that will be offered, and lifestyle issues, such as nutrition and exercise. Major parts of the visit include history, risk identification, physical exam, laboratory testing, education for health promotion, and a detailed plan of care for any risks identified (see Table 2.1) (see also Chap. 1, Tables 1.2–1.5).

History

A comprehensive history should be performed, preferably using standardized record forms (e.g., www.acog.org). Risk assessment should be performed with detailed review of systems. Patients who may benefit from additional care or referral should be identified. **Early ultrasonography should be used to determine the estimated day of delivery (EDD) if there is any uncertainty regarding last menstrual period (LMP)** [13]. Accuracy of EDD is critical for timing of screening tests and appropriate interventions, managing complications, and consideration of delivery timing. It also provides early identification and chorionicity of multiple pregnancies (see "Ultrasonography" later and Chap. 4). Topics such as lifestyle, nutrition, supplements, drugs, environment, vaccinations, prenatal education, and others should be discussed (see "Content of Prenatal Care"). Prenatal diagnosis and screening for aneuploidy (Chap. 5) and genetic screening (Chap. 6) should be reviewed.

Physical exam

The physical exam should be both general (Table 2.1) and directed by any risks identified in the history (see Chap. 1).

Weight and height should be determined at the initial prenatal visit in order to determine body mass index (BMI) [**BMI** = weight (kg)/height squared (m^2)]. BMI should be based on weight at time of conception or the earliest known weight in pregnancy.

TABLE 2.1: Suggested Prenatal Care Counseling, Screening, and Intervention

Initial Visit ≤14 wk	Visits at 14–24 wk	24–28 wk	28–34 wk	34–41 wk
Assessments/Procedures				
• Complete history and risk identification • Assessment of EDB by LMP and sizing; ultrasound if indicated • Baseline BP screening • Weight and BMI • Screening for domestic abuse • Vaccines according to risk status and season • Referral for specialist care according to history • Offer 11–13 6/7 wk aneuploidy screening ultrasound	• Fetal heart tones • Fundal height • Fetal movement • BP • Weight • Screening ultrasound for anatomy	• Fetal heart tones • Fundal height • Fetal movement • BP • Weight • Rh immunoglobulin if indicated • Screening for domestic abuses	• Fetal heart tones • Fundal height • Fetal movement • BP • Weight	• Fetal heart tones • Fundal height/ EFW • Fetal movement • Fetal presentation • BP • Weight • Sweeping of membranes starting at ≥37–38 wk
Laboratory Tests				
• Multiple-marker aneuploidy screen • CBC; Blood type, Rh, antibody screen; Rubella IgG; RPR; HBsAg; HIV • Urine dipstick for protein and glucose • Urinalysis and urine culture • Gonorrhea/Chlamydia[a] • Pap[a] • Additional testing as directed by history and PE[a]	• Multiple-marker aneuploidy screen • Urine dipstick for protein if indicated	• Gestational diabetes screen; repeat CBC and antibody screen • Antibody screen if indicated • Urine dipstick for protein	• Urine dipstick for protein	• Group B strep • Urine dipstick for protein • HIV
Education/Counseling				
• Cessation of harmful substances • Exercise/Activity • Nutrition • Nutrition • Weight gain • Supplements • Food safety • Breastfeeding	• Review and discuss results of testing	• Preterm labor s/sx	• Preterm labor s/sx • Preeclampsia s/sx	• Labor symptoms/ when to call • Preeclampsia s/sx • Postdates management • Breastfeeding
Education/Counseling Not Limited to Specific Weeks Gestation				
• Danger signs • Dental care • Family planning • Labor preparation, options, s/sx to report • Travel • TOLAC				
Assessments/Procedures				
• Complete history and risk identification • Assessment of EDB by LMP and sizing; ultrasound if indicated • Baseline BP screening • Weight and BMI • Screening for domestic abuse • Vaccines according to risk status and season • Referral for specialist care according to history • Offer 11–13 6/7 wk aneuploidy screening ultrasound	• Fetal heart tones • Fundal height • Fetal movement • BP • Weight • Screening ultrasound for anatomy	• Fetal heart tones • Fundal height • Fetal movement • BP • Weight • Rh immunoglobulin if indicated • Screening for domestic abuses	• Fetal heart tones • Fundal height • Fetal movement • BP • Weight	• Fetal heart tones • Fundal height/ EFW • Fetal movement • Fetal presentation • BP • Weight • Sweeping of membranes starting at ≥37 wk

TABLE 2.1 (Continued): Suggested Prenatal Care Counseling, Screening, and Intervention

Initial Visit ≤14 wk	Visits at 14–24 wk	24–28 wk	28–34 wk	34–41 wk
Laboratory Tests				
• Multiple-marker aneuploidy screen • CBC; Blood type, Rh, antibody screen; Rubella IgG; RPR; HBsAg; HIV • Urine dipstick for protein and glucose • Urinalysis and urine culture • Gonorrhea/Chlamydia[a] • Pap[a] • Additional testing as directed by history and PE[a]	• Multiple-marker aneuploidy screen • Urine dipstick for protein if indicated	• Gestational diabetes screen; repeat CBC and antibody screen • Antibody screen if indicated • Urine dipstick for protein	• Urine dipstick for protein	• Group B strep • Urine dipstick for protein • HIV
Education/Counseling				
• Cessation of harmful substances • Exercise/Activity • Nutrition • Weight gain • Supplements • Food safety • Breastfeeding	• Review and discuss results of testing	• Preterm labor s/sx	• Preterm labor s/sx • Preeclampsia s/sx	• Labor symptoms/ when to call • Preeclampsia s/sx • Postdates management • Breastfeeding
Education/Counseling Not Limited to Specific Weeks Gestation				
• Danger signs • Dental care • Family planning		• Labor preparation, options, s/sx to report • Travel • TOLAC		

Source: Adapted from a review of current prenatal care guidelines from four major groups: U.S. Veterans Health Administration, Department of Veteran Affairs, and Health Affairs, Department of Defense; Institute for Clinical Systems Improvement; the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists; and the American Academy of Family Physicians [146].

Abbreviations: EDB, expected date of birth; LMP, last menstrual period; BP, blood pressure; BMI, body mass index; EFW, estimation of fetal weight; RPR, rapid plasma regain; HIV, human immunodeficiency virus; CBC, complete blood count; PE, physical exam; TOLAC, trial of labor after cesarean; s/sx, signs and symptoms; wk, weeks.

[a] See text, only in certain circumstances.

Categories of BMI are in Table 2.2. Women with **obesity** are at increased risk for diabetes, shoulder dystocia, cesarean section, and other complications and have better outcomes with a lower (or no) total weight gain. Women who are underweight (<50 kg or <120 lb) also are at increased risk for LBW and PTB and have better outcomes with a higher total weight gain (see "Nutrition").

Blood pressure is recommended at each prenatal visit. Initial blood pressure evaluation may help to identify women with chronic hypertension, while subsequent blood pressure readings aid in preeclampsia screening. A diastolic blood pressure of >80 at booking is associated with later risks of preeclampsia [14]. Significant risks are associated with both hypertension and preeclampsia in pregnancy. This simple, inexpensive, and widely accepted screening tool may help identify abnormal trends in blood pressure over time. Blood pressure should be taken in the sitting position using an appropriately sized cuff and correct technique (see Chap. 1 in *Maternal-Fetal Evidence Based Guidelines*).

TABLE 2.2: Body Mass Index (BMI) Categories

Weight Category	BMI
Underweight	<18.5
Normal weight	18.5–24.9
Overweight	25–29.9
Obesity (class I)	30–34.9
Obesity (class II)	35–39.9
Extreme obesity (class III)	>40

Pelvic exam

Routine pelvic exam early in pregnancy is not as accurate for assessment of gestational age as ultrasound (see Chap. 4) and is not a reliable predictive test of PTB or cephalopelvic disproportion later in pregnancy (see also Chaps. 7 and 18), and so it is not recommended for these assessments. Abdominal and pelvic examination to detect gynecologic pathology can be included in the initial examination, and women should be asked about cervical cancer screening. In this setting, cervical cancer screening can be recommended according to guidelines if not current (Chap. 34).

Laboratory screening

Recommended initial universal laboratory screening is listed in Table 2.1. Other lab testing may be ordered if other risks or conditions are present.

ABO/Rh (D) type and antibody screen

Testing for blood group, Rh status, and atypical red cell antibodies at the initial visit is recommended. Unsensitized RhD-negative women should be offered anti-D immunoglobulin at 28 weeks (see Chap. 55 in *Maternal-Fetal Evidence Based Guidelines*).

Anti-D immunoglobulin should also be offered for any invasive procedure (e.g., amniocentesis, chorionic villus sampling [CVS], percutaneous umbilical blood sampling [PUBS]); for bleeding; for partial molar pregnancies, spontaneous abortion, and elective termination; and for any condition that might be associated with fetal-maternal hemorrhage, such as abdominal trauma, external cephalic version, or placental abruption. It may also be offered for threatened abortion and for ectopic pregnancy, although the evidence is not as strong. Du-positive women do not need anti-D immunoglobulin (see Chap. 55 in *Maternal-Fetal Evidence Based Guidelines*).

Complete blood count

Recommended at the first prenatal visit to identify anemia (hemoglobin and hematocrit) and to screen for thalassemia (mean corpuscular volume [MCV]). Pregnant women identified with anemia (Hgb <11.0 g/dL in the first trimester) should be treated as per Chap. 14 in *Maternal-Fetal Evidence Based Guidelines*. Initial determination of platelet count (optimally also before pregnancy) may help identify chronic thrombocytopenias and aid in the diagnosis of gestational thrombocytopenia or HEELP (hemolysis, elevated liver enzyme levels, and a low platelet count) syndrome later in pregnancy.

Rubella antibody

Screen all women at first encounter. Nonimmune pregnant women should be counseled to avoid exposure and seek immunization postpartum (see Chap. 40 in *Maternal-Fetal Evidence Based Guidelines*).

Syphilis screening

All pregnant women should be screened with a serologic test for syphilis at the first prenatal visit. Women who are at high risk, live in areas of high syphilis morbidity, or are previously untested should be screened at 28 weeks and again at delivery (see Chap. 37 in *Maternal-Fetal Evidence Based Guidelines*).

HBsAg

Screen at initial encounter, and rescreen high-risk populations in the third trimester. Postnatal intervention is recommended in all hepatitis B surface antigen (HBsAg)–positive women to reduce the risk of viral transmission to the neonate. Pregnancy and breastfeeding are not contraindications to immunization in women who are at risk for acquisition of the hepatitis B virus (see Chap. 32 in *Maternal-Fetal Evidence Based Guidelines*).

HIV serology

Screening is recommended for all pregnant women. The "opt-out" approach is recommended. It should be emphasized that testing not only provides the opportunity to maintain maternal health, but interventions can be offered to dramatically reduce the risk of viral transmission to the fetus (see Chap. 34 in *Maternal-Fetal Evidence Based Guidelines*).

Urine dipstick for protein

Screening for proteinuria should occur at the initial visit and routinely after 20 weeks in women at risk for preeclampsia. Urine dipsticks for protein do not reliably detect the variable elevations in albumin that may occur in preeclampsia and may not be indicated at each visit in low-risk women [15]. In women at high risk for preeclampsia, the 24-hour collection is a reasonable screen for proteinuria as a baseline at the first prenatal visit and when other signs or symptoms of preeclampsia are present. The proteinuria/creatinine (P/C) ratio may be used as a screening test as a good predictor for remarkable proteinuria, since it seems to be highly predictive for diagnosis to detect proteinuria over 1 gram but inadequate in detecting lower levels (see Chap. 1 in *Maternal-Fetal Evidence Based Guidelines*) [16].

Urine dipstick for glucose

Glycosuria ≥250 mg/dL (equivalent to 1+) on urine dipstick in the first or second trimester is associated with abnormal GDM screening later in pregnancy. The presence of significant glycosuria before 24–28 weeks is an indicator for earlier gestational glucose screening (see Chaps. 4 and 5 in *Maternal-Fetal Evidence Based Guidelines*).

Urine culture for asymptomatic bacteriuria

Screening for bacteriuria is recommended at the first prenatal visit for all women. Pregnant women with asymptomatic bacteriuria are at an increased risk for symptomatic infection and pyelonephritis. There is also a positive relationship between untreated bacteriuria and LBW/PTB. Treatment of asymptomatic bacteriuria prevents these complications (see Chap. 18 in *Maternal-Fetal Evidence Based Guidelines*).

Cervical cancer screening

Cervical cancer screening should be obtained if not current according to guidelines. Pap smear screening should be initiated at age 21, regardless of onset of sexual activity. Routine screening intervals have also been extended to every 3 years for women in their 20s without human papillomavirus (HPV) co-testing and every 5 years in women over 30 with the addition of HPV co-testing. Colposcopy can be performed during pregnancy, and a plan can be made for treatment postpartum (see Chap. 34).

Selective (only women with risk factors) laboratory screening

Hepatitis C serology

A test for hepatitis C antibodies should be performed in pregnant women at increased risk for exposure, such as those with a history of intravenous (IV) drug abuse, exposure to blood products or transfusion, organ transplants, kidney dialysis, etc. (see Chap. 33 in *Maternal-Fetal Evidence Based Guidelines*).

Chlamydia screening

All women of age <25 years (strongest risk factor), multiple sex partners, new partner within the past 3 months, single marital status, inconsistent use of barrier contraception, previous or concurrent sexually transmitted infection (STI), vaginal discharge, mucopurulent cervicitis, friable cervix, or signs of cervicitis on physical examination should be screened. Some agencies advocate universal chlamydia screening. Rescreen in the third trimester if at increased risk for infection. Screening using polymerase chain reaction (PCR) technology is most accurate (see Chap. 36 in *Maternal-Fetal Evidence Based Guidelines*).

Gonorrhea screening

All women of age <25 years, prior STI, multiple sexual partners, having a partner with a past history of any sexually transmitted disease (STD), sex work, drug use, and inconsistent condom use should be screened for gonorrhea. Some agencies advocate universal gonorrhea screening. Rescreen in the third trimester if at increased risk for infection. Screening using PCR technology is most accurate (see Chap. 33 in *Maternal-Fetal Evidence Based Guidelines*).

Bacterial vaginosis

There is **no benefit** to routine screening and treatment for asymptomatic bacterial vaginosis. Consideration can be given to screening and treating women with a prior PTB, but given the inconclusive evidence, we do not recommend it as routine. However, those women who are symptomatic should be screened (see Chap. 18).

Genital herpes

Routine serologic or other screening for herpes simplex virus (HSV) in asymptomatic pregnant women is not recommended. In the absence of lesions during the third trimester, routine serial cultures are not indicated for women with a history of recurrent genital herpes (see Chap. 52 in *Maternal-Fetal Evidence Based Guidelines*).

Varicella

Screening is indicated if a woman has had neither past infection nor vaccination. Varicella vaccine (live attenuated) is not recommended during pregnancy, but sero-negative women should be advised to take appropriate precautions (see Chaps. 40 and 53 in *Maternal-Fetal Evidence Based Guidelines*).

Tuberculosis

QuantiFERON Gold or purified protein derivative (PPD) can be offered to high-risk women at any gestational age in pregnancy to screen for tuberculosis, and follow-up chest x-ray is recommended for recent converters. High-risk factors include human immunodeficiency virus (HIV) disease, homeless or impoverished women, prisoners, recent immigrants from areas where tuberculosis is prevalent, and others (see Chap. 26 in *Maternal-Fetal Evidence Based Guidelines*).

Cytomegalovirus

Routine testing is not recommended. Good hand washing and practicing universal precautions are recommended to prevent transmission (see Chap. 49 in *Maternal-Fetal Evidence Based Guidelines*) [17].

Parvovirus

Routine screening is not recommended, but can be considered for high-risk groups (see Chap. 51 in *Maternal-Fetal Evidence Based Guidelines*).

Toxoplasmosis

Universal screening is not recommended in the United States, where the prevalence is low. Education regarding prevention of the disease should be addressed (Table 2.3) (see Chap. 50 in *Maternal-Fetal Evidence Based Guidelines*).

Follow-up visits

Follow-up visits should provide for the following:

- Follow-up physical exam, laboratory screening, and testing as indicated
- Ongoing assessment of risk factors and plan for intervention as indicated
- Education and health promotion directed to individual plan of care
- Opportunity for discussion and questions

Follow-up physical exam

- **Weight:** Weight is usually taken at each visit, as optimal weight gain (Figure 2.1) is associated with better outcomes. Excessive, unexplained weight gain can be a sign of preeclampsia.
- **Blood pressure:** Blood pressure should be taken and recorded at each visit.
- **Fetal heart tones:** Fetal heart rate should be assessed and recorded at each visit after the first trimester.
- **Symphyseal-fundal height measurement:** Fundal height can be performed at each visit after 20 weeks. Fundal height measurement may help detect fetal growth restriction (FGR) and macrosomia, but there is poor intrauser and interuser reliability. There is probably some value in evaluating trends, and although it will not affect the underlying condition, it may affect decision-making on fetal surveillance. **There is insufficient evidence to show whether this measurement has any impact, beneficial or not, on pregnancy outcomes, with no effect in the only one trial** (see also Chap. 47 in *Maternal-Fetal Evidence Based Guidelines*) [18]. The best screening tool for diagnosing FGR is ultrasound biometry (see Chap. 4).
- **Cervical examination:** Routine digital examination of the cervix is not recommended as a screening measure for prevention of PTB (see Chap. 18).

Sweeping or "stripping" of membranes during cervical exam at ≥37 weeks reduces the rate of late-term delivery (see Chap. 22). Cervical examination may assist in the identification of abnormal presentation, and therefore the opportunity to offer appropriate intervention (i.e., version).

- **Fetal movement:** There is no evidence that formalized kick counts reduce the incidence of fetal death in the healthy singleton (see Chap. 58 in *Maternal-Fetal Evidence Based Guidelines*) [19]. Nonetheless, women may be instructed to be aware of daily fetal movements from at or around 28 weeks.
- **Leopold maneuvers:** Historically, this set of maneuvers was performed at each visit from 34 weeks on to estimate fetal weight and determine presentation. Ultrasound should be used instead as necessary.
- **Clinical pelvimetry:** Measurement of the bony birth canal is of limited, unproven value in predicting dystocia during delivery (see Chap. 7).

TABLE 2.3: Prevention of Foodborne Illnesses

Foodborne Illness to Avoid	Preventive Strategy
Listeriosis	Cook meat thoroughly, including luncheon meats; avoid raw or smoked meats or fish, pates, unpasteurized cheese, and raw milk.
Toxoplasmosis	Cook meat and wash fruits and vegetables thoroughly; avoid cat litter; wear gloves when gardening outdoors.
Escherichia coli and Salmonella	Follow food-handling guidelines noted earlier.
Methylmercury	Avoid consumption of large, mercury-containing fish.

- **Routine evaluation for edema:** Edema has traditionally been a part of the evaluation for preeclampsia, but by itself, it is neither specific nor sensitive.

Follow-up laboratory screening

- **10 6/7–13 6/7 weeks: Serum aneuploidy screening, with nuchal translucency screening by ultrasound** (combined screening) (see later), should be offered to every pregnant woman. Consider cell-free DNA aneuploidy testing (also called noninvasive prenatal testing [NIPT]) in high-risk or intermediate-risk women. A policy of universal screening for fetal aneuploidy with NIPT as first-line screening may be also considered even if the cost-effectiveness is still a subject of debate. Randomized controlled trials showed that first-trimester risk assessment for trisomy 21 with a detailed ultrasound examination followed by cell-free DNA was associated with a significant reduction in false-positive rate [20] and better maternal reassurance and better maternal satisfaction [21] compared to the first-trimester combined screening with nuchal translucency and biochemistry (see Chap. 5) (Table 2.1).
- **14–21 weeks:** The second part of serum aneuploidy screening (best done at 16–18 weeks) should be offered to all pregnant women interested in prenatal diagnosis of aneuploidy (see Chap. 5). Counseling regarding the variety of screening options and the limitations of testing should be made available to all pregnant women.
- **24–28 weeks:** Women with risk factors for GDM should be screened with either one-step or two-step tests, since intervention (diet, exercise, glucose monitoring, and, as necessary, medical therapy) prevents maternal and perinatal morbidities (see Chap. 5 in *Maternal-Fetal Evidence Based Guidelines*). **The one-step approach is associated with better perinatal outcomes**, including lower incidence of large for gestational age (LGA) and neonatal intensive care unit (NICU) admission to neonatal hypoglycemia, compared to the two-step approach (see Chap. 5 in *Maternal-Fetal Evidence Based Guidelines*). Universal **glucose challenge screening for GDM** is the most sensitive approach, but the following women are at low risk and less likely to benefit from testing (must meet all of the following criteria): Age <25 years; ethnic origin of low risk (not Hispanic, African, Native American, South or East Asian, or Pacific Islander); BMI <25; no previous personal or family history of impaired glucose tolerance; and no previous history of adverse obstetric outcomes associated with GDM. Antibody screening and hemoglobin and hematocrit are also repeated. Repeat syphilis and HIV screening in the early third trimester and at delivery can be considered for high-risk populations (see Chaps. 34 and 37 in *Maternal-Fetal Evidence Based Guidelines*).
- **36–37 weeks: Group B streptococcus (GBS)** is a significant cause of morbidity and mortality in neonates. Approximately 10–30% of pregnant women are asymptomatically colonized with GBS in the vagina or rectum. Vertical transmission of this organism from mother to fetus occurs most commonly after the onset of labor or rupture of membranes. **All women should be screened for GBS colonization by rectovaginal culture at 36–37 weeks of gestation**. Colonized women should be treated with IV antibiotics (penicillin is the first choice if not allergic) in labor or with rupture of membranes (see Chap. 39 in *Maternal-Fetal Evidence Based Guidelines*).

Ultrasonography (see Chap. 4)

Ultrasound has not been proven harmful to the mother or fetus.

- **First-trimester "fetal dating" ultrasonography (before 14 weeks):** First-trimester ultrasound is more accurate than LMP to determine gestational age. First-trimester ultrasound also allows earlier detection of multiple pregnancies, aneuploidy screening with nuchal translucency, and diagnosis of nonviable pregnancies. In women with prior cesarean section, ultrasound performed before 10 weeks, ideally at around 6–8 weeks, should be performed to rule out the risk of cesarean scar pregnancy.
- **Second-trimester "fetal anatomy" ultrasound:** An ultrasound to screen for structural anomalies is ideally performed between 18 and 22 weeks. Routine use of ultrasound reduces the incidence of postterm pregnancies, induction of labor for postterm pregnancy, increases early detection of multiple pregnancies, increases earlier detection of major fetal anomalies when termination of pregnancy is possible, increases detection rates of fetal malformations, and decreases admission to the special care nursery [22, 23]. Given the benefits mentioned, all pregnant women should be offered a second-trimester ultrasound. No significant differences are detected for substantive clinical outcomes such as perinatal mortality, possibly because of insufficient data (see Chap. 4). Transvaginal ultrasound cervical length (TVU CL) screening of all singleton gestations, even those without a prior spontaneous preterm birth, and is recommended [24]. Institutions prepared to intervene for a short cervix of a patient carrying multiple gestations should offer TVU CL to these patients as well (see Chap. 18).
- **Third-trimester "fetal growth" ultrasound:** In low-risk or unselected populations, routine third-trimester ultrasound has not been associated with improvements in perinatal mortality [25]. Selective ultrasound in later pregnancy is of benefit in specific situations [26], such as calculation of interval growth for suspected FGR, assessment of amniotic fluid index for suspected oligohydramnios or hydramnios, and assessment of malpresentation (see Chap. 4). Gestational age for third-trimester "fetal growth" ultrasound is also a subject of debate. For example, an ultrasound at 28–30 weeks may detect early-onset FGR, but would miss late-onset FGR, which may be detected at 34–36 weeks.
- Routine umbilical artery or other Doppler ultrasound in low-risk or unselected patients has not been shown to be of benefit.

Content of prenatal care

The content of prenatal care is extensive and reviewed in detail not only in this chapter but also in most other chapters in this book, as well as its companion, *Maternal-Fetal Evidence Based Guidelines*. In Chap. 1, see Table 1.2 for topics to be reviewed, Table 1.3 for screening, Table 1.4 for laboratory tests, Table 1.5 for vaccinations, Table 1.6 for interventions for all women, and Table 1.7 for interventions for women with risk factors. Prenatal care usually incorporates, among other things, the following:

- **Prenatal education and reassurance** (regarding drugs, environment, lifestyle, nutrition, supplements, vaccinations, preventive measures, preparation for L&D, depression, breastfeeding, etc.)
- Provision of evidence-based screening tests at appropriate intervals (Table 2.1)
- Risk assessment
- Problem-oriented visits as needed
- Condition-specific care for high-risk patients

Content issues that should be included in prenatal care such as drugs and environment, lifestyle, nutrition, supplements, vaccinations, prenatal education, and others are described next.

Drugs and environment

Substance abuse

Screening for use and counseling for cessation of tobacco, alcohol, and recreational or illicit drug use is recommended (see Chaps. 22 and 23 in *Maternal-Fetal Evidence Based Guidelines*). Maternal smoking, as well as exposure to secondhand smoke, is dangerous to both the woman and her fetus. Provider support and educational material tailored to pregnancy are shown to increase smoking cessation by 70% and reduce LBW and PTB [27–29], as well as the number of women who continue to smoke in late pregnancy [29].

Alcohol use at any level in pregnancy cannot be supported, although deleterious effects at low-to-moderate levels are difficult to quantify [30]. The evidence from the limited number of studies suggests that **education and psychological interventions may promote abstinence from alcohol or reduce alcohol consumption among pregnant women**. However, results were not consistent, and the paucity of studies, the number of total participants, the high risk of bias of some of the studies, and the complexity of interventions limit our ability to determine the type of intervention that would be most effective in increasing abstinence from, or reducing the consumption of, alcohol among pregnant women [31]. Counseling may be effective in reducing substance abuse in pregnancy, although women with addictions will need specialized interventions. **Screening and brief intervention (SBI)** for unhealthy alcohol use has demonstrated efficacy in some trials. There is some evidence regarding the acceptability and efficacy of computer-delivered SBI plus tailored mailings in women who screened positive for alcohol risk [32]. There is insufficient evidence to recommend the routine use of home visits for women with a drug or alcohol problem [33]. However, a cluster RCT among urban South African mothers showed that a home-visiting intervention improved the emotional health of low-income mothers and that relative to standard care, intervention mothers were significantly less likely to report depressive symptoms and alcohol abuse [34].

Over-the-counter, alternative/Complementary, and prescription medications

Due to the possibility of adverse fetal effects, medication use, including alternative remedies, should be limited to circumstances where benefit outweighs risk. Beneficial medications should be continued in pregnancy when safe for both the mother and fetus (see specific disease guidelines in *Maternal-Fetal Evidence Based Guidelines*).

Environmental/Occupational risks and exposures

In general, working is not associated with poor pregnancy outcome. Some workplace exposures, such as toxic chemicals, radiation (>5 rad), heavy repeated lifting, prolonged (>8 hours) standing, excessive (>80/week) work hours, and high fatigue score, may be associated with pregnancy complications, but there is insufficient evidence on the effect of avoidance of these risks (see also Chap. 17). There are insufficient safety data for paint, solvents, hair dyes, fumes, anesthetic drugs, etc., with no absolute evidence of harm. Hot tubs, saunas, etc., should avoid temperatures >102°F to avoid risk of dehydration, especially in the first trimester.

Domestic violence

Domestic violence during pregnancy is associated with increased risk of PTB, LBW, second- and third-trimester bleeding, and fetal injury. Domestic violence may escalate during pregnancy. As such, providers need to be alert to signs and symptoms of abuse and provide opportunities for private disclosure. However, so far, there is insufficient evidence to assess the effectiveness of interventions for domestic violence on pregnancy outcome [35].

Lifestyle

Work

There is insufficient evidence to recommend exact work hours and when to take off from work before delivery (if at all). Work accommodations are often necessary and helpful to allow a pregnant woman to continue working and earning an income. Pregnant women should not be discriminated against by employers. The website www.pregnantatwork.org provides online tools health care professionals can use to prepare notes drafted using language that increases the likelihood that a patient will receive the accommodations she needs to continue doing her job safely. Occupational lifting guidelines have been published [36].

Exercise

Regular exercise during low-risk pregnancies is beneficial, as it increases overall maternal fitness and sense of well-being. Aerobic training is an effective tool in maternal weight gain control in pregnancy [37] and **decreases the risk of GDM** [38]. Moreover, regular exercise during pregnancy appears to modestly **increase the chance for vaginal delivery** among healthy pregnant women [39]. Structured physical exercise programs appear also to be safe for the neonate [40] and **reduce the risk of having a large newborn without a change in the risk of having a small newborn** [41]. Furthermore, there is some evidence that exercise may be **effective in treating depression** during pregnancy [42]. Healthy diet and exercise during pregnancy can **reduce the risks of excessive gestational weight gain, cesarean section, maternal hypertension, and macrosomia**, as well as **neonatal respiratory morbidity**, particularly for high-risk women receiving combined diet and exercise interventions [38]. However, most of the studies included in the meta-analysis were carried out in developed countries and therefore it is not clear if these findings are widely applicable [43]. In another meta-analysis, exercise was associated with a lower (by 600 g) gestational weight gain [44]. Possible **maternal** benefits include **improved cardiovascular function, limited pregnancy weight gain, decreased musculoskeletal discomfort, reduced incidence of muscle cramps and lower limb edema, mood stability, and attenuation of GDM and gestational hypertension**. **Fetal** benefits include **decreased fat mass, improved stress tolerance, and advanced neurobehavioral maturation** [45]. **For most pregnant women, at least 30 minutes of moderate exercise is recommended on most days of the week. There is no target heart rate that is right for**

TABLE 2.4: Examples of Safe and Unsafe Physical Activities during Pregnancy

The following activities are safe to initiate or continue[a]:

- Walking
- Swimming
- Stationary cycling
- Low-impact aerobics
- Yoga, modified[b]
- Pilates, modified
- Running or jogging[c]
- Racquet sports[cd]
- Strength training[c]

The following activities should be avoided:

- Contact sports (e.g., ice hockey, boxing, soccer, and basketball)
- Activities with a high risk of falling (e.g., downhill snow skiing, water skiing, surfing, off-road cycling, gymnastics, and horseback riding)
- Scuba diving
- Sky diving
- "Hot yoga" or "hot Pilates"

Source: Adapted from Physical activity and exercise during pregnancy and the postpartum period. Committee Opinion No. 650. American College of Obstetricians and Gynecologists. Obstet Gynecol 2015; 126:135–42. [Guideline].

[a] In women with uncomplicated pregnancies in consultation with an obstetric care provider.

[b] Yoga positions that result in decreased venous return and hypotension should be avoided as much as possible.

[c] In consultation with an obstetric care provider, running or jogging, racquet sports, and strength training may be safe for pregnant women who participated in these activities regularly before pregnancy.

[d] Racquet sports wherein a pregnant woman's changing balance may affect rapid movements and increase the risk of falling should be avoided as much as possible.

every pregnant woman. Walking, swimming, and other sports with low chance of loss of balance are recommended (Table 2.4) [46]. Avoidance of contact sports and sports with high chance of loss of balance or injury should be recommended. Special considerations may be made for professional athletes at the discretion of the patient and provider. Hypoglycemia and dehydration should be avoided. It is important to advise women to be careful while stretching, as the hormone relaxin can leave joints vulnerable to overstretching and injury [46]. It is important for clinicians to keep emphasizing that **exercise is medicine** [47].

Yoga

Yoga in pregnancy is associated with lower pain and discomfort, as well as lower perceived stress and improved quality of life in physical domains in the three RCTs evaluating its effects [48].

Travel

Counseling should include the proper use of passenger restraint systems in automobiles with the lap belt below the abdomen, reduction of risk of venous thromboembolism during long-distance air travel by walking and exercise, and provision of care and prevention of illness during travel abroad.

Sex and sexuality

Intercourse has not been associated with adverse pregnancy outcomes. Some women have a progressive decrease in sexual desire during the pregnancy, most markedly in the third trimester. Couples are often concerned that intercourse may harm the pregnancy, which can lead to decreased frequency of sexual intercourse during pregnancy [49]. Most women desire more communication regarding sex in pregnancy from their care providers. Provider counseling should be reassuring in the absence of pregnancy complications. Semen is a source of prostaglandin, and pyospermia is associated with preterm prelabor rupture of membranes (PPROM). Also, female orgasm and nipple stimulation can increase contractions [50]. Therefore, intercourse may have adverse effects for pregnancies with preterm cervical dilatation and/or shortening, but this is not well studied. PTB and other complications of pregnancy do not seem increased in most studies of sex in pregnancy. **Most studies report that sexual activity is associated with better pregnancy outcomes**, probably because women who are sexually active are healthier to begin with compared to women with less sexual activity [51].

Nutrition

Energy (calorie)/Protein supplementation

A meta-analysis of 17 RCTs provided evidence that **antenatal nutritional education**, with the goal of increasing energy and protein intake in pregnant women, appears to be effective in **reducing the risk of PTB and of LBW** and effective in increasing the head circumference at birth and the birth weight **among undernourished women** [52]. **Balanced energy and protein supplementation seems to improve fetal growth and may reduce the risk of stillbirth and infants born small for gestational age (SGA)**. However, **high-protein supplementation does not seem to be beneficial and may be harmful** to the fetus, increasing the risk of SGA. Balanced-protein supplementation alone has no significant effects on perinatal outcomes [52].

Cholesterol-lowering diet

A cholesterol-lowering diet with omega-3 fatty acids and dietary counseling does not affect cord or neonatal lipids but is associated with a 90% reduction in PTB <37 weeks in one trial (see also Chap. 18) [53]. More evidence is needed for a recommendation.

Low–glycemic index diet

A low–glycemic index diet appears to be beneficial to both the mother and child in reducing the incidence of abnormal glucose tolerance tests, LGA infants, and ponderal indices. The numbers of studies and subjects are small, however, and therefore considered inconclusive [54]. Studies evaluating the effects of different types of dietary advice for women with GDM did not find any significant benefits for the diets investigated [55].

Antigen avoidance diet

Prescription of an antigen avoidance diet (e.g., avoiding chocolate or nuts) to a pregnant woman is unlikely to reduce her child's risk of atopic disease, and such a diet may adversely affect maternal or fetal nutrition [56].

Probiotics

A probiotic capsule intervention among women with abnormal glucose tolerance had no impact on glycemic control [57].

Food safety

Food safety and prevention of foodborne illness and infection are suggested in Tables 2.3 and 2.5.

BMI and weight gain

BMI is utilized in counseling a woman on optimal weight gain in pregnancy (Table 2.2) [58–70].

TABLE 2.5: Food Safety in Pregnancy

Clean: Wash hands thoroughly with soap and water, before and after handling food, using the bathroom, changing diapers, or handling pets. Wash cutting boards, dishes, utensils, and countertops with soap and water. Rinse raw fruits and vegetables well under running water.

Separate: Separate raw meats and seafood from fresh or prepared foods. Use a separate cutting board for raw meats and seafood. Place prepared food on a clean plate.

Cook: Cook foods thoroughly. Avoid allowing foods to sit at temperatures between 40°F and 140°F (4°C and 60°C). Discard foods left out at room temperature for more than 2 hours. Avoid foods made with raw eggs.

Chill: Maintain refrigerator temperature at 40°F (4°C) or below and the freezer at 0°F (–18°C).

Suggested weight gain in pregnancy is shown in Figure 2.1 [71]. **Women who are underweight are at increased risk for LBW and PTB and have better outcomes with a higher total weight gain** [66]. **Excessive weight gain in women with a normal BMI can be prevented with dietary and lifestyle counseling** [61–68]. For example, a program of education on recommended gestational weight gain (GWG), application of a personalized weight graph, formalized prescription of exercise, and regular monitoring of GWG at every antenatal visit is associated with a significant reduction in GWG [69]. Obesity is associated with cardiovascular disease; diabetes; hypertension; stroke; osteoarthritis; gallstones; endometrial, breast, and colon cancer; cardiomyopathy; fatty liver; obstructive sleep apnea; urinary tract infections; other complications; and most importantly, mortality. Pre-pregnancy obesity and excessive gestational weight gain are associated with increased risk of childhood obesity for the fetus. **Obese pregnant** women are specifically at increased risk for miscarriage, congenital malformations, GDM, hypertension, preeclampsia, stillbirth, cesarean birth, labor abnormalities, macrosomia, anesthesia complications, wound infection, and thromboembolism. These women **have better maternal outcomes with lower (or no) total weight gain** (Table 2.6) (see also Chap. 3 in *Maternal-Fetal Evidence Based Guidelines*) [59, 60, 66, 67, 70]. Some studies have reported a small increased risk of SGA with weight loss in obese women; however, this is not really an increase from the population baseline risk. Obese women who gain weight have larger babies (incidence of SGA <5%), while those who lose weight have a normal incidence of SGA (i.e., ≤10%) [72]. Moreover, all other neonatal outcomes are the same or better, with no weight gain or some moderate weight loss in obese pregnant women (Table 2.6) [60, 72].

Caffeine

Moderate caffeine consumption (less than 200 mg per day) does not appear to be a contributing factor in miscarriage or PTB.

Reducing the caffeine intake of regular coffee drinkers (3+ cups/day) during the second and third trimester by an average of 182 mg/day did not affect birth weight or length of gestation in one RCT [73]. A meta-analysis from two RCTs concluded that there is insufficient evidence to confirm or refute the effectiveness of caffeine avoidance on birth weight or other pregnancy outcomes; moreover, they found that reducing the caffeine intake of regular coffee drinkers (3+ cups/day) during the second and third trimester did not affect PTB or SGA rate [74].

Supplements

Multivitamin

There is **insufficient evidence** to suggest replacement of iron and folate supplementation with a multiple-micronutrient supplement. A reduction in the number of LBW and SGA babies and maternal anemia has been found with a multiple-micronutrient supplement compared to supplementation with two or fewer micronutrients or none or a placebo, but analyses revealed no added benefit of multiple-micronutrient supplements compared with iron and folic acid supplementation [75, 76]. These results are limited by the small number of studies available. There is also insufficient evidence to identify which micronutrients are more effective, to assess adverse effects, and to say that excess multiple-micronutrient supplementation during pregnancy is harmful to the mother or the fetus [75, 76]. Therefore, there is **insufficient evidence** to recommend routine multivitamin supplementation for all women, or even only for women who are underweight, have poor diets, are smokers, are substance abusers, are vegetarians, have multiple gestations, or others. **Excess (>1) prenatal vitamin intake per day should be avoided**. **No prenatal multivitamin supplement has been shown to be superior to another**. Use of multivitamin supplements not specific for pregnancy should be discouraged, as often excess doses can pose risks to the pregnancy. Each supplement, including each vitamin supplement, should be studied for safety and efficacy individually.

Folic acid

Folic acid supplementation is recommended, with a **minimum of 400 mcg/day for all women** (93% decrease in neural tube defects [NTDs]) and **4 mg/day for women with prior children with NTD** (69% decrease in NTDs) [77, 78]. Supplementation should **start at least 1 month before conception and continue until at least 28 days after conception** (time of neural tube closure). Given the unpredictability of conception and that 50% of pregnancies are unplanned, all reproductive-age women should be on folic acid supplementation. Because in several countries the baseline serum folate level is only 5 ng/mL and increases in this level are directly proportional with a decrease in the incidence of NTD, some experts have advocated 5 mg of folic acid per day as optimal

TABLE 2.6: Weight Gain Suggestions for Overweight and Obese Women

Pre-Pregnancy Weight Category	Our Suggested Total Weight Gain Range (lb)	IOM Recommendations (lb)
Overweight (BMI 25–29.9 kg/m²)	6–20 (2.7–9.0 kg)	15–25 (6.8–11.4 kg)
Class I obesity (BMI 30–34.9 kg/m²)	5–15 (2.3–6.8 kg)	11–20 (5–9.1 kg)
Class II obesity (BMI 35–39.9 kg/m²)	–9–9 (–4.0–4.0 kg)	11–20 (5–9.1 kg)
Class III obesity (BMI >40 kg/m²)	–15–0 (–6.8–0 kg)	11–20 (5–9.1 kg)

Abbreviation: IOM, Institute of Medicine.

supplementation [79]. No increase in ectopic pregnancy, miscarriage, or stillbirth has been associated with folate supplementation, but it might increase (nonsignificant trend) the incidence of multiple gestations by 40% [77–82]. However, a multicenter prospective cohort study showed that children whose mothers used folic acid supplement dosages higher than 5 mg/mL had a lower mean psychomotor scale score than children whose mothers used a recommended folic acid supplement dosage (i.e., 400 mcg/day) [82]. Folic acid supplementation has been associated (one non-RCT study) with a decrease in severe language delay at 3 years of age [81]. **Fortifying basic foods such as grains** with added folate is associated with an increase in supplementation of only 140–200 mcg/day and with only a 20–50% decrease in the incidence of NTDs, with the potential for large-scale prevention [80]. Women taking antiseizure medications, other drugs that might interfere with folic acid metabolism, those with homozygous methylenetetrahydrofolate reductase (MTHFR) enzyme mutations, or those who are obese may need higher doses of folate supplementation. Women with first-trimester diabetes mellitus or exposure to valproic acid or high temperatures might not experience a decrease in NTD risk with folate supplementation due to these risks (see also Chap. 1).

Vitamin A

In pregnancy, some extra vitamin A is required for growth and tissue maintenance in the fetus, for providing fetal reserves, and for maternal metabolism. However, vitamin A in its synthetic form as well as in large doses as retinol (preformed vitamin A found in cod liver oil and chicken or beef liver) is teratogenic. It is recommended that pregnant women ingest vitamin A as β-carotene and limit the ingestion of retinol during pregnancy. In vitamin A–deficient populations (where night blindness is present) and in HIV-positive women, vitamin A supplementation reduces maternal night blindness and anemia**. Excess vitamin A intake can cause birth defects and miscarriages at doses >25,000 IU/day. Vitamin A supplements should be avoided, with maximum daily intake prior to and during pregnancy probably 5000 IU and certainly ≤10,000 IU, respectively. Vitamin A supplementation may be beneficial in women with vitamin A deficiency, especially in prevention of night blindness, in developing countries**. Optimal duration of supplement use cannot be evaluated. One large population-based trial in Nepal shows a possible beneficial effect on maternal mortality after weekly vitamin A supplements. Night blindness, associated with vitamin A deficiency, was assessed in a nested case-control study within this trial and found to be reduced but not eliminated. There is insufficient evidence to support vitamin A supplementation as an intervention for anemia [83, 84].

Vitamin B6 (pyridoxine)

There is **insufficient evidence** to evaluate pyridoxine supplementation during pregnancy [85]. There are few trials reporting few clinical outcomes, and mostly with unclear trial methodology and inadequate follow-up. There is not enough evidence to detect clinical benefits of vitamin B_6 supplementation in pregnancy and/or labor other than one trial suggesting protection against dental decay [86]. For the aim of decreasing dental decay or missing/filled teeth, pyridoxine supplementation 20 mg/day (lozenges or capsules) is associated with a decreased incidence of these outcomes in pregnant women [86]. Pyridoxine has been used in the management of **nausea and vomiting** in pregnancy. It is now considered category A in combination with doxylamine as Diclegis, which is the only FDA-approved treatment for nausea and vomiting of pregnancy. Studies done for FDA approval of the drug showed no adverse outcomes and demonstrated safety and good tolerance by women when used in the recommended dose of up to 4 pills (10 mg/10 mg) per day (see Chap. 9 in *Maternal-Fetal Evidence Based Guidelines*).

Vitamin C

The **data are insufficient** to assess if vitamin C supplementation, either alone or in combination with other supplements, is beneficial during pregnancy for either low- or high-risk women. There may be an associated increased risk of PTB with vitamin C supplementation (RR 1.38, 95% CI 1.04–1.82, 3 trials, 583 women) [87]. No other difference in outcome is noted between vitamin C supplementation versus no treatment or placebo. There are very limited trials available to assess whether vitamin C supplementation may be useful for all pregnant women. Usually the women involved in the trials were either at high risk of preeclampsia or PTB or the women had established severe early-onset preeclampsia (see also Chap. 1 in *Maternal-Fetal Evidence Based Guidelines*). No difference is seen between women supplemented with vitamin C alone or in combination with other supplements compared with placebo for the risk of stillbirth, neonatal death, LBW, or intrauterine growth restriction [87].

Vitamin D

There is **insufficient evidence** to evaluate the effects of vitamin D supplementation during pregnancy [88–92]. Vitamin D 1000 IU/day in the third trimester is associated with no consistent effect on incidence of LBW [88]. **Neonatal hypocalcemia is less common** with vitamin D supplementation compared to placebo [88]. Vitamin D supplementation during pregnancy is associated with increased circulating 25(OH)D levels, birth weight, and birth length but with no effects on maternal-fetal outcomes [89]. There are limited data to assess any benefit of vitamin D supplements for complete vegetarians and women with extremely limited exposure to sunlight. Vitamin D supplementation of vitamin D–deficient pregnant women prevents neonatal vitamin D deficiency [90]. Vitamin D plus calcium has no effect on duration of pregnancy, type of delivery, and infant anthropometric indicators [91]. However, low maternal vitamin D levels in pregnancy ≤50 nmol/l may be associated with an increased risk of preeclampsia, gestational diabetes, PTB, and SGA [92].

Vitamin E

There is **insufficient evidence** to assess if vitamin E supplementation, either alone or in combination with other supplements, is beneficial during pregnancy [93]. All evidence tested women at high risk of preeclampsia or with established preeclampsia and assessed vitamin E in combination with other supplements (usually vitamin C) (see Chap. 1 in *Maternal-Fetal Evidence Based Guidelines*). There is no convincing evidence that vitamin E supplementation alone or in combination with other supplements results in other important benefits or harms [93].

Magnesium

Numerous studies demonstrate an association between magnesium supplementation and decreased incidences of LBW, SGA, antenatal hospitalization, and antenatal hemorrhage. The majority of RCTs are of poor quality, except one judged to be of high quality, which did not support these associations. There is **insufficient high-quality evidence** to show that dietary magnesium

supplementation during pregnancy is beneficial [94]. Including high- and low-quality trials, oral magnesium treatment from before the 25th week of gestation is associated with a lower frequency of PTB, a lower frequency of LBW, and fewer SGA infants compared with placebo [87]. In addition, magnesium-treated women have less hospitalization during pregnancy and fewer cases of antepartum hemorrhage than placebo-treated women. Incidences of preeclampsia and all other outcomes are similar. In the analysis of one high-quality trial, no differences between magnesium and placebo groups are seen. Poor-quality trials are likely to have resulted in a bias favoring magnesium supplementation.

Calcium

Calcium supplementation is associated with a **reduction of the incidence of preeclampsia in pregnancy in all women, particularly for women at high risk of hypertension and in women with low dietary calcium intake** (e.g., <600 mg/day) [95]. The minimum dose in the Cochrane review was 1 g/day. Further research is needed to determine whether dietary sources of calcium confer the same benefit and at what amount. There is insufficient evidence to determine optimum dosage and the effect on other important maternal and fetal outcomes. There is no overall reduction in PTB, although there is a **reduction in PTB among women at high risk of developing hypertension**. Benefits are considered to outweigh an anomalous increase in the risk of HELLP syndrome, which was small in absolute numbers. There is no evidence of any effect of calcium supplementation on stillbirth or death before discharge from hospital. In women at high risk of hypertension, calcium supplementation is associated with fewer babies with birth weight <2500 g. In one study, childhood systolic blood pressure >95th percentile was reduced (see also Chap. 1 in *Maternal-Fetal Evidence Based Guidelines*) [95].

Iron

There is no evidence to advice against a policy of routine iron and folate supplementation in pregnancy. Iron supplementation is associated with the **prevention of low hemoglobin at birth or at 6 weeks postpartum** [96]. Iron supplementation, however, has no detectable effect on any substantive measures of either maternal or fetal outcome. One trial, with the largest number of participants of selective versus routine supplementation, shows an increased likelihood of cesarean section and postpartum blood transfusion, but a lower perinatal mortality rate (up to 7 days after birth). There are not a lot of data derived from communities where iron deficiency is common and anemia is a serious health problem. There is limited evidence for daily versus intermittent supplementation. High-dose supplementation (80 mg daily) has no clinical advantage over low-dose supplementation (20 mg daily) and is associated with more gastrointestinal (GI) side effects. One RCT suggests adverse effects of hemoconcentration from iron supplementation in nonanemic women. For iron supplementation for women with anemia, see Chap. 14 in *Maternal-Fetal Evidence Based Guidelines*.

Zinc

There is insufficient evidence to evaluate fully the effect of zinc supplementation during pregnancy [97]. Zinc supplementation is associated with a **significant reduction in PTB** (RR 0.86, 95% CI 0.76–0.98; 13 RCTs; 6854 women). These studies were primarily from a low socioeconomic population and **may reflect overall poor nutrition**. Reductions in induction of labor and cesarean delivery are from small studies, with no other differences detected between groups of women who had zinc supplementation and those who had either placebo or no zinc during pregnancy. There is insufficient evidence to assess the best dose, gestational age and duration, and population for zinc supplementation in pregnancy [97].

Iodine

Iodine is essential for normal fetal thyroid and brain development. Iodine supplementation **in populations with low iodine intake and high levels of endemic cretinism** results in an important reduction in the incidence of the condition with no apparent adverse effects. Iodine supplementation is associated with **a reduction in deaths during infancy and early childhood, decreased endemic cretinism at the age of 4 years, and better psychomotor development scores between 4 and 25 months of age** [98]. There are little data, however, on the safety of routine iodine supplementation in populations with normal or low-normal iodine levels. Some data suggest an increased risk of fetal and maternal hypothyroidism from iodine supplementation. The upper levels of safety have not been established [98, 99].

Omega-3

Pregnancy is a time of increased risk for omega-3 deficiency, as omega-3 is used for the developing fetus. Thirty-four RCTs have been performed to assess whether omega-3 supplementation during pregnancy affects maternal-fetal outcomes. Meta-analyses of RCTs [100] show a lack of evidence to support the routine use of omega-3 supplementation during pregnancy, as omega-3 supplementation did not affect PTB, preeclampsia, fetal growth restriction (FGR), gestational diabetes, SGA, postpartum depression, child development, or other maternal or fetal outcomes. Meta-analyses also found that omega-3 supplementation during pregnancy did not prevent PTB in low-risk women [101] or in women with prior PTB [102] and did not prevent recurrent FGR [103].

Oral health care

Oral health care is an important component of general health and therefore should be maintained during pregnancy and through a woman's lifespan. However, although some studies have shown a possible association between periodontal infection and pregnancy outcome such as PTB and preeclampsia, the evidence shows **no improvement in obstetric or perinatal outcomes after dental treatment** during pregnancy. A meta-analysis from 13 RCTs showed that providing periodontal treatment to pregnant women was not associated with a reduction in PTB or perinatal mortality, except for a significant reduction in PTB and LBW in populations with a high occurrence (>20%) of PTB and LBW [104].

Vaccinations

COVID vaccine is safe in pregnancy and should be recommended, as in non-pregnant adults. Immunity to **rubella, varicella, hepatitis B, influenza, tetanus, and pertussis should be assessed at the first prenatal visit [105]. Ideally, needed vaccinations would be provided preconception**. There is no vaccine that is more dangerous to a pregnant woman or her fetus than the disease it is designed to prevent. Recombinant, inactivated, and subunit vaccines, as well as toxoids and immunoglobulins, pose no threat to a developing fetus. Inactivated influenza vaccine should be given by injection, as killed virus to all pregnant women during the influenza season. The live attenuated form of the vaccine (intranasal spray) should not be given during pregnancy. Hepatitis B vaccine can be safely given in pregnancy.

Tetanus, diphtheria, and acellular pertussis vaccine, also known as TDAP or "whooping cough" vaccine, is recommended for all pregnant women after 28 weeks (see Table 1.5 in Chaps. 1 and 40 in *Maternal-Fetal Evidence Based Guidelines*).

Prevention of complications

Please see specific diseases in each chapter of this book and its companion, *Maternal-Fetal Evidence Based Guidelines*. Here are reported only some general, nonspecific interventions.

Antibiotic prophylaxis of pregnant women with no specific risk factor or infection is associated with similar incidence of PPROM, PTB, and postpartum endometritis (see also Chap. 18) [106, 107].

Programs offering **additional social support** (caring family members, friends, and health professionals) for at-risk (e.g., for PTB and LBW) pregnant women are not associated with improvements in any perinatal outcomes, but there is a **reduction in the likelihood of antenatal hospital admission** (RR 0.79, 95% CI 0.68–0.92) and **cesarean birth** (RR 0.87, 95% CI 0.78–0.97) [108].

For issues such as mild hypertension or preeclampsia, small studies suggest that there are no major differences in clinical outcomes for mothers or babies between antenatal day units or hospital admission, but women may prefer day care (see also Chap. 1 in *Maternal-Fetal Evidence Based Guidelines*) [109].

Prenatal education

There is insufficient evidence to assess the effectiveness of formal prenatal education programs. **Prenatal education directed at specific objectives (e.g., promoting breastfeeding and avoiding planned induction of labor) has been demonstrated to be effective** [110–113]. Individualized prenatal education directed toward avoidance of a cesarean delivery does not increase the rate of vaginal birth after cesarean section. As a part of prenatal care, women should be provided with information and instruction regarding their health, including risk avoidance, breastfeeding, what to expect during labor and birth (see "Preparation for Labor and Delivery"), how to obtain care when labor begins, and the value of a support person during the labor process (see Chaps. 7 and 8).

Community interventions

There is encouraging evidence of the value of integrating maternal and newborn care in community settings through a range of interventions that can be packaged effectively for delivery through a range of community health workers and health promotion groups. Such evidence-based available interventions such as immunization to mothers, clean and skilled care at delivery, newborn resuscitation, exclusive breastfeeding, clean umbilical cord care, and management of infections in newborns require facility-based and outreach services. **Implementation of community-based interventional care packages is associated with a trend for reduction in maternal mortality** (RR 0.77, 95% CI 0.59–1.02) **and with significant reductions in maternal morbidity** (RR 0.75, 95% CI 0.61–0.92), **neonatal mortality** (RR 0.76; 95% CI 0.68–0.84), **stillbirths** (RR 0.84, 95% CI 0.74–0.97), **and perinatal mortality** (RR 0.80; 95% CI 0.71–0.91). It also increases the referrals to a health facility for pregnancy-related complications by 40% and improves the rates of early breastfeeding by 94% [113].

Preparation for labor and delivery

Perineal massage with sweet almond oil for 5–10 minutes daily from 34 weeks until delivery is associated with a significantly higher chance of an intact perineum compared to no massage in nulliparous, but probably not multiparous, women [114–116]. The type of oil used during the second stage of labor for the prevention of perineal tears has no effect on the integrity of the perineum; accordingly it seems that there is no perfect oil [117]. For perineal massage in labor, see Chap. 9.

Women should be provided with written information and instruction regarding what to expect during L&D, how to obtain care when labor begins, and the value of a support person during the labor process (see Chaps. 7 and 8).

L&D classes should be encouraged. Compared to no such training, 9 hours of **antenatal classes with training to prepare for L&D** are associated with **arriving to the L&D ward more often in active labor** (RR 1.45, 95% CI 1.26–1.65) and **using less epidural analgesia** (RR 0.84, 95% CI 0.73–0.97) [118].

Compared to standard antenatal education, antenatal education focusing on natural childbirth preparation with training in breathing and relaxation techniques is not associated with any effects on maternal or perinatal outcomes, including similar incidences of epidural analgesia, childbirth, or parental stress, in nulliparous women and their partners [119].

Compared to conventional therapy, intensive counseling therapy for fear of childbirth does not affect the incidence of cesarean sections, but is associated with reduced pregnancy- and birth-related anxiety and concerns and shorter labors in one RCT [120].

In a small RCT, **a specific antenatal education program is associated with a reduction in the mean number of visits to the labor suite before the onset of labor** [4]. It is unclear whether this results in fewer women being sent home because they are not in labor (see also Chap. 7) [120, 121].

Depression in pregnancy and the postpartum period

Between 14% and 23% of pregnant women will experience a depressive mood disorder while pregnant [122–129]. Maternal anxiety, life stress, history of depression, lack of social support, unintended pregnancy, public insurance, domestic violence, lower income, lower education, smoking, single status, and poor relationship quality were associated with a greater likelihood of antepartum depressive symptoms in bivariate analyses. Life stress, lack of social support, and domestic violence continued to demonstrate a significant association in multivariate analyses [123, 124]. Identification of risk factors and screening for depression will facilitate referral for treatment (see Chap. 21 in *Maternal-Fetal Evidence Based Guidelines*).

Between 5% and 7% of women will experience postpartum depression. Risk factors include antenatal depressive symptoms, a history of major depressive disorder, or previous postpartum major depression [123]. If left untreated, postpartum major depression can lead to poor mother–infant bonding, delays in infant growth and development, and an increased risk of anxiety or depressive symptoms in the infant later in life. **Identifying mothers at risk assists in the prevention of postpartum depression compared to intervening on the general population**. The provision of **intensive postpartum support provided by public health nurses or midwives** is associated with 32% less postpartum depression. Interventions with **only a postnatal component** appeared to be more beneficial than interventions that also incorporated an antenatal component. **Individual-based interventions** may be more effective than those that are group-based. Women who received multiple-contact intervention are just as likely to experience postpartum depression as those who received a single-contact intervention [125]. **There is insufficient**

evidence to assess the effectiveness of antidepressants given immediately postpartum in preventing postnatal depression in all women or just in high-risk women [126]. A pilot RCT showed that **prenatal yoga** may be of benefit in the **prevention of postpartum depression** in low-risk women [128]. Moreover, prenatal yoga was also found to be a feasible and acceptable intervention and was associated with reductions in symptoms of anxiety and depression in women (see Chap. 21 in *Maternal-Fetal Evidence Based Guidelines*) [129].

Breastfeeding

Breastfeeding is the best feeding method for most infants and should be strongly encouraged (see Chap. 31). **Counseling and education during pregnancy have been shown to facilitate breastfeeding success** [130]. Breastfeeding education and/or support increased exclusive breastfeeding rates and decreased no-breastfeeding rates at birth and at 1–5 months. Combined individual and group counseling appeared to be superior to either individual counseling alone or group counseling alone. Attitudes of the health care provider are highly associated with breastfeeding success. An antigen avoidance diet during lactation by high-risk women may reduce the child's risk of developing atopic eczema and may reduce atopic eczema in children who already have it during the first 12–18 months, although more trials are needed.

Interventions for common pregnancy complaints

Itching

The differential diagnosis of itching in late pregnancy (>32 weeks) is presented in Chap 10 in *Maternal-Fetal Evidence Based Guidelines*. If the itching is not due to liver disease, and if there is no rash, aspirin (600 mg qid) has been reported to decrease itching [124], but because of potential detrimental fetal effects (closure of ductus arteriosus and oligohydramnios), it should not be used. If there are both itching and a rash, chlorpheniramine 4 mg tid decreased itching in a small trial [131]. However, aspirin 600 mg four times a day—which is not safe during parts of pregnancy—appears to be more effective than chlorpheniramine 5 mg three times a day for relief of itching when no rash is present in a small crossover trial [132].

Stretch marks

Some stretch marks (striae gravidarum) develop in about 50% of women by the end of pregnancy. **There is no high-quality evidence to support the use of any topical preparation in the prevention of stretch marks during pregnancy** [133, 134]. There is also no proven treatment for stretch marks once they have developed [134]. **Olive oil is not effective in preventing the occurrence of striae gravidarum or affecting its severity** [134]. There is no available product that has been shown to prevent the formation of striae gravidarum. Massage with either **Trofolastin cream** or **Verum ointment** is associated in small RCTs with a decrease in the development of striae gravidarum [134]. A small, randomized trial showed that a specific anti–stretch mark cream (emollient and moisturizer containing hydroxyprolisilane C, rosehip oil, ***Centella asiatica*** triterpenes, and vitamin E) had a small effect in reducing severity (but not the incidence) of striae gravidarum during pregnancy (see Chap. 45 in *Maternal-Fetal Evidence Based Guidelines*) [135].

Leg cramps

Leg cramps are reported to occur in 34% of pregnant women in the mid-trimester [136, 137]. **Magnesium lactate or citrate chewable tablets 5 mmol in the morning and 10 mmol in the evening for 3 weeks are associated with one-third of women not having persistent leg cramps** compared to 94% of placebo controls having persistent cramps. A multivitamin with a mineral supplement might decrease leg cramps, but it is unclear which one of the 12 ingredients (or combination) is beneficial. Sodium chloride is associated with a slight reduction, although consideration must be given to the potential effect on blood pressure. **Calcium supplements do not decrease leg cramps compared to placebo**. However, it is unclear whether any of the interventions studied (i.e., oral magnesium, oral calcium, oral vitamin B, or oral vitamin C) provide an effective treatment for leg cramps due to poor study design and trials being too small to address the question satisfactorily.

Calf stretching prior to bedtime does not decrease nocturnal leg cramps in nonpregnant patients [137].

Back and pelvic pain

Back pain is common in pregnancy, given weight gain and its uneven distribution, as well as the softening effects of pregnancy hormones on the musculature.

There is evidence that **exercise** (any exercise on land or in water) may reduce pregnancy-related low back pain, improve functional disability, and reduce sick leave. **Water gymnastics for 1 hour weekly starting at <19 weeks reduces back pain in pregnancy and allows more women to continue to work, with no adverse effects** [138].

Pregnancy-specific exercises, physiotherapy, and acupuncture starting <32 weeks for 10 sessions appear to reduce back and pelvic pain; individual acupuncture sessions are more beneficial than group physiotherapy sessions. Education, other exercises, massage, heat therapy, support belts, analgesic therapy, etc., have not been studied in a trial in pregnancy for back pain relief.

Constipation

Constipation is common in pregnancy, probably because of decreased bowel peristalsis (possibly related to increased progesterone). Constipation is reported by nearly 70% of women in the mid-trimester. In nonpregnant adults, **exercise, increase in water intake, dietary counseling, and certain foods (e.g., prunes)** have been shown to relieve constipation. If these self-help measures are inadequate, the pregnant woman should then try daily bran or wheat fiber supplements. There is insufficient evidence to comprehensively assess the effectiveness and safety of interventions (pharmacological and nonpharmacological) for treating constipation in pregnancy, due to limited data (few studies with small sample size and no meta-analyses). Compared with bulk-forming laxatives, stimulant laxatives (e.g., senna 14 mg or dioctyl sodium succinate 120 mg and dihydroxyanthraquinone 100 mg—Normax) appear to be more effective in improving constipation (moderate-quality evidence), but are accompanied by an increase in diarrhea and abdominal discomfort. **Docusate sodium** is a similar **stimulant laxative**, and it is widely available. Additionally, **dietary fiber supplements** (e.g., 10 mg/day of either corn-based biscuits—Fibermed—or 23 g wheat bran) increase the frequency of defecation and are associated with softer stools [139]. These findings in pregnant women are consistent with nonpregnant evidence.

Varicosities and leg edema

A small RCT (n = 69) shows that rutoside capsules improve leg edema symptoms; however, there are insufficient data to confirm rutoside safety in pregnancy. Another small RCT (n = 43) demonstrates a reduction in leg edema with **reflexology**. Compression stockings are not effective compared to simple resting, but studies do not compare compression stockings to no compression stockings. Leg elevation, compression hosiery, and swimming have not been studied for leg edema/varicosities relief in pregnancy [140].

Hemorrhoids

Hemorrhoids are common during pregnancy, with 13% of women complaining of them in the mid-trimester. **Oral hydroxyethylrutosides decrease symptoms compared to a placebo group in women with hemorrhoids and reduce the signs identified by the health care provider** [141]. Rutosides are associated with mild side effects such as GI discomfort, and their safety data in pregnancy are still insufficient. Constipation is a predisposing factor for hemorrhoids and should be treated. Sitz baths, ice, or ointments have been insufficiently studied for the treatment of hemorrhoids in pregnancy. A small RCT showed that Hai's Perianal Support toilet seat device reduced the symptoms of hemorrhoids in pregnancy and improved the well-being of pregnant women [142].

Heartburn

Heartburn is common during pregnancy, with 53% of women complaining of it in the mid-trimester. There is no large-scale RCT to assess heartburn relief in pregnancy [143].

A consensus document has recommended that **lifestyle and dietary modifications** should remain first-line treatment for heartburn in pregnancy. The measures include reducing and avoiding intake of reflux-inducing foods (e.g., greasy and spicy foods, tomatoes, highly acidic citrus products, and carbonated drinks) and substances such as caffeine. Nonsteroidal antiinflammatory drugs (NSAIDs) should also be avoided. Other lifestyle changes to reduce the risk of reflux, such as avoiding lying down within 3 hours after eating, are advised. However, if heartburn is severe enough to warrant this action, medication should begin after consultation with a health care professional. **Antacids, H_2 blockers, and proton pump inhibitors** all have acceptable safety profiles for the pregnant woman [143–146].

COVID-19 infection

See Chap. 26 for more information on COVID-19 infection. Pregnant persons should follow the **same recommendations as nonpregnant persons** for avoiding exposure to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19). This includes **masking and physical distancing** [147, 148]. **COVID-19 vaccination for pregnant persons,** in particular with nonlive vaccines as the mRNA vaccines (e.g., Pfizer and Moderna), **is recommended** at any time in pregnancy, pre-pregnancy, or postpartum (including during breastfeeding). Vaccination should not be deferred until after delivery or after breastfeeding [149]. To minimize the spread of SARS-CoV-2, many countries offer **testing to all patients admitted to hospital**, regardless of whether they have symptoms or not. This includes offering tests to all women who attend hospitals for urgent or emergency maternity care, including attendance for spontaneous labor and birth, and for planned procedures such as a planned cesarean delivery [147, 148]. **Immunity** to SARS-CcV-2 can be assessed at prenatal visits and/or at hospital admission in both women who had COVID-19 infection and those who had the vaccine to assess risk and guide management.

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3

PHYSIOLOGIC CHANGES

Jason Baxter and Julia Burd

Key points

- **The normal physiologic changes of pregnancy are several and listed in part in Table 3.1.**
- **Normal laboratory values for pregnant women are presented in Table 3.2.**
- **Failure to understand these physiologic changes of pregnancy may result in both undue alarm and costly evaluation of normal symptoms of pregnancy or in the neglect of pathologic conditions whose presentation is dismissed as another "discomfort of pregnancy."**
- **The physician should carefully address the pregnant patient, keeping in mind the question: "How is this presentation affected by the physiology of pregnancy?"**

Background

Over the course of human pregnancy, the significance of physiologic changes that occur is such that it often becomes no longer appropriate for the physician to evaluate her according to standards that have been set through the observation and study of men and nonpregnant women. Some of these physiologic changes are advantageous to the growth and survival of the fetus. Others enhance the ability of the maternal system to compensate for demands of pregnancy, prepare for stress of delivery, and recover from delivery.

Understanding physiologic changes in pregnancy is important in evaluating common symptoms associated with pregnancy, interpreting laboratory values in the parturient, and understanding pathologic conditions to which pregnant women are susceptible. **Failure to understand the normal physiologic changes of pregnancy may result in both undue alarm and costly evaluation of normal symptoms of pregnancy or in the neglect of pathologic conditions whose presentation is dismissed as another discomfort of pregnancy**. The patient will most likely be better served by the physician who carefully addresses her symptoms while **keeping in mind the questions: "How is this presentation affected by the physiology of pregnancy?"** and "What pathologic conditions may be represented by this scenario?" than by the physician who uncritically memorizes laboratory values and makes a diagnosis without considering the interplay between pregnancy and underlying pathophysiology.

Two summary tables are provided. Table 3.1 summarizes the commonly accepted pregnancy-related changes in various physiologic parameters and their importance in the evaluation and management during pregnancy [1]. Table 3.2 provides a summary of laboratory values in each trimester of pregnancy versus in the nonpregnant state based on a recent systematic review and other resources [2–5]. The reader will note that some values show significant overlap between pregnant and nonpregnant states. Some show little change between pregnant and nonpregnant states. Others show trends that clearly increase or decrease with pregnancy. In most cases, it is not possible to consider the effect of pregnancy on laboratory values in a simplistic or formulaic way. Rather, it is the understanding of the underlying physiology that these laboratory values reflect that is the most important in their evaluation during pregnancy.

Cardiovascular/Hemodynamic

An understanding of pregnancy-related hemodynamic changes is crucial in the management of both benign and life-threatening complications of pregnancy, ranging from near-syncopal episodes experienced by many pregnant women to hypotension from obstetric hemorrhage and hypertension, both of which are leading causes of maternal intensive care unit admissions and mortality [6]. Even the ultimate clinical emergency of cardiac arrest is complicated by hemodynamics that are unique to pregnancy.

Hemodynamic changes in pregnancy that have been well established include an **increase in cardiac output and a decrease in both systemic and pulmonary vascular resistance**. There is an **overall increase in heart rate and a decrease in blood pressure. Blood volume, plasma volume, and erythrocyte volume all increase, with a greater relative increase in plasma volume, resulting in a dilutional lowering of hematocrit and other blood indices**. There is also a redistribution of cardiac output with an increase in flow to the uterus, kidneys, skin, and breasts [1]. The renin–angiotensin–aldosterone system is activated in step with estrogen increases and assists in maintaining blood pressure and retaining water and salt despite increased renal excretion [7]. The increase in stroke volume and cardiac output creates a more audible physiologic flow murmur and splitting of the S2 sound during pregnancy, which may be striking upon physical exam.

One longitudinal study followed maternal hemodynamics as measured by thoracic electrical bioimpedance monitoring in 50 healthy pregnant women [8]. The results showed an increase in mean heart rate from 87 ± 2 beats per minute (bpm) at 10–18 weeks to 92 ± 1 bpm at 34–42 weeks. Mean arterial pressure (MAP) decreased significantly after 14 weeks and increased after 29 weeks. Systemic vascular resistance (SVR) increased during the last trimester. This study also found a significantly higher mean cardiac output in nulliparous women compared to multiparous women. Mean cardiac output and stroke volume, which show an overall increase during pregnancy, were found to decrease in the third trimester in this study [8]. A meta-analysis of 39 studies examining cardiac output in pregnancy indicated that cardiac output peaks in the early third trimester at 31% higher than nonpregnant values and quickly returns to baseline in the early postpartum period [9].

Another longitudinal study performed serial echocardiography studies on 35 healthy pregnant women from the early second trimester to 6–12 weeks postpartum [10]. This study showed a significant increase in cardiac output that peaked in the early

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TABLE 3.1: Summary of Physiologic Adaptations during Pregnancy

Parameter	Expected Change	Comments
Cardiovascular System		
Heart size	Increases 12%	Increases diastolic filling and muscle hypertrophy
Murmurs	Physiologic systolic	Ejection murmurs attributable to increased stroke volume usually occur in early or midsystole and are best heard along the left sternal edge
ECG	Positional heart shifts result in changes that resemble ischemia	Heart is pushed upward and forward, deviating electrical axis to the left by 15–20 degrees, causing flattened or inverted T in lead III
Cardiac output	Increases 30%–50% From 4.5 to about 6.0 L/min (by 1.5 L/min) Influenced by maternal position	Greatest increase occurs immediately after delivery with redistribution of blood flow from uterus. Cardiac output then decreases.
Rhythm	Increases atrial and ventricular extrasystole	SVT not infrequent
Heart rate	Increases	Onset of change is first trimester
Stroke volume	Increases	Significant change in second half of pregnancy
Mean arterial pressure	Decreased soon after beginning of pregnancy and midpregnancy (100–110/60–70 mean levels); then returns to pre-pregnant values by third trimester and term	Supine hypotension—decreased venous return due to compression from gravid uterus; increased blood flow through alternative pathways such as paravertebral azygous veins
Pulse pressure	Increases	
Venous pressure	Increases in femoral system; unchanged in arms	
Systemic vascular resistance	Decreases	
Pulmonary BP	Unchanged	
Blood flow to uterus	Increases by 500 mL/min Increases from 1%–3% of CO to 17%–20%	No autoregulation
Blood flow to kidneys	Increases by 400 mL/min	
Blood flow to skin	Increases by 300–400 mL/min	
Blood flow to breasts	Increases by 200 mL/min	
Respiratory System		
Anatomy	Increases subcostal angle from 68 to 103 degrees → 3-cm increase in transthoracic diameter	Increased upper respiratory capillary engorgement can cause increased congestion, epistaxis, and intubation trauma
Tidal volume	Increases by 300 mL or 40%	
Expiratory reserve volume	Decreases by 200 mL	Cephalad displacement of diaphragm
Inspiratory capacity	Increases by 300 mL	
Functional residual volume	Decreases by 500 mL	
Minute volume	Increases by 40% or 3 L/min beginning in first trimester	Increased rate of induction of, and emergence from, inhaled anesthetics
Maximum breathing capacity	Unchanged	
Forced expiratory volume	Unchanged	
Peak expiratory flow rate	Unchanged	
Pulmonary diffusing capacity	Decreases by 4 mL/min/mmHg	
Oxygen requirement	Increases by 30–40 mL/min	
Carbon dioxide output	Increases; expressed as respiratory quotient	
Carbon dioxide pressure	Decreases from 35–40 mmHg to 28–30 mmHg	
Oxygen pressure	Increases	
pH	Mild increase (7.40–7.44 is normal)	Compensated respiratory alkalosis
PCO_2	Decrease (30–31 mmHg is normal)	
PO_2	Mild increase (100–104 mmHg is normal)	
Renal System and Homeostasis		
Glomerular filtration rate	Increases from 97 mL/min to 128 mL/min by 10 wk	Increased renal clearance of certain drugs and vitamins
Glucose excretion	Increased	Random glycosuria
Protein excretion	Increased (up to 300 mg/24 hr is normal)	
Renin, angiotensin I and II	Increased	Diminished vascular response causes less pressor effect from angiotensin
Anatomic changes	Dilation of renal calyces and ureters to pelvic brim; "physiologic" hydronephrosis, right > left	Increased risk of pyelonephritis; screen for asymptomatic bacteriuria
Potassium	Increased retention	

(*Continued*)

TABLE 3.1 (Continued): Summary of Physiologic Adaptations during Pregnancy

Parameter	Expected Change	Comments
Sodium	Increased retention	
Urine output	No significant change	
Vitamin excretion	Increased loss of folate, B_{12}, and ascorbic acid	
Osmolality	Decreases 10 mOsm/kg first trimester, then stable	
Sodium	Decreases 3 mEq/L first trimester, then stable	
Potassium	Decreases 0.5 mEq/L	
Calcium	Decreased total and ionized	Increased intestinal absorption of calcium and increased bone turnover
Magnesium	Decreases 10%–20% in first half of pregnancy	
Chloride	Unchanged	
Bicarbonate	Decreases markedly (18–22 mEq/L is normal)	Compensates for decrease in PCO_2
Total protein	Decreases from 72 g/L to 62 g/L	
Albumin	Decreases from 47 g/L to 36 g/L	
Urea, creatinine, and uric acid	Decrease in first trimester; stabilize in second trimester; increase toward term	
Vitamin B_6	Decreases	
Blood glucose	Fasting levels **decrease** in first trimester, then unchanged	Postprandial levels remain elevated longer, prolonging return to fasting state. Increased glucose levels allow passive diffusion across placenta to fetus
Folate	Decreases 50% toward term	
Vitamin B_{12}	Decreases 50% or more	B_{12} levels in folate-deficient women will increase with folate supplementation alone
Endocrine System		
Pituitary gland	Increases to 50% greater than adult male	Attributable to increase of prolactin-secreting cells in anterior lobe
Prolactin	Increases from 300 mIU/L to 5000 mIU/L	Estrogen stimulates hyperplasia and hypertrophy of pituitary lactotrophs
Follicle-stimulating hormone and luteinizing hormone	Decrease to nearly undetectable	
Melanocyte-stimulating hormone	Increased	Likely responsible for linea nigra, chloasma, and increased areolae pigmentation
Thyroid-stimulating hormone	Normal range is unchanged	May be suppressed during late first to early second trimester due to hCG-mediated increase in TH production—subtle effect may be exacerbated by conditions that increase hCG levels, such as hyperemesis, molar pregnancies, and multiples
Thyroid-binding globulin	Increases—doubles by end of first trimester; triples by term	Due to estrogen effect on liver
Thyroxine (T_4) and triiodothyronine (T_3)	Increased total circulating amount; unchanged free fraction	Fetal thyroid hormone production commences at 18 wk
Reverse T_3	Unchanged in maternal circulation; increased in cord blood	
Cortisol	Increased to 3 × nonpregnant values	Episodic pattern of release is maintained.
Aldosterone	Increased twofold by term	
Deoxycorticosterone	Increased by 20–100 ×	
Testosterone	Increased total amount; decreased free fraction	
Androstenedione	Increases	Tenfold increase rate of transformation to estradiol and estrone
DHEA	Unchanged or small decrease	Precursor for steroid hormone synthesis by placenta
Pancreas	Hypertrophy of islets due to hyperplasia of B cells	
Insulin	Increases fasting levels toward term; hyperplasia of pancreatic B cells	Proportionally less increase of glucagons compared to insulin; so insulin:glucagon ratio is increased
Glucagon	Increases fasting levels	
Glucose	Slight decrease	Especially fasting levels
Parathyroid hormone	Increased during end of pregnancy	Maintains calcium levels in face of increased renal absorption and transfer to fetus
Progesterone	Markedly increases	Production originates in corpus luteum over first 7–8 wk; then placenta takes over
Estradiol	Markedly increases	

TABLE 3.1 (Continued): Summary of Physiologic Adaptations during Pregnancy

Parameter	Expected Change	Comments
17-Hydroxyprogesterone	Increases	
Estriol	Increases	
Human placental lactogen (hPL)	Increases 5000-fold from 0.002 μU/mL to 10 mU/mL	
hCG	Increases to maximum values by 8–10 wk	Peak 93 U/mL; term 14 U/mL
Relaxin	Peaks at 10 wk	
Gastrointestinal System		
Appetite	Increases	
Gastric reflux	Increases	Cardiac sphincter laxity and anatomic displacement; treated during labor and delivery/anesthetic procedures with nonparticulate oral antacids
Gastric secretion	Decreased acidity; increased volume	"Full stomach" effect increases risk of aspiration
Gastric motility	Decreases	
Intestinal absorption	Increased	
Intestinal transit time	Delayed	
Large intestine	Greater absorption; slower transit time	
Gallbladder	Larger due to passive dilation	
Hematologic System		
Plasma volume	40%–60% **increase** from 12 to 36 wk; 70%–100% increase in multiple gestations	Offsets blood loss at delivery
Total erythrocyte volume	Increases 15%–30%	Greater increase with iron supplementation
Hematocrit	Decreases 3%–5% by 36 wk	Physiologic anemia due to greater proportionate increase in plasma volume compared to erythrocyte volume; less change with iron supplementation
Hemoglobin	Decreases	
Mean corpuscular volume	Unchanged	Best indicator of iron status. Slight increase with iron supplementation.
Erythrocyte sedimentation rate	Significantly increased	Provides little diagnostic value; combined with increase in white blood cell (WBC) can cause false suspicion for infection
WBC count	Increases 8% by term and may increase further postpartum	Predominantly due to increase in neutrophils
Serum iron	Decreases 35% by term	
Serum transferrin	Increases by 100% or more by second trimester	Total iron-binding capacity (TIBC) markedly increased
TIBC	Increases by 25%–100%	
Serum ferritin	Decreases markedly (even with iron supplementation)	Nadir 30% or less of normal values. Best test to assess iron-deficiency anemia in pregnancy
Erythropoietin	Increases fourfold	
α-Fetoprotein	Increases	Larger increase in neural tube defects, abdominal wall defects, and fetal death
Glutamic-oxaloacetic transaminase and glutamic-pyruvic transaminase	Unchanged	
Alkaline phosphatase	Increases	Heat stable fraction formed by placenta
Lipids	Increase	Triglycerides, cholesterol, phospholipids, and free fatty acids each increase progressively.
Fibrinogen	Increases 2 g/L by term	Overall increased tendency toward thrombosis
Factors VII, VIII, IX, and X	Increase	
Factors XI and XIII	Decrease by about 30%	
Antithrombin III	Decreases	
Fibrin, FDP	Increase progressively	
Protein C	Unchanged	
Protein S	Decreases	Protein S–binding protein levels fluctuate in pregnancy, making screening more reliable in nonpregnant women

Source: See further Ref. [1].

Abbreviations: ECG, electrocardiogram; min, minute; SVT, supraventricular tachycardia; BP, blood pressure; CO, cardiac output; wk, weeks; hr, hour; hCG, human chorionic gonadotropin; TH, thyroid hormone; DHEA, dehydroepiandrosterone; FDP, fibrin degradation products.

TABLE 3.2: Normal Reference Ranges in Pregnant Women

	Nonpregnant Adult	First Trimester	Second Trimester	Third Trimester
Hematology				
Erythropoietin (U/L)	4–27	12–25	8–67	14–222
Ferritin (ng/mL)	10–150	6–130	2–230	0–116
Folate, red blood cell (ng/mL)	150–450	137–589	94–828	109–663
Folate, serum (ng/mL)	5.4–18	2.6–15	0.8–24	1.4–20.7
Hemoglobin (g/dL)	12–15.8	11.6–13.9	9.7–14.8	9.5–15
Hematocrit (%)	35.4–44.4	31–41	30–39	28–40
Iron, total binding capacity (µg/dL)	251–406	278–403		359–609
Iron, serum (µg/dL)	41–141	72–143	44–178	30–193
Mean corpuscular hemoglobin (pg/cell)	27–32	30–32	30–33	29–32
Mean corpuscular volume (μm^3)	79–93	81–96	82–97	81–99
Platelet ($\times 10^9$/L)	165–415	174–391	155–409	146–429
Mean platelet volume (μm^3)	6.4–11	7.7–10.3	7.8–10.2	8.2–7.4
Red blood cell count ($\times 10^6/mm^3$)	4–5.2	3.42–4.55	2.81–4.49	2.71–4.43
Red cell distribution width (%)	<14.5	12.5–14.1	13.4–13.6	12.7–15.3
White blood cell count ($\times 10^3/mm^3$)	3.5–9.1	5.7–13.6	5.6–14.8	5.9–16.9
Neutrophils ($\times 10^3/mm^3$)	1.4–4.6	3.6–10.1	3.8–12.3	3.9–13.1
Lymphocytes ($\times 10^3/mm^3$)	0.7–4.6	1.1–3.6	0.9–3.9	1–3.6
Monocytes ($\times 10^3/mm^3$)	0.1–0.7	0.1–1.1	0.1–1.1	0.1–1.4
Eosinophils ($\times 10^3/mm^3$)	0–0.6	0–0.6	0–0.6	0–0.6
Basophils ($\times 10^3/mm^3$)	0–0.2	0–0.1	0–0.1	0–0.1
Transferrin (mg/dL)	200–400	254–344	220–441	288–530
Transferrin, saturation without iron (%)	22–46		10–44	5–37
Transferrin, saturation with iron (%)	22–46		18–92	9–98
Coagulation				
Antithrombin III, functional (%)	70–130	89–114	88–112	82–116
D-dimer (µg/mL)	0.22–0.74	0.05–0.95	0.32–1.29	0.13–1.7
Factor V (%)	50–150	75–95	72–96	60–88
Factor VII (%)	50–150	100–146	95–153	149–211
Factor VIII (%)	50–150	90–210	97–312	143–353
Factor IX (%)	50–150	103–172	154–217	164–235
Factor XI (%)	50–150	80–127	82–144	65–123
Factor XII (%)	50–150	78–124	90–151	129–194
Fibrinogen (mg/dL)	233–496	244–510	291–538	373–619
Homocysteine (µmol/L)	4.4–10.8	3.34–11	2–26.9	3.2–21.4
International normalized ratio	0.9–1.04	0.89–1.05	0.85–0.97	0.80–0.94
Partial thromboplastin time, activated (sec)	26.3–39.4	24.3–38.9	24.2–38.1	24.7–35
Prothrombin time (sec)	12.7–15.4	9.7–13.5	9.5–13.4	9.6–12.9
Protein C, functional (%)	70–130	78–121	83–133	67–135
Protein S, total (%)	70–140	39–105	27–101	33–101
Protein S, free (%)	70–140	34–133	19–113	20–65
Protein S, functional activity (%)	65–140	57–95	42–68	16–42
Tissue plasminogen activator (ng/mL)	1.6–13	1.8–6	2.4–6.6	3.3–9.2
Tissue plasminogen activator inhibitor-1 (ng/mL)	4–43	16–33	36–55	67–92
Von Willebrand factor (%)	75–125			121–260
Blood Chemical Constituents				
Alanine transaminase (U/L)	7–41	3–30	2–33	2–25
Albumin (g/dL)	4.1–5.3	3.1–5.1	2.6–4.5	2.3–4.2
Alkaline phosphatase (U/L)	33–96	17–88	25–126	38–229
α1-Antitrypsin (mg/dL)	100–200	225–323	273–391	327–487
Amylase (U/L)	20–96	24–83	16–73	15–81
Anion gap (mmol/L)	7–16	13–17	12–16	12–16
Aspartate transaminase (U/L)	12–38	3–23	3–33	4–32

TABLE 3.2 (Continued): Normal Reference Ranges in Pregnant Women

	Nonpregnant Adult	First Trimester	Second Trimester	Third Trimester
Bicarbonate (mmol/L)	22–30	20–24	20–24	20–24
Bilirubin, total (mg/dL)	0.3–1.3	0.1–0.4	0.1–0.8	0.1–1.1
Bilirubin, unconjugated (mg/dL)	0.2–0.9	0.1–0.5	0.1–0.4	0.1–0.5
Bilirubin, conjugated (mg/dL)	0.1–0.4	0–0.1	0–0.1	0–0.1
Bile acids (μmol/L)	0.3–4.8	0–4.9	0–9.1	0–11.3
Calcium, ionized (mg/dL)	4.5–5.3	4.5–5.1	4.4–5	4.4–5.3
Calcium, total (mg/dL)	8.7–10.2	8.8–10.6	8.2–9	8.2–9.7
Ceruloplasmin (mg/dL)	25–63	30–49	40–53	43–78
Chloride (mEq/L)	102–109	101–105	97–109	97–109
Creatinine (mg/dL)	0.5–0.9	0.4–0.7	0.4–0.8	0.4–0.9
γ-Glutamyl transpeptidase (U/L)	9–58	2–23	4–22	3–26
Lactate dehydrogenase (U/L)	115–221	78–433	80–447	82–524
Lipase (U/L)	3–43	21–76	26–100	41–112
Magnesium (mg/dL)	1.5–2.3	1.6–2.2	1.5–2.2	1.1–2.2
Osmolality (mOsm/kg H_2O)	275–295	275–280	276–289	278–280
Phosphate (mg/dL)	2.5–4.3	3.1–4.6	2.5–4.6	2.8–4.6
Potassium (mEq/L)	3.5–5	3.6–5	3.3–5	3.3–5.1
Prealbumin (mg/dL)	17–34	15–27	20–27	14–23
Protein, total (g/dL)	6.7–8.6	6.2–7.6	5.7–6.9	5.6–6.7
Sodium (mEq/L)	136–146	133–148	129–148	130–148
Urea nitrogen (mg/dL)	7–20	7–12	3–13	3–11
Uric acid (mg/dL)	2.5–5.6	2–4.2	2.4–4.9	3.1–6.3
Metabolic and Endocrine Tests				
Aldosterone (ng/dL)	2–9	6–104	9–104	15–101
Angiotensin-converting enzyme (U/L)	9–67	1–38	1–36	1–39
Cortisol (μg/dL)	0–25	7–19	10–42	12–50
Hemoglobin A1c (%)	4–6	4–6	4–6	4–7
Parathyroid hormone (pg/mL)	8–51	10–15	18–25	9–26
Parathyroid hormone–related protein (pmol/L)	<1.3	0.7–0.9	1.8–2.2	2.5–2.8
Procalcitonin (μg/L)[a]	0.02-0.06	0.02-0.05	0.01-0.08	0.01-0.15
Renin, plasma activity (ng/mL/hr)	0.3–9		7.5–54	5.9–58.8
Thyroid-stimulating hormone (μIU/mL)	0.34–4.25	0.6–3.4	0.37–3.6	0.38–4.04
Thyroxine-binding globulin (mg/dL)	1.3–3	1.8–3.2	2.8–4	2.6–4.2
Thyroxine, free (ng/dL)	0.8–1.7	0.8–1.2	0.6–1	0.5–0.8
Thyroxine, total (μg/dL)	5.4–11.7	6.5–10.1	7.5–10.3	6.3–9.7
Triiodothyronine, free (pg/mL)	2.4–4.2	4.1–4.4	4–4.2	
Triiodothyronine, total (ng/dL)	77–135	97–149	117–169	123–162
Vitamins and Minerals				
Copper (μg/dL)	70–140	112–199	165–221	130–240
Selenium (μg/L)	63–160	116–146	75–145	71–133
Vitamin A (retinol) (μg/dL)	20–100	32–47	35–44	29–42
Vitamin B_{12} (pg/mL)	279–966	118–438	130–656	99–526
Vitamin C (ascorbic acid) (mg/dL)	0.4–1			0.9–1.3
Vitamin D, 1,25-dihydroxy (pg/mL)	25–45	20–65	72–160	60–119
Vitamin D, 24,25-dihydroxy (ng/mL)	0.5–5	1.2–1.8	1.1–1.5	0.7–0.9
Vitamin D, 25-hydroxy (ng/mL)	14–80	18–27	10–22	10–18
Vitamin E (α-tocopherol) (mg/mL)	5–18	7–13	10–16	13–23
Zinc (μg/dL)	75–120	57–88	51–80	50–77
Autoimmune and Inflammatory Mediators				
C3 complement (mg/dL)	83–177	62–98	73–103	77–111
C4 complement (mg/dL)	16–47	18–36	18–34	22–32
C-reactive protein (mg/L)	0.2–3		0.4–20.3	0.4–8.1
Erythrocyte sedimentation rate (mm/hr)	0–20	4–57	7–47	13–70
IL-6 (pg/mL)[b]		13.8–41.1	13.1–44.4	

(*Continued*)

TABLE 3.2 (Continued): Normal Reference Ranges in Pregnant Women

	Nonpregnant Adult	First Trimester	Second Trimester	Third Trimester
Immunoglobulin A (mg/dL)	70–350	95–243	99–237	112–250
Immunoglobulin G (mg/dL)	700–1700	981–1267	813–1131	678–990
Immunoglobulin M (mg/dL)	50–300	78–232	74–218	85–269
Sex Hormones				
Dehydroepiandrosterone sulfate (μmol/L)	1.3–6.8	2–16.5	0.9–7.8	0.8–6.5
Estradiol (pg/mL)	<20–443	188–2497	1278–7192	6137–3460
Progesterone (ng/mL)	<1–20	8–48		99–342
Prolactin (ng/mL)	0–20	36–213	110–330	137–372
Sex hormone–binding globulin (nmol/L)	18–114	39–131	214–717	216–724
Testosterone (ng/dL)	6–86	26–211	34–243	63–309
17-Hydroxyprogesterone (nmol/L)	0.6–10.6	5.2–28.5	5.2–28.5	15.5–84
Lipids				
Cholesterol, total (mg/dL)	<200	141–210	176–299	219–349
High-density lipoprotein cholesterol (mg/dL)	40–60	40–78	52–87	48–87
Low-density lipoprotein cholesterol (mg/dL)	<100	60–153	77–184	101–224
Very-low-density lipoprotein cholesterol (mg/dL)	6–40	10–18	13–23	21–36
Triglycerides (mg/dL)	<150	40–159	75–382	131–453
Apolipoprotein A-I (mg/dL)	119–240	111–150	142–253	145–262
Apolipoprotein B (mg/dL)	52–163	58–81	66–188	85–238
Cardiac				
Atrial natriuretic peptide (pg/mL)			28.1–70.1	
B-type natriuretic peptide (pg/mL)	<167		13.5–29.5	
Creatine kinase (U/L)	39–238	27–83	25–75	13–101
Creatine kinase-MB (U/L)	<6			1.8–2.4
Troponin I (ng/mL)	0–0.8			0–0.064 (intrapartum)
Blood Gas				
pH	7.38–7.42 (arterial)	7.36–7.52 (venous)	7.4–7.52 (venous)	7.41–7.53 (venous) 7.39–7.45 (arterial)
PO_2 (mmHg)	90–100	93–100	90–98	92–107
PCO_2 (mmHg)	38–42			25–33
Bicarbonate (HCO_3^-) (mEq/L)	22–26			16–22
Renal Function Tests				
Effective renal plasma flow (mL/min)	492–696	696–985	612–1170	595–945
Glomerular filtration rate (GFR) (mL/min)	106–132	131–166	135–170	117–182
Filtration fraction (%)	16.9–24.7	14.7–21.6	14.3–21.9	17.1–25.1
Osmolarity, urine (mOsm/kg)	500–800	326–975	278–1066	238–1034
24-hr albumin excretion (mg/24 hr)	<30	5–15	4–18	3–22
24-hr calcium excretion (mmol/24 hr)	<7.5	1.6–5.2	0.3–6.9	0.8–4.2
24-hr creatinine clearance (mL/min)	91–130	69–140	55–136	50–166
24-hr creatinine excretion (mmol/24 hr)	8.8–14	10.6–11.6	10.3–11.5	10.2–11.4
24-hr potassium excretion (mmol/24 hr)	25–100	17–33	10–38	11–35
24-hr protein excretion (mg/24 hr)	<150	19–141	47–186	46–185
24-hr sodium excretion (mmol/24 hr)	100–260	53–215	34–213	37–149

Source: Adapted from Ref. [2], except as indicated.

[a] Adapted from Refs. [4, 5].

[b] Adapted from Ref. [3].

Abbreviations: sec, second; hr, hour; min, minute.

third trimester and was maintained until term. The detected 46%–51% increase in cardiac output was attributed to a 15% increase in heart rate and a 24% increase in stroke volume [10]. **The changes in heart rate occur early in pregnancy, whereas those of stroke volume occur later, with the net effect of a progressively increasing cardiac output as gestation progresses**. Again, significant variation in cardiac output changes in the late third trimester was attributed to patient factors, precluding confident conclusions regarding the behavior of cardiac output at the very end of pregnancy. Maternal cardiac output was found to correlate with maternal body surface area and with fetal birth weight. Left ventricular mass and left ventricular mass index increased to maximal levels at term but remained well below the cutoff for a diagnosis of left ventricular hypertrophy. This increase corresponded to an increase in mean blood pressure at term, as well as to an increase in left atrial size and a decrease in left ventricular diastolic filling value. These changes may explain some of the variations in cardiac output in the third trimester and may be relevant to the vulnerability of pregnant women to pulmonary edema during hypertensive crisis [10]. Recent research has indicated that these changes in left ventricular mass on echocardiogram are associated with increased dyspnea in pregnancy [11].

Perhaps the most common hemodynamic complaint that must be evaluated during pregnancy is that of **syncope or near-syncope**, which provides a useful example of how an understanding of pregnancy physiology is useful in clinical evaluation. Syncope is defined as a transient loss of consciousness and posture, caused by decreased cerebral perfusion that may result from hypotension, changes in heart rate, or changes in blood volume or redistribution. The decreased SVR of pregnancy makes pregnant women particularly susceptible to this condition, with 28% of gravidas experiencing at least one episode of presyncope, 10% experiencing recurrent presyncopal episodes, and 5% experiencing outright syncope [12]. The overwhelming majority of syncopal episodes are benign neurocardiogenic syncope, but there are also several potentially dangerous conditions in the differential diagnosis of syncope. An understanding of the vasovagal reflex at the root of most syncopal episodes helps the clinician to manage benign syncopal episodes while being alert for signs and symptoms that may point to a more serious underlying condition. The most common trigger of syncope is venous pooling that results in a drop in venous return and a subsequent drop in cardiac output. This results in stimulation of arterial baroreceptors, which trigger catecholamine stimulation of atria and ventricles. The resultant vigorous cardiac contraction in volume-depleted chambers stimulates cardiac mechanoreceptors or C-fibers which, in susceptible individuals, can result in paradoxical stimulation of the dorsal vagal nucleus. This stimulation is paradoxical because, in the face of low SVR and cardiac output, there is a further decrease in sympathetic tone and an increase in vagal tone causing vasodilation and bradycardia and the clinical presentation of presyncope or syncope [12]. The reflex may be initiated by emotional stimuli in some individuals or may be initiated by compression of the inferior vena cava by the gravid uterus causing a decrease in venous return and intracardiac pressure. Less common conditions that may present with symptoms of syncope include cerebrovascular accidents, seizures, cardiac arrhythmias or valvular disease, cardiomyopathy, pericardial tamponade, myocardial infarction, congenital heart defects, thromboembolic phenomenon, anemia, hypoglycemia, or electrolyte disorders [12]. Further evaluation for such conditions should be prompted when an apparent syncopal episode is accompanied by focal neurologic findings, prolonged loss of consciousness or postictal confusion, carotid or subclavian bruits, a pathologic cardiac murmur, or electrocardiogram (ECG) or laboratory abnormalities [12].

The events that are precipitated by a decrease in venous return can also explain the occurrence of **supine hypotension** in pregnancy. The commonly recommended "leftward tilt" position is intended to displace the uterus off of the inferior vena cava, which runs to the right of midline. This position should be used to avoid supine hypotension when recumbent, as well as when performing surgery on the parturient in the second half of pregnancy. A more extreme application of this physiology comes in the performance of perimortem cesarean section during maternal cardiac arrest. The procedure is purported not only so to allow fetal survival but also so that the evacuation of the uterus may allow an increase in venous return and cardiac output that may increase the chance for maternal survival [13]. In order to optimize maternal and fetal survival, it is recommended that the procedure be performed within 4 minutes of cardiac arrest due to the inadequacy of chest compressions in producing adequate cardiac output during pregnancy and the susceptibility of both mother and fetus to anoxic brain injury (see also Chaps. 1 and 2 in *Maternal-Fetal Evidence Based Guidelines*) [13].

Respiratory

During pregnancy, the respiratory system undergoes alterations that are reflected in pulmonary function tests and in acid–base balance. These are important in the evaluation of dyspnea in pregnancy, the management of pregnancy with coexisting pulmonary diseases such as asthma, and the recognition of acute pulmonary complications of pregnancy.

Pregnancy is associated with a significant increase in ventilatory drive both at rest and during exercise [14]. **Minute ventilation increases** mostly due to an **increase in tidal volume** with little or no increase in respiratory rate [6, 14, 15]. Alveolar ventilation increases, along with an **increase in arterial partial pressure of oxygen (PaO_2) and alveolar partial pressure of oxygen (PAO_2) and a decrease in arterial partial pressure of carbon dioxide ($PaCO_2$), with a compensatory decrease in serum bicarbonate, with an overall mild increase in pH, reflecting a state of compensated respiratory alkalosis** [14]. These changes occur early in pregnancy and are almost fully established by 7–8 weeks' gestation [14]. This may be due to stimulation of the ventilatory drive by progesterone and/or estrogen. Ventilatory equivalents for CO_2 and O_2 are increased both at rest and during exercise throughout pregnancy. The underlying mechanism for the increased ventilatory drive during pregnancy is not fully understood, but theories have included an increased sensitivity to chemoreflexive drives to breathe (due to hypercapnia or hypoxia) versus a hormone-mediated increase in the neural drive to breathe [14].

Uterine enlargement and abdominal distension result in a 4- to 5-cm cephalad displacement of the diaphragm and a 5- to 7-cm increase in thoracic circumference. This results in a **decrease in expiratory reserve volume, residual volume, and functional residual capacity**. There is a compensatory increase in inspiratory capacity, while total lung capacity and vital capacity do not change [14]. Chest wall compliance is increased, but inspiratory muscle strength is preserved with an overall increase in the oxygen cost of breathing [14]. However, it is important to recognize that there is **no significant change in the parameters of forced vital capacity, peak expiratory flow rate (PEFR), or forced expiratory volume in 1 second (FEV_1) during pregnancy**.

Physiologic **dyspnea** of pregnancy, experienced by 60%–70% of healthy pregnant women, must be clinically distinguished from more serious respiratory conditions. Physiologic dyspnea tends to be an isolated symptom that begins in early pregnancy, plateaus or improves as pregnancy progresses, and does not interfere with daily activities [16]. The mechanism for physiologic dyspnea has not been conclusively defined, but pregnant women with dyspnea have been demonstrated to have an increase in minute ventilation and tidal volume and a decrease in end-tidal CO_2 pressure compared to pregnant women who do not report dyspnea [16]. The perception of physiologic dyspnea during pregnancy has been associated with increased sensitivity to hypoxia and hypercapnia, suggesting an increased chemosensitivity causing an increased central inspiratory drive in pregnant women who experience dyspnea. However, the chemical stimuli of hypoxia and hypercapnia are both reduced in pregnancy, causing others to suggest a neural mechanism [14]. In spite of the common symptom of physiologic dyspnea, **pregnancy has not been found to be associated with a decrease in aerobic work capacity or with an increased perception of breathlessness during exercise** [14]. On the contrary, exercise in pregnancy has been noted to increase the rate of vaginal delivery and decrease rates of gestational diabetes, hypertensive disorders of pregnancy, and preterm birth [17].

While measurement of FEV_1 requires a spirometer, measurement of PEFR correlates well with FEV_1 and can be measured with a relatively inexpensive spirometer (peak flow meter), which patients can be taught to use at home. Again, **these parameters do not change due to pregnancy, so any detected worsening should be treated appropriately and not attributed to pregnancy or to physiologic dyspnea**. In the evaluation of severe acute asthma exacerbations with the potential for impending respiratory arrest, knowledge of physiologic changes of pregnancy is particularly important in the interpretation of blood gases (Table 3.1). The normal parturient lives in a state of compensated respiratory alkalosis with a lower partial pressure of carbon dioxide (PCO_2) compared to that of nonpregnant patients. Thus, significant CO_2 retention may be present in spite of values that are high-normal for nonpregnant patients.

While physiologic dyspnea and asthma exacerbation are two of the most common causes of dyspnea in pregnancy, the obstetrician must also be alert to other pulmonary complications to which the parturient is susceptible, such as pulmonary embolism and pulmonary edema. Pulmonary edema may occur as a result of preeclampsia, peripartum cardiomyopathy, or the use of certain tocolytics. It is important that the prevalence of pulmonary symptoms in pregnancy not be met with complacency by the obstetrician, for it may signify a life-threatening condition for the pregnant woman.

Endocrine

Pregnancy-related endocrine alterations include the production of hormones that are specific to pregnancy, an increase in other reproductive hormones, and alterations in the level and function of nonreproductive hormones, especially of thyroid hormones. There is a significant contribution of steroid hormone secretion by the fetal-placental unit. This section provides a brief description of the changes in reproductive hormones during gestation followed by a more in-depth review of the behavior and clinical application of thyroid hormones during pregnancy.

Pregnancy-specific hormones include human chorionic gonadotropin (hCG) and relaxin. **Relaxin** is detectable in maternal serum by the time of missed menses and peaks at 10 weeks' gestation, then declines over the course of the second and third trimesters [18]. Relaxin is secreted by the corpora lutea of pregnancy and is thought to have an important role in early pregnancy maintenance that has not yet been clearly elucidated [19]. **hCG** also peaks at approximately 10 weeks' gestation. The reproductive hormones **estradiol, progesterone, testosterone, prolactin, and 17-hydroxyprogesterone** all increase significantly during gestation. Initially the corpus luteum and maternal ovarian tissue make the greatest contribution to steroid hormone concentrations, but as of 9 weeks' gestation, aromatization of dehydroepiandrosterone sulfate by the placenta becomes the predominant source of maternal steroids [20]. The elevated estradiol levels stimulate increased hepatic production of sex hormone–binding globulin and thyroxin-binding globulin. Estrogen also induces hypertrophy and hyperplasia of pituitary lactotrophs with a resultant increase in prolactin levels corresponding to the increase in estradiol levels throughout gestation [20]. Meanwhile, there is a reflexive decrease in follicle-stimulating hormone and luteinizing hormone to almost undetectable levels, as would be expected.

One longitudinal study assayed reproductive hormone levels in the blood of 60 healthy women drawn during the first, second, and third trimesters of uncomplicated pregnancies [20]. Mean progesterone levels increased steadily from 49 nmol/L at 5 weeks' gestation to 584 nmol/L at term. Mean 17-hydroxyprogesterone levels are more stable during the first and second trimesters at 12.2 nmol/L but then increase threefold to 36 nmol/L by term. Mean testosterone increased from 3.3 nmol/L at 5 weeks to 5.7 nmol/L at 40 weeks. Mean serum estradiol levels increased during the first trimester from 1.64 nmol/L at 5 weeks to 11.13 nmol/L at 16 weeks and then increased fivefold to 53.44 nmol/L at 40 weeks. Mean sex hormone–binding globulin levels increase rapidly during the first half of gestation, from 71 nmol/L at 5 weeks to 392 nmol/L at 25 weeks, and then remain relatively constant until 40 weeks. Mean levels of dehydroepiandrosterone sulfate decreased from 5.8 mmol/L at 5 weeks to 2.7 mmol/L at midgestation, where they remained rather constant until term. Mean prolactin concentration rose from 294 milli-international units (mIU) to 1106 mIU at 16 weeks. Prolactin levels then continued to increase to a mean of 4092 mIU at 35 weeks and to 4293 mIU at 40 weeks. Mean androstenedione levels increase gradually from 8.1 nmol/L at 5 weeks to 10.6 nmol/L at 40 weeks [14].

Other hormonal alterations include an increase in aldosterone, cortisol, parathyroid hormone, parathyroid-related hormone, and renin [2]. Deoxycorticosterone increases. Androstenedione increases with an increase in the transformation to estrone and estradiol [1]. Fasting levels of both insulin and glucagon increase [1]. There is an increase in melanocyte-stimulating hormone to which can be attributed the pregnancy-related increases in pigmentation seen in the areola and the linea nigra and in chloasma [1].

The function of the **thyroid gland** is crucial to a healthy gestation (see also Chaps. 6 and 7 in *Maternal-Fetal Evidence Based Guidelines*). The interplay between maternal and fetal thyroid function can cause confusion for the obstetrician. Early fetal development is dependent on maternal thyroid function, and both hypothyroidism and hyperthyroidism can have important maternal and fetal effects. The risks of thyroid dysfunction extend well into the postpartum period. The effects of subclinical thyroid disease are more controversial. Symptoms of hyperthyroidism and hypothyroidism can mimic symptoms of normal pregnancy. For example, symptoms such as fatigue, muscle cramps, palpitations, thyromegaly, and constipation can be common in normal

pregnancy, but progressive symptoms of insomnia, intellectual slowness, or weight loss should be evaluated [21].

Thyroid-binding globulin increases due to stimulation of synthesis by estrogen as well as decreased hepatic clearance. **Total thyroxine (TT_4) and total triiodothyronine (TT_3) both increase, while resin triiodothyronine uptake (RT_3U) decreases**. Structural similarities between hCG and thyroid-stimulating hormone (TSH) may result in an hCG-mediated increase in free thyroxine (FT_4) and the free thyroxine index, as well as a decrease in TSH in the first trimester. However, these changes, sometimes referred to as gestational transient thyrotoxicosis, are typically self-limited and do not tend to result in values that are outside the normal range for nonpregnant individuals. TSH levels normalize in the second trimester and increase again in the third trimester due to increased need for thyroid hormone (see also Chaps. 6 and 7 in *Maternal-Fetal Evidence Based Guidelines*) [21].

Iodine requirements during pregnancy increase by greater than 50% due to increased maternal thyroxine production to maintain maternal and fetal euthyroidism and increased renal iodine clearance [22]. Plasma iodine levels decrease. This is associated with an increase in the size of the maternal thyroid gland. Longitudinal studies of thyroid ultrasonography in pregnancy show a mean increase in thyroid size of 10%–30%, which is noticeable in most women but not associated with abnormalities in thyroid function tests [21]. Iodine supplementation results in a less substantial increase in thyroid gland size [22]. While ultrasound or laboratory evaluation is not necessary in the pregnant patient with a mild diffuse increase in thyroid size, a significant goiter or thyroid nodule must be evaluated, as in any patient. A woman who is marginally iodine deficient may be able to compensate with increased thyrotropin stimulation of the thyroid to achieve euthyroidism but become hypothyroid when faced with the increasing iodine requirements of pregnancy [22].

Thyroid homeostasis is important for healthy fetal development. The fetal thyroid begins to concentrate iodide at 10–12 weeks. Thyroid hormone necessary for fetal brain development before this time must be provided by the maternal system [21, 23]. Thyroid hormone synthesis in the fetus is controlled by the fetal pituitary gland by 20 weeks. **Small amounts of T_4 and T_3 pass the placenta, but TSH does not cross the placenta. Thyroid-releasing hormone (TRH) and iodide do cross the placenta** [21]. Maternal hypothyroidism has been associated with abnormal intelligence quotient testing and pediatric neurodevelopment in offspring, particularly when untreated [23]. While severe maternal iodine deficiency can lead to cretinism in the offspring, it is less clear whether mild-to-moderate iodine deficiency leads to more subtle cognitive or neurologic dysfunction. Iodine supplementation in iodine-deficient populations has been found to substantially reduce the relative risk of cretinism and to improve psychomotor and cognitive test scores in the offspring [22].

Hyperemesis gravidarum is associated with elevated levels of hCG, an increase in FT_4, and a decrease in TSH (biochemical hyperthyroidism). However, this is largely transitory and rarely associated with clinical hyperthyroidism. Thus routine measuring of thyroid function in hyperemesis is not indicated in the absence of other signs of hyperthyroidism such as weight loss or persistent tachycardia [21]. Furthermore, treatment of transient hyperthyroidism associated with elevated hCG and hyperemesis should not be undertaken in the absence of evidence of intrinsic thyroid disease (see also Chap. 9 in *Maternal-Fetal Evidence Based Guidelines*) [21]. A large prospective observational study of 25,765 pregnant women who underwent thyroid screening in pregnancy showed no difference in pregnancy complications or in perinatal morbidity and mortality in women with subclinical hyperthyroidism [24].

Hematologic

Pregnancy is characterized by both quantitative and qualitative changes in the hematologic system. These changes can be adaptive to normal pregnancy but can also put the pregnant women at increased risk for certain pathologic conditions. Anemia and thrombocytopenia are commonly diagnosed during pregnancy, as will be discussed later. Measurements of the acute-phase response, such as erythrocyte sedimentation rate, C-reactive protein, and white blood cell count, have been found to increase during pregnancy. This presents a challenge in the evaluation of pregnant women suspected to have various infectious or inflammatory conditions, but careful clinical assessment allows the practitioner to distinguish between physiologic and pathologic abnormalities in these tests. Pregnancy also has important effects on the coagulation system, with the creation of an overall **hypercoagulable state**. This section also reviews the theories and limitations of the evidence surrounding the diagnosis of thrombophilia during pregnancy.

Anemia is usually defined as a hemoglobin less than 11 g/dL and hematocrit less than 33% in the first trimester, hemoglobin less than 10.5 g/dL and hematocrit less than 32% in the second trimester, and hemoglobin less than 11 g/dL and hematocrit less than 33% in the third trimester (see also Chap. 14 in *Maternal-Fetal Evidence Based Guidelines*). Anemia may be caused by decreased production of red blood cells, increased destruction of red blood cells, or blood loss. Anemia in pregnancy is complicated by increased iron requirements and an expanded blood volume. Blood volume increases by about 50%, while red blood cells increase by only about 25%, resulting in an anemia of dilution, as measured by hemoglobin and hematocrit, that is physiologic in pregnancy. **Iron requirements increase** in order to support the increase in red blood cell mass, to meet the requirements of the fetus and placenta, and to prepare for blood loss during delivery. **Iron-deficiency anemia** is characterized by microcytosis and hypochromatosis. Iron studies reveal a decrease in total iron and ferritin and an increase in total iron-binding capacity (TIBC). **Ferritin levels** have the highest sensitivity and specificity for iron deficiency, with levels less than 10–15 μg/dL being diagnostic of iron deficiency [25]. Iron supplementation, as well as screening for iron deficiency, during pregnancy is recommended by the Centers for Disease Control and Prevention (CDC). The typical diet contains 15 mg of elemental iron per day, while the recommended dietary daily allowance during pregnancy is 27 mg/day (see Chap. 14 in *Maternal-Fetal Evidence Based Guidelines*) [26].

Iron-deficiency anemia in pregnancy has been associated with an increased risk of low birth weight, prematurity, perinatal mortality, postpartum depression, and poor mental and psychomotor testing in offspring. Severe anemia (less than 6 g/dL) has been associated with abnormal fetal oxygenation, abnormal fetal heart rate patterns, reduced amniotic fluid volumes, cerebral vasodilation, and fetal death. Transfusion may be indicated for fetal indications in the case of anemia of this severity [26]. Factors that increase the risk for iron deficiency in pregnancy include young maternal age, heavy menses, short interpregnancy interval, low socioeconomic status, and non-Hispanic black race [26]. Dietary factors can have a significant effect on

iron levels, not only due to levels of consumption of iron-rich foods but also due to consumption of foods that significantly enhance or inhibit iron absorption.

Megaloblastic macrocytic anemia may be caused by deficiency of folic acid and vitamin B_{12} and by pernicious anemia. Nonmegaloblastic macrocytic anemia may be caused by alcoholism, hypothyroidism, liver disease, aplastic anemia, or increased reticulocyte count. The most common cause of onset of macrocytic anemia during pregnancy in the United States is folic acid deficiency [26]. During pregnancy, daily folic acid requirements increase from 50 μg to 400 μg [26]. Women who have had gastric surgery and those with Crohn disease may be at risk of vitamin B_{12} deficiency in pregnancy [26].

The performance of complete blood counts as a part of routine prenatal screening results in a frequent diagnosis of **thrombocytopenia** in asymptomatic pregnant women. The mean platelet count in pregnant women is lower than in nonpregnant women (average 213,000/μL), with **7%–12%%** of pregnant women meeting criteria for the diagnosis of thrombocytopenia by delivery [27]. Manifestations of thrombocytopenia include epistaxis, petechiae, and ecchymosis, although frequently there are no clinically significant effects. Clinically significant spontaneous bleeding is rare except with exceptionally low platelet counts, and platelet transfusion is only recommended for surgery if platelet count is less than 50,000/μL [27]. **The most common cause of thrombocytopenia in pregnancy is gestational thrombocytopenia**, which is an apparently benign condition whose underlying physiology is not well understood. However, thrombocytopenia in pregnancy may also be caused by more severe underlying conditions such as preeclampsia, human immunodeficiency virus infection, immune thrombocytopenic purpura (ITP), systemic lupus erythematosus, antiphospholipid antibody syndrome, hypersplenism, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, congenital thrombocytopenia, or medication effect [27]. Most of these conditions can be ruled out by history, physical exam, and exclusion of underlying diagnoses.

The most difficult differential usually comes down to gestational thrombocytopenia versus **ITP**. These conditions cannot be reliably differentiated with antiplatelet antibody testing or any other diagnostic test. **A platelet count <100,000/μL is typically more concerning for ITP, and a platelet count <50,000/μL is almost certainly ITP as opposed to gestational thrombocytopenia** [27]. In order to be classified as gestational thrombocytopenia, several conditions must be satisfied. **Gestational thrombocytopenia is mild, with platelet counts typically greater than 75,000/μL**. There is no history of significant bleeding and no history of thrombocytopenia prior to pregnancy. Platelet counts generally return to normal within 4–8 weeks following delivery, and there is an extremely low risk of fetal or neonatal thrombocytopenia. ITP is a clinical diagnosis and a diagnosis of exclusion of other systemic disorders known to be associated with thrombocytopenia. Although it can be associated with elevated antiplatelet antibodies, this is not a recommended part of the diagnostic evaluation [27].

Women with gestational thrombocytopenia are not at risk for maternal or fetal hemorrhage or bleeding complications [27], whereas immunologic thrombocytopenia such as ITP and neonatal alloimmune thrombocytopenia (NAIT) have the potential for fetal complications. Both are characterized by increased platelet destruction. In retrospective studies, **8%–20% percent of neonates born to mothers with ITP may develop platelet counts less than 50,000/μL** [28, 29]. This may result in findings such as purpura, ecchymosis, or melena. Less commonly, fetal intracranial hemorrhage develops in 1% of deliveries, unrelated to mode of delivery. Therefore, the American Congress of Obstetricians and Gynecologists (ACOG) recommends no change in the route of delivery based on ITP alone. However, the use of vacuum extractors and fetal scalp electrodes should be avoided due to the increased risk of hemorrhage [27].

Onset of thrombocytopenia during the third trimester should prompt consideration of hypertensive disorders of pregnancy, which are associated with 5%–21% of cases of maternal thrombocytopenia, and decreasing platelet count is considered a sign of worsening of disorders of this spectrum (see also Chap. 1 in *Maternal-Fetal Evidence Based Guidelines*). When combined with hemolytic anemia and elevated liver tests, thrombocytopenia is indicative of the diagnosis of hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome. These disorders are associated with an increase in platelet consumption, but the underlying physiology is not known. Platelet function may be reduced even if platelet counts are normal, and thrombocytopenia may occur prior to other manifestations of gestational hypertension. Hemorrhage is uncommon in the absence of disseminated intravascular coagulation. Neonatal thrombocytopenia following gestational hypertension is increased in premature infants but not in term infants [27].

Pregnancy is associated with significant alterations in the **coagulation system**. **There is a decrease in protein S levels as well as in coagulation factors XI and XIII. There is an increase in coagulation factors I, VII, VIII, IX, and X. D-dimer and fibrinogen levels** also increase. The overall result is the creation of a **hypercoagulable state** that is exacerbated by venous stasis and compression of the inferior vena cava and pelvic veins by the enlarging uterus [30]. This places the pregnant woman at increased risk for such phenomena as deep venous thrombosis and pulmonary embolism, which are further elevated when pregnancy is associated with other high-risk states such as obesity, prolonged immobility (bed rest), or surgery (see also Chap. 28 in *Maternal-Fetal Evidence Based Guidelines*). Consideration of these risks is important in the evaluation of the pregnant patient with unilateral lower extremity edema or acute dyspnea. They also warrant caution and the responsibility to practice evidence-based medicine rather than erroneously recommending "bed rest" for treatment of conditions ranging from threatened abortion, to preterm contractions, to gestational hypertension.

Gastrointestinal

Changes in gastrointestinal physiology lead to some of the most commonly described discomforts of pregnancy ranging from nausea and vomiting in early pregnancy to more persistent symptoms of gastroesophageal reflux and constipation. However, gastrointestinal symptoms may reflect coexisting diseases or may even herald life-threatening complications of pregnancy such as severe preeclampsia and HELLP syndrome or acute fatty liver of pregnancy (AFLP). Once again, it becomes crucial for the obstetric care provider to be skilled in recognizing signs and symptoms that result from normal pregnancy physiology and distinguishing those of more serious conditions.

There are several recognizable effects of pregnancy on gastrointestinal function. Gastric secretion acidity declines but volume increases, and relaxation of the cardiac sphincter leads to greater esophageal reflux [1]. Combined with a **decrease in gastric and**

intestinal motility, this leads to the "full stomach" effect that puts pregnant women at increased risk of aspiration. This, combined with increased airway edema, increases the risks of general endotracheal anesthesia during pregnancy. Thus, for anesthesia purposes, all pregnant women are considered to have a full stomach. Precautions to reduce aspiration risk include the use of nonparticulate oral antacids prior to induction of anesthesia, the use of rapid-sequence induction methods, and the use of a cuffed endotracheal tube [1].

During pregnancy, there is a decrease in colonic motility and an increase in water absorption, leading to **constipation** as a common complaint among pregnant women. A prospective study of constipation in pregnancy found that one in two women reports constipation at some point in pregnancy, with rates of 24%, 26%, 16%, and 24% in first, second, third trimesters, and postpartum, respectively. Constipation is more likely in women with a prior history of constipation and in women taking iron supplements. The study did not include nonpregnant controls, but historic controls indicate a constipation rate of 7% in a similar age group [31].

The most common gastrointestinal symptom of pregnancy is **nausea and vomiting** (see also Chap. 9 in *Maternal-Fetal Evidence Based Guidelines*). As many as 80% of women report nausea during pregnancy, and it is also the most common reason for hospitalization in the first trimester [32, 33]. Nausea is generally considered a normal symptom of early pregnancy, and morning sickness has been associated with improved pregnancy outcomes such as reduced risk of miscarriage, preterm birth, low birth weight, and perinatal death. This is theorized to be due to a placental etiology for nausea and vomiting, which is increased by early development of a healthy and robust placenta [33]. However, the exact etiology of this symptomatology is not known. It has been hypothesized that nausea and restricted intake in the mother create an environment that is favorable for early placental development [34] or that it confers an evolutionary advantage by causing the mother to avoid the ingestion of foods that may be dangerous to the developing fetus [33]. Numerous psychological theories have also been proposed to explain the phenomenon of nausea and vomiting in pregnancy. Nausea in pregnancy is commonly attributed to hCG levels, but conclusive evidence of the underlying physiology is lacking. Experience of nausea is also correlated with elevated estradiol levels and inversely correlated with prolactin levels [32]. Estrogens in oral contraceptive pills have shown a dose-related effect of nausea and vomiting. Smoking decreases both hCG and estrogen, and a reduced rate of nausea and vomiting of pregnancy has been demonstrated in smokers. Increased placental mass, as found in multiple gestations and gestational trophoblastic disease, has been found to increase the risk of nausea and vomiting and of hyperemesis gravidarum [33].

It is important for nausea and vomiting of pregnancy to be distinguished from that resulting from other pathologic conditions. Complacency in the evaluation of pregnant patients with nausea and vomiting may result in undertreatment of distressing symptoms, development of hyperemesis gravidarum, or failure to diagnose a coexisting underlying disease. Nausea and vomiting of pregnancy typically start before 9 weeks' gestation and are not accompanied by fever, abdominal pain, or headache [33]. Deviation from this presentation should prompt evaluation for other etiologies. The differential diagnosis includes gastrointestinal disorders such as gastroenteritis, gastroparesis, achalasia, biliary tract disease, hepatitis, intestinal obstruction, peptic ulcer disease, pancreatitis, and appendicitis. Genitourinary conditions that may cause nausea and vomiting include pyelonephritis, uremia, ovarian torsion, kidney stones, and degenerating myoma. Nausea and vomiting may also be due to metabolic disorders such as diabetic ketoacidosis, porphyria, Addison disease, and hyperthyroidism or neurologic disorders such as pseudotumor cerebri, vestibular lesions, migraines, or central nervous system tumors. Finally, drug-related toxicity, psychologic factors, or pregnancy-related complications such as preeclampsia and AFLP may present with nausea and vomiting [33].

Patients who are taking a multivitamin at the time of conception have reduced rates of nausea and vomiting [33]. There is good evidence to support the use of vitamin B_6 alone or combined with doxylamine for the treatment of nausea and vomiting in pregnancy. Ginger supplements have also been shown to reduce severity of nausea and vomiting [33, 35]. Numerous antiemetics have also shown acceptable safety and efficacy against nausea and vomiting, with no antiemetics demonstrating superiority in a meta-analysis [36]. A single database study of 1349 patients demonstrated an increase in cardiac septum defects with Zofran administered in early pregnancy (odds ratio [OR] 1.62, 95% CI 1.04–2.14) [37], but this should not stop providers from prescribing Zofran if it effects symptomatic relief. Hospitalization, intravenous fluids, and enteral nutrition may be used in rare cases of continued weight loss in spite of these therapies (see also Chap. 9 in *Maternal-Fetal Evidence Based Guidelines*). Treating nausea and vomiting earlier in the course can help prevent progression to hyperemesis and the need for these more invasive treatments [33].

Renal system and homeostasis

Pregnancy-related changes in the urinary tract include dilation of calyces, pelvis, and ureters. Ureteral dilatation and mild hydronephrosis may be noted as early as the first trimester and is present in 90% of gravidas by term. Obstructive and humoral mechanisms have been proposed for this dilatation, with obstruction by the gravid uterus and ovarian venous plexus likely causing the dilatation above the pelvic brim [38, 39]. Dextrorotation of the gravid uterus, likely due to the sigmoid colon on the left and posterior to the uterus, causes the mechanical obstruction at the pelvic brim on the right more than the left. One important adverse consequence of this ureterocalyceal dilatation is the increased incidence of pyelonephritis among gravidas with asymptomatic bacteriuria.

There are significant increases in renal blood flow and in glomerular filtration rate (GFR) in pregnancy [1]. Indeed, GFR increases up to 50% higher than in the nonpregnant state. As a result, serum urea and creatinine levels decline in pregnancy [40]. This can have significant effects on renal clearance of vitamins and pharmaceutical agents. There is a lowering of the threshold for glucose excretion, which may result in significant random glucosuria even in the absence of gestational diabetes. This glycosuria may also contribute to the increased susceptibility of pregnant women to urinary tract infections.

There is also a marked increase in ureteral pressure in the third trimester while standing or sitting that is decreased when in the lateral recumbent position [38]. This has implications for collection of 24-hour urine samples, as retention of urine in the dilated collecting system may result in an incomplete sample. This may be alleviated by instructing the patient to lie in the lateral recumbent position for about 45 minutes before the discard void prior to starting the collection and again before the final void of the sample [38]. Proteinuria is considered abnormal if excessive of 300 mg/24 hours in pregnant patients [38].

Relaxin and nitric oxide (NO) have been implicated as key factors in mediating the renal vasodilation and glomerular hyperfiltration that are characteristic of normal human pregnancy. In vivo, relaxin administration to male and nonpregnant female rats produced physiologic changes that mimicked normal pregnancy, with a decrease in systemic vascular resistance along with significant increases in effective renal plasma flow (RPF) and, hence, GFR [40].

Pregnancy is associated with altered tubular function and therefore altered reabsorption of protein, glucose, amino acids, and uric acid. In contrast to tubular function, our knowledge of the factors that govern gestational changes in serum electrolytes is somewhat more definitive. Total body sodium increases on an average by 3–4 mEq/day, ultimately producing a net balance of 900–1000 mEq, and total body potassium also increase by up to 320 mEq by the end of gestation [40]. Despite the net increase in body stores of sodium and potassium (Table 3.1), serum levels of both electrolytes decrease during pregnancy (Table 3.2). Therefore, pregnancy is characterized by an increase in total body electrolyte stores, albeit with decreases in serum levels. Clinicians must recognize that increments in serum electrolytes that still fall within the normal range may constitute meaningful aberrations in electrolyte balance. Furthermore, conditions prone to either electrolyte retention or loss may be exacerbated during pregnancy [40].

Pharmacokinetics

It may be helpful to conclude with a final clinical topic that illustrates many of the previously described physiologic changes: that of pharmacokinetics. **The four major events involved in pharmacokinetics (absorption, distribution, metabolism, and excretion) are potentially altered by physiologic changes of pregnancy in a number of organ systems**. Absorption is affected by changes in gastric pH, gastric emptying, and small intestine motility. Increased cardiac output and heightened blood flow to the stomach and small intestine can increase absorption [41]. Changes in plasma volume, body fat, and total body water affect drug distribution, and the proportion of unbound fraction of certain drugs may increase due to a decrease in protein concentration. Metabolism is affected by upregulation or downregulation of various enzymes. For example, liver cytochrome p-450 activities increase, while CYP1A2 activity decreases and extrahepatic cholinesterase activity decreases [41]. Drug excretion is affected by the increased renal blood flow and elevated GFR of pregnancy, as well as by increased respiratory elimination [41]. This has important implications for both the maintenance of therapeutic drug levels and the avoidance of toxicity. **Clinical evidence to guide pharmacologic therapy in pregnancy is limited**, in part due to the frequent elimination of women of reproductive age from pharmacokinetic trials. A review of the National Library of Medicine database shows that **there are a very limited quantity of pharmacokinetic data for pregnancy**, and thus evidence-based recommendations for dosing and scheduling of drugs during pregnancy are sparse [41].

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4

ULTRASOUND

L. M. Porche, S. P. Chauhan, and A. Abuhamad

Key points

- There is **no evidence that ultrasound examination during pregnancy is harmful**. Prenatal exposure to ultrasound is not associated with adverse influence on school performance, physical, or neurologic function.
- Ultrasound should be performed by **trained and experienced professionals**, with continuing education and ongoing quality-monitoring programs.
- **Routine use of ultrasound** in pregnancy increases early detection of **multiple pregnancies, major fetal anomalies, abnormalities of amniotic fluid, and fetal growth**.
- **Ultrasound examination is the best method to estimate accurate gestational dating in pregnancy**.
- **Ultrasound** dating in the first trimester is most accurate for gestational age assessment. **Ultrasound examination at first prenatal visit** (**usually *first trimester***) versus at 18–20 weeks **provides more precise estimate of gestational age and may be associated with less maternal worry**. First-trimester ultrasound **allows earlier detection of multiple pregnancies, screening for Down syndrome with nuchal translucency,** and **diagnosis of nonviable pregnancies**.
- **All pregnant women should** also **be offered a *second-trimester* ultrasound for optimal anatomy evaluation**. If only one ultrasound will be done in pregnancy, it should be done in the second trimester at about 20 (18–22) weeks.
- Measurement of **cervical length** (CL) by transvaginal ultrasound (TVU) has been shown to be an effective predictor of preterm birth. When a short CL ≤25 mm is detected before 24 weeks, interventions such as vaginal progesterone in singletons without prior preterm birth (PTB) and cerclage in singletons with prior PTB (these women would already be on progesterone, given the prior PTB) have been associated with a decrease in PTB and perinatal morbidity and mortality.
- In low-risk or unselected populations, **routine *third-trimester* (>24 weeks) pregnancy ultrasound has not been associated with improvements in perinatal mortality**, albeit the sample size might lack power to detect a difference.
- In **low-risk or unselected populations**, **routine Doppler ultrasound examination** in the third trimester does **not reduce perinatal mortality**.
- In pregnancies with fetal growth restriction, umbilical artery Doppler assessment is associated with a **reduction in perinatal deaths and obstetric interventions**.
- **Intrapartum ultrasound can be used to assess fetal head position and station** in the setting of arrested labor or in preparation for operative vaginal delivery.
- **Suspected placenta accreta spectrum should be referred to a center with experience** diagnosing and managing patients with this condition.

Safety of ultrasonography

The main concern about the safety of ultrasound is based on tissue temperature elevation from energy transfer and its possible effect of cavitations, or the formation of microbubbles in the tissues exposed to ultrasound waves. The effect of ultrasound on tissues has been studied with animal experimentation and has suggested an adverse effect. In humans, however, the information comes from epidemiologic data and population studies. **No epidemiologic studies have shown harmful effects in humans**.

There is no consistent evidence that ultrasound examination during pregnancy is harmful. Studies have shown that prenatal exposure to ultrasound is not associated with adverse effects on children's physical or cognitive development [1]. Even multiple ultrasound exams during pregnancy were not shown to adversely affect speech, language, behavior, or neurologic function on postnatal follow-up at 8 years of age [2]. In a randomized trial comparing those receiving a second-trimester ultrasound to those who remained unexposed, there was no significant difference in school performance up to age 15–16 [3]. Overall, ultrasound in pregnancy is not associated with adverse maternal or perinatal outcome; however, there may be a weak association between exposure to ultrasound and non-right-handedness in boys [4].

Despite the lack of evidence suggesting harmful effect, ultrasound is a form of energy and may produce secondary effects in the tissues it traverses. Obstetrical ultrasound in pregnancy should be considered a medical procedure for the evaluation of the fetus and maternal pelvic organs. Current expert consensus recommends that **ultrasound be only performed with valid medical indications, with the shortest duration possible and at the lowest settings. Adhering to the ALARA principle (As Low As Reasonably Achievable)** helps avoid unnecessary exposure to ultrasonic waves. Sonographers and sonologists should familiarize themselves with the mechanical and thermal indices during ultrasound examinations. **Exposing the fetus to ultrasonography with no anticipation of medical benefit is unjustified** [5, 6].

Quality

Levels of expertise vary between different health care centers. Since ultrasound efficiency is operator-dependent, **continuing education and ongoing quality-monitoring programs are important** strategies in each center offering ultrasound diagnosis. The ongoing risks of "false-negative" tests and/or misinterpretation of the images obtained (either false-positives or wrong diagnoses) can be minimized if those examinations are carried out and interpreted by **trained and experienced professionals**. Sensitivity of ultrasound screening for pregnancy varies widely. **Appropriate ultrasound laboratory accreditation, certification of staff, documentation of findings, and continuous**

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careful quality control are important components of ultrasound competency [5, 6].

Informed consent and patients' expectations

Even though a formal written informed consent is not always needed **before the examination, every pregnant woman should be informed on expectations about the obstetric ultrasound, as well as its benefits and risks**. Patients should know that ultrasound evaluation is a screening test with wide variations in detection rates for fetal anomalies and that all ultrasound diagnoses, especially false-positive and false-negative ones, can put both mother and fetus at risk.

Whether the sex of the fetus should be revealed to the patient with a singleton gestation should be addressed. It may be harmful for the physician–patient relationship to withhold this information, especially if the patient previously requested it. Although a moral conflict may exist in some cultures around the world where this information is used by the patient for voluntary abortions based on sex selection and sex preferences [7], **in general disclosing fetal gender during ultrasound can benefit not only the doctor–patient relation but also the parent–child relationship** [8].

During high-feedback ultrasound scans, women can see the screen and they receive detailed explanations of the images. In low-feedback ultrasound scans, only the operator can see the screen and the women are told the results at the end of the scan. Compared to low-feedback ultrasound, women who had high-feedback fetal ultrasound are significantly more likely to stop smoking and avoid alcohol during pregnancy, with a trend favoring the women's increased use of positive adjectives to describe their feelings after the ultrasound [9].

Routine vs. selective use of ultrasound

Routine (i.e. performed on every pregnant woman) ultrasound examination is associated with the following, compared to **selective** ultrasound examination (i.e. performed only on women with specific indications) [1]:

1. **Increases the early detection of multiple pregnancies**.
2. **Increases the detection of major fetal anomalies**.
3. **Reduces the incidence of late-term and post-term pregnancies and rates of induction of labor for late-term pregnancy** by allowing a more precise estimation of gestational age.
4. **No significant differences are detected for clinical outcomes such as perinatal mortality**. The effect of ultrasound on perinatal mortality is dependent on the detection rate of fetal malformations and on the uptake of pregnancy termination for anomalies in the population at study.

If one routine ultrasound examination is done, it is usually performed at 18–22 weeks (<24 weeks). Earlier examination provides more accurate assessment of gestational age; later examination (e.g. 20–22 weeks) allows more complete inspection of fetal anatomy. **In the obese population, transabdominal ultrasound screening may have better completion rates if delayed by 2 weeks** (20–22 weeks' gestation) [10], and transvaginal ultrasound at 12–16 weeks may offer better fetal anatomy screening (see later in this chapter).

Gestational age dating in pregnancy

Precise estimation of gestational age is extremely important for optimal obstetric care, including evaluation of fetal growth, interpretation of maternal screening markers, choosing the appropriate gestational age to perform interventions, and management of preterm and late-term pregnancies.

For gestational age estimation, cardinal numbers should be preferred to ordinal numbers to avoid confusion. So week 1 is 1–7 days after last menstrual period (LMP), week 2 is 8–14 days, etc. In clinical practice, gestational weeks are used to estimate dating, not months. If a lay person asks, "How many months am I?" then 6 weeks of gestation can be equated approximately to 1 month, etc., and 38 weeks = 9 months. **Definitions of gestational age**, while not uniformly accepted, **are shown in Table 4.1** [10].

Ultrasound examination is the best method to determine gestational age and estimated due date (EDD) [10]. The first day of the LMP should be asked of all pregnant women to determine when the dating ultrasound should be performed. Compared with LMP, ultrasound-based gestational age is more precise due to errors in patient recall and variations in cycle length and timing of ovulation [10, 11]. The error, even with certain LMP, is due often to late ovulation (>14 days after LMP). Some have stated that there is no reason to use LMP for dating when adequate ultrasound data are available by 24 weeks [10, 11].

Ultrasound-based gestational age estimates are lower than LMP-based gestational age estimates and generate a higher rate of preterm birth and lower rate of post-term birth. The Naegele rule (add 7 days to first day of LMP, add 1 year, take back 3 months), manual assessment of uterine size, quickening, etc., should not be used unless ultrasound dating is unavailable.

In general, **the earlier the ultrasound, the more accurate the dating**. Multiple parameters and equations have been evaluated to estimate gestational age. **The crown–rump length (CRL) is associated with the most accurate estimation, up to and including 13 6/7 weeks of gestation with an accuracy of ±2–7 days**. For pregnancies in the second trimester, beyond 14 weeks' gestation, the head circumference or biparietal diameter (BPD) appears to be the best single-measurement predictor of gestational dating. BPD is most accurate for dating early, between 12 and 14 weeks. Combining three or more parameters improved dating slightly over a single biometric parameter [12]. A combination of BPD, head circumference (HC), abdominal circumference (AC), and femur length (FL) is commonly used for dating by ultrasound in the second and third trimesters [13]. Repeated examinations improve the prediction only marginally, and the

TABLE 4.1: Definition of Gestational Age Periods in Pregnancy

Period	Gestational Age (Weeks)
First trimester	0–13 6/7
Second trimester	14 0/7–27 6/7
Third trimester	28 0/7 to delivery
Preterm	20 0/7–36 6/7
Late preterm	34 0/7–36 6/7
Term	37 0/7–41 6/7
Early term	37 0/7–38 6/7
Full term	39 0/7–40 6/7
Late term	41 0/7–41 6/7
Post term	42 0/7 to delivery

Source: Adapted from Ref. [10].

TABLE 4.2: Gestational Age Dating by Ultrasound

Gestational Age by Ultrasound (Weeks)	Best Ultrasound Parameter(s)	EDD Changed If Discrepancy from LMP Dates More Than (Days)
<9	CRL	5
9 0/7–13 6/7	CRL	7
14 0/7–15 6/7	BPD, HC, AC, FL	7
16 0/7–21 6/7	BPD, HC, AC, FL	10
22 0/7–27 6/7	BPD, HC, AC, FL	14
≥28 0/7	BPD, HC, AC, FL	21

Source: Adapted from Ref. [16].

Note: IVF pregnancies can be dated by the date of embryo transfer minus 14 days to obtain LMP and then EDC by Naegele rule. There is no need to ever change dating in these pregnancies.

Abbreviations: CRL, crown–rump length; BPD, biparietal diameter; HC, head circumference; AC, abdominal circumference; FL, femur length.

TABLE 4.3: Indications for First-Trimester Ultrasound

- Confirmation of the presence of an intrauterine pregnancy
- Confirmation of cardiac activity
- Estimation of gestational age
- Diagnosis or evaluation of multiple gestations, including determination of chorionicity
- Evaluation of suspected ectopic pregnancy
- Evaluation of cause of vaginal bleeding
- Evaluation of pelvic pain
- Evaluation of suspected gestational trophoblastic disease
- Assessment for certain fetal anomalies, such as anencephaly
- Measurement of the nuchal translucency when part of a screening program for aneuploidy
- Imaging as an adjunct to chorionic villus sampling, embryo transfer, and localization and removal of an intrauterine device
- Evaluation of maternal pelvic mass and/or uterine abnormalities

Source: Adapted from Refs. [5, 6].

EDD should always be set by the earliest ultrasound due to a smaller prediction error. While prediction of gestational age by ultrasound can be very accurate, prediction of date of delivery remains less accurate, with an error of usually ≥7–8 days, given other biologic factors.

Other parameters that may play a role in estimating gestational age include trans-cerebellar diameter (TCD) and long bone measurements. The TCD is an accurate predictor of gestational age and can be used between 14 and 28 weeks reliably with the use of nomograms. There is some reliability in gestational age prediction even up to 35 weeks, and TCD is spared the effects from intrauterine growth restriction and so can be used to assess pregnancies at risk for this complication [14]. The presence of epiphyses in the lower extremities usually signifies a gestational age of >32 weeks [15].

The American College of Obstetricians and Gynecologists (ACOG) has published specific guidelines to guide amendment of dating when ultrasound and LMP are discrepant. Ultrasound dating is adopted when discrepancy is noted. Knowledge about LMP, regularity of cycles, oral contraceptive (OCP) use, and unusual bleeding are clinically helpful but imprecise regarding dating. **Ultrasound dating is best** and often corrects dating by even a "certain" LMP [16]. Table 4.2 shows dating criteria based on ultrasound results.

Ultrasound examinations by trimester

First trimester

Ultrasonographic evaluation in the first trimester (0–13 6/7 weeks) is the most accurate method to determine exact gestational age, as discussed earlier. **Ultrasound examination at the first prenatal visit versus at 18–20 weeks provides more precise estimate of gestational age and may be associated with less maternal worry**. First-trimester ultrasound also allows **earlier detection of multiple pregnancies, nonviable pregnancies, certain fetal anomalies, and screening for Down syndrome and other aneuploidy with nuchal translucency (NT)** [1, 6, 17]. Current guidelines recommend the routine use of ultrasound in the first trimester for the appropriate indications (Table 4.3). Guidelines for the performance of the detailed-first trimester ultrasound were recently introduced for high-risk pregnancies [5, 10].

Transvaginal scanning is preferred for dating early in the first trimester. It is also useful in cases of a pregnancy resulting from ovulation induction or other assisted reproductive technologies, first-trimester bleeding, or increased risk of aneuploidy and should be used if transabdominal examination is inconclusive for diagnosis. First-trimester screening for congenital defects by transvaginal ultrasound is an option for pregnant women who meet certain criteria, such as a very high risk for congenital anomalies (e.g. very elevated Hgb A1c) and who may elect termination based on abnormal results. It should be done by experienced sonographers and the findings confirmed at 18–22 weeks [10]. In a randomized controlled trial (RCT), 38% of major malformations and 69% of lethal malformations were detected by a 12- to 14-week ultrasound [18]. In a meta-analysis, 51% of malformations were found to have been detected by 11- to 14-week ultrasound [19].

The **NT** is a physiologic fluid-filled space at the back of the fetal neck measured for aneuploidy screening between weeks $10^{6/7}$ and $13^{6/7}$ of gestation. Increase in NT has been associated with chromosomal and anatomic abnormalities in the fetus. First-trimester screening for aneuploidy between 10 6/7 and 13 6/7 weeks (or CRL 45–84 mm) combines NT measurement with maternal serum markers to provide individualized risk assessment. Early risk determination permits choosing the most appropriate definitive diagnostic procedures, like chorionic villus sampling, allowing women to prepare for a child with health problems and also providing the option of earlier pregnancy termination (see Chap. 5) [6].

Indications for first-trimester ultrasound as endorsed by the ACOG, American Institute of Ultrasound in Medicine (AIUM), Society for Maternal Fetal Medicine (SMFM), American College of Radiology (ACR), and Society of Radiologists in Ultrasound (SRU) are shown in Table 4.3, and essential elements of first-trimester ultrasound are listed in Table 4.4 [5, 6].

Ultrasound diagnosis of anembryonic or embryonic demise

Diagnostic criteria for the diagnosis of nonviable pregnancy in the first trimester is a subject that has undergone recent revision. Balancing risk of harming a viable intrauterine pregnancy must be balanced with intervention for a nonviable one. Some criteria are routinely used (Table 4.5), usually based on **transvaginal ultrasound**: absence of cardiac activity with an embryo of a

TABLE 4.4: Essential Elements of First-Trimester Ultrasound

- Gestational sac (location, mean diameter)
- Yolk sac (diameter)
- Crown–rump length of embryo (CRL)[a]
- Development of fetal anatomy in early pregnancy
- Fetal viability (cardiac activity should be seen in embryo >7 mm)
- Fetal number (amnionicity and chorionicity has to be reported for multiples)
- Ultrasound features of early pregnancy failure (e.g. ectopic pregnancy, hydatidiform mole)
- Uterus, adnexa, cervix, and cul de sac
- If possible, the appearance of the nuchal region should be assessed and specific measurement of nuchal translucency measured as part of desired screening
- Any other abnormalities (e.g. leiomyomata, etc.)

Source: Adapted from Refs. [5, 6, 20].

[a] CRL is a more accurate indicator of gestational age than gestational sac size.

certain length, absence of an embryo with a gestational sac of a certain size, and absence of an embryo by a certain time in pregnancy [20].

A gestational sac is normally noted within the uterus by 5 weeks of gestation. Shortly thereafter at approximately 5 ½ weeks in a normal pregnancy, the yolk sac appears, followed by the fetal pole at 6 weeks. When measuring the gestational sac, dimensions are recorded in three orthogonal planes; the average of the measurements is the mean sac diameter. A **mean gestational sac diameter of ≥25 mm without an embryo** is diagnostic of pregnancy failure (e.g. anembryonic pregnancy, or blighted ovum) with positive predictive value approaching 100% [21] (See also Chap. 16). An intrauterine gestational sac should be visible by transvaginal ultrasound with a serum beta-human chorionic gonadotropin (B-hCG) of >1500 mIU/mL. If this is not the case, ectopic pregnancy should be suspected.

Fetal cardiac activity is usually seen once the fetal pole is visible around 6 weeks of gestation. A CRL cutoff of 5 mm without cardiac activity was previously used to diagnose nonviable pregnancy, but a literature review showed that there have been pregnancies that met this criterion that went on to be viable [21, 22]. Interobserver variability in measurements can also lead to inaccurate diagnosis of failed pregnancy. Adopting a **CRL cutoff of 7 mm with no visible cardiac activity** brings the specificity of this finding for diagnosing failed pregnancy (e.g. embryonic demise, or missed abortion) close to 100% [20].

Since the presence of intrauterine structures in a viable pregnancy appear in a predictable sequence at standard time intervals [23], aberrations in this sequence can indicate abnormal pregnancy. Abnormal pregnancy should thus be suspected in the **absence of an embryo with a heart beat ≥14 days after seeing a gestational sac without a yolk sac, or ≥11 days after presence of a gestational sac with a yolk sac** [20]. The presence of normal embryonic cardiac activity in the uterine cavity in the first trimester has a >90% prediction for a live birth in both symptomatic and asymptomatic pregnancies (See also Chap. 16).

TABLE 4.5: Criteria for Diagnosis of Embryonic or Anembryonic Demise

Diagnosis	Criteria
Anembryonic pregnancy	Mean gestational sac diameter ≥25 mm without an embryo
Embryonic demise	CRL ≥7 mm with no visible cardiac activity
Anembryonic pregnancy	No embryo with cardiac activity: ≥14 days after gestational sac without yolk sac Or ≥11 days after gestational sac with yolk sac

Source: Adapted from Ref. [20]. (See also Chap. 16.)

Abbreviation: CRL, crown–rump length.

Precautions and pitfalls

Physiologic midgut herniation is normal at 7–11 weeks; it resolves at ≥12 weeks; do not confuse with omphalocele. The rhombencephalon can appear as a cystic mass up until 8–10 weeks and should not be confused with a CNS anomaly; ventriculomegaly cannot be assessed well in the first trimester. The amnion and chorion are expected to be fused by 14 weeks.

Second trimester (aka "Anatomy," "Morphology," or "Standard" ultrasound)

If just a single exam is to be done during pregnancy, the best timing for such ultrasound screening of the fetal anatomy and dating is the early to mid-second trimester (18–22 weeks) [1] to obtain an accurate estimation of gestational age and a satisfactory inspection of the fetal anatomy. This is therefore usually called the anatomy, morphology, or standard ultrasound examination (nomenclature such as Level I, II, etc., ultrasound is controversial and less descriptive). All **pregnant women should be offered a second-trimester ultrasound**, whether or not they have had a first-trimester ultrasound. **The estimated sensitivity to detect fetal anomalies varies widely**, with higher rates of detection for major anomalies than for minor anomalies and some organs (e.g. neural tube defect) vs others (e.g. heart) [19]. The detection of major fetal anomalies is often reported at about 50%–70% even in the best centers [18]. The detection of fetal cardiac malformations is particularly poor, with often not more than 20%–30% of major heart malformations detected [24]. A "**detailed" ultrasound** can be performed with the aim to detect anomalies or markers associated with fetal aneuploidy (see later) [25].

While the best time for detection of most malformations is around 20–24 weeks, it is important for women to obtain this information as early as possible. In some circumstances, more than one second-trimester ultrasound is necessary, especially if the initial second-trimester ultrasound is performed at 18–19 weeks. Experts have suggested essential elements for the standard second-trimester ultrasound (Table 4.6) [5, 6].

There can be other types of follow-up ultrasounds. **Limited ultrasound examination** is performed when a specific question requires investigation. Examples include assessment of amniotic fluid volume, fetal viability, biophysical profile, to guide amniocentesis, to localize the placenta in antepartum bleeding, or to evaluate fetal position. A limited ultrasound is only appropriate if a prior complete standard ultrasound examination has been done. A **detailed ultrasound examination** should be considered for a patient who, by history, clinical evaluation, or prior scanning evaluation, is at an increased risk for a fetal anatomic or physiologic abnormality. This ultrasound examination must be done by personnel with expertise in obstetric ultrasonography and maternal and fetal diseases [25]. Elements of the detailed exam can be found in the AIUM Practice Parameter for second- and third-trimester obstetric ultrasounds [25].

TABLE 4.6: Essential Elements of Standard Second-Trimester Ultrasound

System	Components
Head and neck	Lateral cerebral ventricles
	Choroid plexus
	Midline falx
	Cavum septum pellucidi
	Cerebellum
	Cisterna magna
Face	Upper lip
Chest	Cardiac activity
Heart	Four-chamber view
Thorax	Left ventricular outflow tract
	Right ventricular outflow tract
	Three-vessel view (if technically feasible)
	Three-vessel trachea view (if technically feasible)
Abdomen	Stomach (presence, size, situs)
	Kidneys
	Urinary bladder
	Cord insertion site into fetal abdomen
	Umbilical cord vessel number
Spine	Cervical
	Thoracic
	Lumbar
	Sacral spine
Extremities	Legs
	Arms
	Hands
	Feet
Genitalia	In multiple gestations
	When medically indicated
Placenta	Location
	Relationship to internal os
	Appearance
	Placental cord insertion
Standard evaluation	Fetal number
	Presentation
	Qualitative or semi-quantitative estimate of amniotic fluid
Maternal anatomy	Cervix (transvaginal when indicated)
	Uterus
	Adnexa
Biometry	Biparietal diameter
	Head circumference
	Femur length
	Abdominal circumference
	Fetal weight estimate

Source: Adapted from Refs. [5, 6].

Other specialized examinations include but are not limited to fetal Doppler studies, biophysical profile, cervical length, 3D imaging, and fetal echocardiography (see later).

Third trimester

The potential benefit of a third-trimester ultrasound examination greatly depends on the quality of prior ultrasounds and maternal indications. If the first and only ultrasound is in the third trimester, it probably has similar benefits to the routine second-trimester ultrasound, with the exception of accurate dating and early anomaly detection of the latter. Ultrasound evaluations in the third trimester generally involve assessments of fetal growth, amniotic fluid volume, evaluation of the placenta, and evaluation of fetal well-being (possibly biophysical profile or Doppler studies). Examples of possible indications for third-trimester ultrasound based on maternal and fetal risk factors are shown in Table 4.7.

The third trimester is the time when abnormalities of fetal growth and amniotic fluid become more apparent. One study showed that routine serial ultrasound examinations in the third trimester significantly increased detection of amniotic fluid abnormalities and abnormal fetal growth in low-risk women when compared to fundal height or indicated ultrasound [26].

In low-risk women, ultrasound examinations at 30–32 weeks and at 36–37 weeks **significantly decrease the likelihood of newborns with growth restriction**, though they do increase the rate of antenatal intervention. This RCT included 1998 women, and investigators calculate over 30,000 women are required for a trial to show a significant decrease in neonatal mortality [27]. In a meta-analysis, there was no difference in antenatal, obstetric, and neonatal interventions in women screened with >24 weeks (late) ultrasound vs. those not screened. There was a slightly higher caesarean section rate in women screened with late ultrasound, but this difference did not reach statistical significance. Routine late pregnancy ultrasound was not associated with improvements in overall perinatal mortality [28]. In a recent RCT, performing a growth ultrasound at 36 weeks was more sensitive in detecting severe fetal growth restriction (FGR) than a scan at 32 weeks (61% vs. 32%). **But despite increased sensitivity, this was not associated with significant differences in perinatal outcomes** [29]. Routine screening for FGR in the third trimester has been investigated also in a large prospective cohort study and may increase detection of fetuses that will go on to be small-for-gestational-age infants, to 57% in routine screening from 20% in selected screening [30]. **Currently, there are insufficient data to recommend routine screening for growth restriction in the third trimester without indication, but many experts advocate its routine use based on the data just described**. There are insufficient data about the potential psychological effects of routine ultrasound in late pregnancy and limited data about its effects on both short- and long-term neonatal and childhood outcome.

FGR is defined as sonographically estimated fetal weight or abdominal circumference of less than the 10th percentile for gestational age. Recent guidelines recommend a diagnosis of severe FGR as estimated fetal weight of less than the third percentile for gestational age. Population-based fetal weight formula, such as the Hadlock formula, is recommended for use. FGR can be categorized as early or late onset. Early-onset FGR is diagnosed prior to 32+0 weeks' gestation. Late-onset FGR is diagnosed after 32+0 weeks' gestation. Detailed anatomic survey should be completed and genetic screening confirmed. Diagnostic amniocentesis with chromosomal microarray should be offered if FGR and fetal anomaly or polyhydramnios is detected regardless of the age at diagnosis. Suggested ultrasound follow-up, antenatal surveillance, and delivery guidelines can be found in the SMFM consult series on this topic [31] (see Chap. 47 in *Maternal-Fetal Evidenced Based Guidelines*).

Large for gestational age (LGA) is defined as an estimated fetal weight or an actual birth weight (BW) of at least the 90th percentile for gestational age. At term a fetus can be LGA without being macrosomic, defined as birth of 4000 grams or more (i.e. BW ≥90th percentile but below 4000 grams). At 37–39 weeks, about 1% of newborns are LGA without being macrosomic.

TABLE 4.7: Suggested Ultrasound Surveillance for Specific Conditions

Condition	Start of Ultrasounds (Weeks)	Frequency of Ultrasounds for Growth (Every X Weeks)
Chronic HTN on medications	24	4
Gestational HTN	At diagnosis	4
Preeclampsia	At diagnosis	4
GDMA1	30–32	once
GDMA2	At diagnosis	4
Pregestational DM on medications	24	4
Fetal growth restriction	At diagnosis	3
Maternal age at delivery ≥35 years	30–32	once
Concordant, non FGR di/di twins	24	4
Mono/di twins	24	4
Mono/mono twins	24	3
Prior unexplained IUFD	28	4
SLE or renal disease	24	4
Organ Transplant	28	4
Hypothyroidism or hyperthyroidism	30–32	once
Maternal cardiac disease	28	4
Oligohydramnios (MVP <2 cm)	At diagnosis	3–4
Polyhydramnios (MVP >8 cm)	At diagnosis	3–4
Sickle cell disease	24	4
Fetal arrhythmia	At diagnosis	4

For expanded suggestions for antepartum fetal testing (e.g. NST, BPs, etc.) and timing of delivery, see Chaps. 23 and 58 in *Maternal-Fetal Evidence Based Guidelines*.

Abbreviations: HTN, hypertension; GDMA, gestational diabetes mellitus; DM: diabetes mellitus; FGR, fetal growth restriction; di/di, dichorionic diamniotic; mono/di, monochorionic diamniotic; mono/mono, monochorionic monoamniotic; IUFD, intrauterine fetal demise; SLE, systemic lupus erythematosus; MVP, maximum vertical pocket.

Compared to newborns whose weight is between the 10th and 89th percentile for gestational age, the nonmacrosomic LGA are at increased risk for adverse outcomes for the mother–newborn dyad, irrespective of whether the individual has diabetes or not. The adverse maternal outcomes among these LGA include increased rate of blood transfusion, ruptured uterus, unplanned hysterectomy, and admission to the intensive care unit (ICU); the complications among nonmacrosomic newborns include stillbirth, Apgar score <5 at 5 minutes, assisted ventilation, seizure, and neonatal death [32, 33].

In the United States, in 2018, there were upward of 290,000 newborns that were macrosomic [34]. Compared to those with BW below 4000 grams, deliveries of those with a weight of at least 4000 grams is associated with a significantly increased likelihood of prolonged labor, chorioamnionitis, cesarean delivery, third- or fourth-degree laceration, postpartum hemorrhage, shoulder dystocia, peripheral neurologic injury, seizure, need for intubation, and neonatal and infant mortality. To avert these multitude of complications, a third-trimester ultrasound exam combined with delivery at term is reasonable.

A meta-analysis by Magro-Malosso et al. [35], which included pooled data from four RCTs, reported on 1190 nondiabetic individuals who were either **induced for macrosomia at 38 weeks** or managed expectantly. Compared to expectant management, those who were induced had a significant decreased rate of fracture and newborns with actual BW ≥4000 grams or of ≥4500 grams. The induction, however, did not decrease the rate of shoulder dystocia, low Apgar score at 7 minutes, brachial plexus palsy, and intracranial hemorrhage. While the authors of the meta-analysis advocate for induction for macrosomia at 38 weeks, it is noteworthy that the ACOG practice bulletin on the topic has a level B (based on limited or inconsistent scientific evidence) recommendation that induction for macrosomia should be deferred until 39 weeks. ACOG's rationale for awaiting delivery until 39 weeks, rather than at 38 weeks, is that currently there is insufficient evidence for the benefits of reducing shoulder dystocia outweigh the purported harms of early delivery [36].

In summary, if on the sonographic exam the fetus is considered to be LGA or macrosomic, induction at 38 weeks can be considered (see Chap. 48 in *Maternal-Fetal Evidenced Based Guidelines*).

Placental grading as an adjunct to third-trimester ultrasound examination was associated with a significant reduction in the stillbirth rate in one 1987 trial [37]. In one study 15,122 patients were evaluated for Grannum grade III placental calcifications prior to 28 weeks of gestation. Grade III placental appearance prior to term was independently associated with increased risk of stillbirth after controlling for tobacco use [38]. A literature review from 2018 examined Grannum grade III placentas in the third trimester and their association with poor fetal and neonatal outcomes. They found a fivefold increased risk for labor induction (OR 5.41; 95% CI 2.98-9.82). Negative outcomes associated with grade III placenta include increased meconium in amniotic fluids (OR 1.68; 95% CI 1.17-2.39), low birth weight (odds ratio [OR] 1.63; 95% CI 1.19–2.22) and perinatal death (OR 7.41; 95% CI 4.94–11.09). On the other hand, there was no significant difference in abnormal fetal heart rate tracing, low Apgar score of less than 7 at 5 minutes, need for neonatal resuscitation, or admission to the neonatal ICU [39]. **More research is needed in placental grading before recommendations can be made for its routine**

TABLE 4.8: Polyhydramnios

	Amniotic Fluid Index	Deepest Vertical Pocket	Incidence	Risk of Fetal Abnormality[a]	Risk of Neonatal Abnormality[b]
Polyhydramnios, overall, cm	≥24.0	≥8 cm	0.3%–1.0%		
Mild, cm	24.0–29.9	8–11	65%–70%	6%–10%	1%
Moderate, cm	30.0–34.9	12–15	20% of total	10%–15%	2%
Severe, cm	≥35.0	≥16	<15% of total	20%–40%	10%

Source: Adapted from Ref. [44].

[a] Chance that fetal anomaly will be identified prenatally.

[b] Chance that neonatal abnormality will be identified in cases without a detected prenatal anomaly.

use for the prediction of poor perinatal outcome or interventions to improve outcomes.

Oligohydramnios is sonographically defined as a single deepest vertical pocket of <2 cm or an amniotic fluid index of <5 cm. It can be caused by ruptured membranes, fetal malformations, or maternal conditions that cause poor placenta perfusion [40]. It is associated with increased risk for stillbirth, cord compression, and compromised fetal lung development depending on the gestational age at onset. One meta-analysis showed that when compared to women with normal amniotic fluid, those with oligohydramnios at term had significantly higher rates of labor induction (OR 7.56, CI 4.58–12.48) and cesarean section (OR 2.07, CI 1.77–2.41). There were higher rates of an Apgar score <7 at 1 and 5 minutes (OR 1.53, CI 1.03–2.26 and OR 2.01, CI 1.3–3.09, respectively) and admission to the neonatal ICU (OR 1.47, CI 1.17–1.8). They found no difference in cord pH <7.1 or meconium [41]. The ACOG recommend starting antenatal surveillance for diagnosis of oligohydramnios at 28 weeks' gestation or at the time of diagnosis [42], and delivery is currently recommended between 36+0 and 37+6 weeks' gestation [43].

Polyhydramnios is sonographically diagnosed as a single deepest vertical pocket of ≥8 cm or amniotic fluid index of ≥24 cm (preferred) after 20 weeks' gestation. Once polyhydramnios is diagnosed, a detailed ultrasound should be performed to rule out fetal anomaly such as gastrointestinal obstruction, craniofacial abnormality, neuromuscular problems, or abnormality leading to high-output heart failure. Results of oral glucose tolerance testing should also be confirmed, as osmotic diuresis from gestational diabetes can also lead to polyhydramnios. Polyhydramnios is considered mild if the single deepest vertical pocket is 8–11 cm or the amniotic fluid index is 24–29.9 cm (Table 4.8). Mild polyhydramnios can be monitored, but antenatal surveillance and early delivery are not recommended. Moderate to severe polyhydramnios is an indication for antenatal surveillance and delivery between 39+0 and 39+6 weeks' gestation. Ultrasound can also be used to guide amnioreduction. Amnioreduction is only recommended for severe polyhydramnios (deepest vertical pocket ≥16 cm or amniotic fluid index ≥35 cm) that is associated with significant maternal discomfort and dyspnea (see Chap. 59 in *Maternal-Fetal Evidence Based Guidelines*) [44].

Doppler

Umbilical artery

In low-risk or unselected populations, routine Doppler ultrasound examination, usually of the umbilical artery and fetal vessels at around 28–34 weeks, does not result in increased antenatal, obstetric, and neonatal interventions, and no overall differences are detected for substantive short-term clinical outcomes such as perinatal mortality [45]. On the other hand, **the use of umbilical artery Doppler ultrasound in pregnancies with FGR is associated with a reduction in perinatal deaths and obstetric interventions** [46]. Guidelines published by the SMFM confirm a decrease in induction of labor, cesarean delivery, and perinatal death with use of umbilical artery Doppler assessment in high-risk pregnancies with FGR. Surveillance with umbilical artery Doppler studies should be started once growth restriction is suspected in the viable fetus [31, 47]. Guidelines for the technical aspects of Doppler use in pregnancy are available [48] (see Chap. 47 in *Maternal-Fetal Evidence Based Guidelines*).

Middle cerebral artery

Fetal middle cerebral artery (MCA) peak systolic velocity (PSV) Doppler has been used to evaluate fetal anemia in cases of maternal red cell alloimmunization, parvovirus infection, or twin–twin transfusion syndrome in monochorionic twins. Fetal MCA Dopplers are considered a screening test that requires a confirmatory test for diagnosis (fetal blood sampling) at the initiation of therapy (transfusion). **MCA-PSV is regarded as the best noninvasive screening test for fetal anemia** [49, 50] (see Chap. 55 in *Maternal-Fetal Evidence Based Guidelines*).

Ductus venosus

The ductus venosus (DV) is a vascular shunt that connects the umbilical vein to the inferior vena cava in the fetus. This waveform is reflective of downstream pressure in the right atrium. In high-resistance states (increased uteroplacental resistance), the DV shows absent or reversed flow in late diastole. A small retrospective study showed that reversed flow in the DV in addition to increased MCA is associated with perinatal mortality in fetuses less than 32 weeks' gestation [51]. A meta-analysis including data from 2267 patients confirmed these data, showing moderate predictive value for fetal outcomes in high-risk pregnancies with placenta insufficiency [52]. A randomized trial did not show significant perinatal benefits adding DV screening to fetal heart rate monitoring alone for antepartum monitoring of the growth-restricted fetus [53]. Therefore, there are insufficient data to currently recommend the use of DV Doppler in the routine evaluation and management of the fetal growth-restricted (FGR) fetus [47] (see Chap. 47 in *Maternal-Fetal Evidence Based Guidelines*).

Uterine artery

The Doppler waveform of the uterine artery has been shown to reflect high-impedance placental circulation by the presence of a waveform notch and low diastolic flow in association with hypertension and preeclampsia. Studies have shown an association between abnormal uterine artery Doppler and early-onset

preeclampsia, but predictive value is low. Current evidence has not shown a benefit to performing routine midpregnancy uteroplacental Doppler ultrasound for prevention of preeclampsia, FGR, or adverse pregnancy outcome [54, 55] (see Chap. 47 in *Maternal-Fetal Evidence Based Guidelines*). Furthermore, there is currently a paucity of data to recommend the use of uterine artery Doppler in the clinical management of hypertensive pregnancies [55].

Biophysical profile

A fetal biophysical profile (BPP) score is a specialized obstetric ultrasound consisting of monitoring of fetal movements, tone and breathing, and assessment of amniotic fluid volume, with or without fetal heart rate monitoring. BPP has been used to identify babies that may be at high risk of poor pregnancy outcome. While information gained from a BPP regarding fetal status can help guide clinical management, available evidence from randomized trials does not support the use of BPP as an isolated test of fetal well-being in high-risk pregnancies. Additional evidence from larger trials is needed (see Chap. 58 in *Maternal-Fetal Evidence Based Guidelines*) [56].

Cervical length

Transvaginal ultrasound (TVU) for the measurement of cervical length (CL) has been shown to be predictive of spontaneous preterm birth (PTB) in all populations studied so far, including singletons and multiple gestations, either asymptomatic or with symptoms of preterm labor. TVU CL can be effective in evaluating the need for such interventions as cervical cerclage or progesterone supplementation, as well as more effective management of women with symptoms of preterm labor (PTL) [57–60].

TVU CL screening is considered **universal** when offered routinely to all singleton gestations without a prior spontaneous PTB at the time of the anatomy ultrasound (i.e. 18–24 weeks). Both the ACOG and SMFM have published guidelines indicating that universal TVU CL screening **is deemed reasonable**, but not mandatory [61, 62]. We, as well as other societies, **recommended** it. About 1% of singletons without a prior spontaneous PTB develops a TVU CL ≤20 mm before 24 weeks [63] and should be started on vaginal progesterone daily until 36 weeks [64, 65]. Over two-thirds of academic maternal-fetal medicine units in the United States perform universal CL screening [66].

Women with a history of spontaneous PTB prior to 37 weeks' gestation had routinely been offered progesterone supplementation [67]. A statement released by the SMFM in 2019 in response to the PROLONG trial showing no improvement suggested these findings were due to a difference in study populations. Given this discrepancy, women at highest risk should still be offered intramuscular or vaginal progesterone as a component of shared decision-making with their provider [68]. In addition, current recommendations are for screening of these high-risk women (history of spontaneous PTB) with serial TVU CL ultrasounds every 2 weeks from 16 to 24 weeks' gestation. In those (about 40%) with TVU CL ≤25 mm, a cerclage should be offered (see Chap. 17) [69].

TVU CL screening of singletons presenting between 24 and 34 weeks with symptoms of PTL has been associated with both lower evaluation and triage time and significantly less incidence of PTB (see Chap. 18) [70].

Three-dimensional ultrasound

Three-dimensional (3D) ultrasound examination is not considered a required modality for all pregnant women at this time [4], but it can add accuracy in the assessment of the fetus identified to have anomalies by two-dimensional (2D) ultrasound (especially facial anomalies, neural tube defects, and skeletal malformations). Three-dimensional ultrasound allows the acquisition of volume measurements, which can depict topographic anatomy not able to be seen on 2D imaging. New technology allows for 3D reconstruction of vascular structures, further characterizing vessel relationship [71], vascular malformations, and vascular invasion. It has not been shown to have a clear clinical advantage over traditional ultrasound in routine settings [6].

Routine 3D ultrasound (versus the traditional 2D ultrasound) among low-risk women has not shown a significant impact on maternal-fetal bonding [72]. Additionally, 3D/4D (four-dimensional) ultrasound in women at risk for having a fetus with congenital anomalies does not reduce maternal anxiety compared with conventional 2D ultrasound alone [73].

Use of nondiagnostic recreational 3D ultrasound is not recommended in accordance with the ALARA principle [5].

Fetal echocardiography

The incidence of moderate to severe congenital heart disease (CHD) has been reported at 6–13 per 1000 live births [74, 75], with most affected infants born to pregnancies without identifiable risk factors [76]. Fetal cardiac evaluation is an important part of the prenatal ultrasound examination. Basic cardiac screening to be completed during the midtrimester ultrasound during every pregnancy includes the four-chamber view and evaluation of the right and left outflow tracts [5, 10]. An in-depth evaluation of fetal cardiac structures should be performed if the screening exam is abnormal or incomplete or when there are maternal or fetal indications (Table 4.9) [77, 78]. Fetal echocardiography is usually performed between 18 and 22 weeks. Main areas of evaluation include visceral situs, atrial and ventricular anatomy, valvular structure and function, and orientation and morphology of the great vessels. Grayscale, color, and spectral Doppler imaging are required, while spectral Doppler and M-mode should be used as needed to evaluate suspected anomalies [79]. These structures are usually best seen in the second trimester, but experienced technicians and sonologists may be able to detect cardiac anomalies in the first trimester. One prospective observational study showed a sensitivity and specificity of 88% and 100%, respectively, for detection of cardiac anomalies when using the four-chamber view, three-vessel view, and three-vessel trachea view to screen an unselected patient population in the first trimester [80].

Intrapartum ultrasound

Ultrasound during active labor is not routinely used, though studies have shown that it can improve precision and reproducibility over clinical exam alone. The International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) published a guideline outlining parameters that can be assessed and how to obtain these specific measurements [81].

Clinical exam of fetal position and station has been proven to be inaccurate with a rate of error from 20% to 70%, with high interobserver variability [82]. Ultrasound thus can be used to objectively determine fetal head position, station,

TABLE 4.9: Indications for Fetal Echocardiography

	Indicated	Consider
Fetal Factors	Suspected cardiac structural anomaly	Systemic venous anomaly • Persistent right umbilical vein • Left superior vena cava • Absent ductus venosus
	Suspected cardiac function abnormality	
	Hydrops fetalis	
	Persistent fetal tachycardia (>180 bpm)	
	Persistent fetal bradycardia (<120 bpm)	
	Frequent or persistent fetal arrhythmia	
	Major extracardiac anomalies	
	Nuchal translucency of 3.0 mm or greater or >95th percentile for gestational age	
	Chromosomal abnormality by invasive testing or cell-free fetal DNA	
	Monochorionic twins	
Maternal Factors	Pregestational diabetes	Selected teratogen exposure (paroxetine, carbamazepine, or lithium)
	Gestational diabetes dx in the first or early second trimester	Antihypertensive medication limited to angiotensin-converting enzyme inhibitors
	In vitro fertilization	Autoimmune disorder with SSA antibody positive without prior affected fetus
	Phenylketonuria	Second degree relative of fetus with CHD
	Autoimmune disorder with SSA antibody with prior affected fetus	
	First-degree relative of fetus with CHD	
	First- or second-degree relative of with disease of Mendelian inheritance with potential cardiac manifestations	
	Retinoid exposure	
	First-trimester rubella infection	

Source: Adapted from Refs. [65, 79].
Abbreviations: DNA, deoxyribonucleic acid; dx, diagnosis; CHD, congenital heart disease; SSA, Sjogren's syndrome-related antigen A antibodies.

descent, and attitude. All of these parameters contribute to assessment of arrested labor and need for obstetric interventions. Indications for intrapartum ultrasound include slower-than-expected labor or arrest of labor in the first stage, slow progress or arrest of descent, evaluation of fetal head position and station prior to operative vaginal delivery, and objective assessment of fetal head malpresentation [81].

When performing ultrasound during active labor, the equipment used should be optimal for the information to be obtained. It is recommended to use an ultrasound machine with a curvilinear 2D probe with a wide sector and low frequency (<4 MHz), as this yields the best insonation in the laboring patient. Practically, the machine should also turn on quickly, have a battery power option, have long battery life, and have an efficient recharging time.

Head position is routinely assessed via transabdominal ultrasound. Placement of the probe is transversely on the maternal abdomen, obtaining an axial view of the fetal trunk. Spine position can be ascertained in this view. Suprapubic placement of the probe will obtain an axial view of the fetal head. Position of occiput, fetal orbits, or the midline cerebral echo (that represents the falx cerebri) will indicate fetal head position.

Transperineal ultrasound is more accurate in determining fetal station and progress into and through the pelvic outlet. It can also help to identify caput succedaneum and molding. This exam is performed by placing a covered probe vertically or transversely between the labia and applying gentle pressure to bring anatomic landmarks into view. The major landmarks of interest are the pubic symphysis, which appears as an oblong echogenic structure anteriorly, and the fetal calvarium. Useful parameters for assessment of fetal station include angle of progression (AoP), fetal head direction, head–perineum distance (HPD), and midline angle (MLA) (see the ISUOG guideline for details on how to obtain and interpret these measurements) [81].

Ultrasound during active labor may be used as an adjunct to clinical exam to assess fetal position and station. Its use should be considered in the setting of assessing arrest disorders and planned operative delivery (see Chaps. 8 and 9).

Placenta accreta spectrum

Placenta accreta spectrum (PAS) represents abnormal adherence of the placenta to the myometrium. It occurs in 3/1000 deliveries and has increased in frequency over the last 50 years, likely mirroring the increased cesarean delivery rate [83]. Risk factors for PAS include number of prior cesarean deliveries, other uterine surgery, assisted reproduction, and anterior low-lying placentation or placenta previa [84]. PAS increases the risk for maternal morbidity, including intrapartum hemorrhage, need for blood transfusion, cesarean hysterectomy, and ICU admission. Due to the increased likelihood of adverse maternal outcomes with undiagnosed PAS, prenatal diagnosis with ultrasound is of paramount importance.

Ultrasound along with clinical history can be used to identify patients at increased risk for placenta accreta. Ultrasound findings

suggestive of placenta accreta in the first trimester include vascular lacunae, implantation into the prior cesarean scar, and low implantation of the gestational sac. Ultrasound findings suggestive of PAS in the second and third trimester include vascular lacunae, hypervascularity of the placenta, loss of the retroplacental clear space, myometrial thinning with bulging of the lower uterine segment, irregularity of the posterior bladder mucosa, and hypervascularity of the placenta and placental-myometrial interface [83, 84].

Reported performance of these markers varies widely in the literature. Many studies have touted ultrasound as highly sensitive and specific for PAS, but they may have been subject to selection bias with only high-risk cases being studied [85]. A study completed in 2014 with six physicians reading ultrasounds showed a sensitivity of only 53% and accuracy of 64% [86]. This suggests that the detection rate of all comers is lower, but that those with a high clinical likelihood are well-identified in a center of excellence, where there is expertise in imaging, identifying, and managing PAS. Furthermore, sonographic markers of PAS are commonly noted in low-risk pregnancies [87] and should be followed up. Suggested criteria for referral to a center of excellence are listed in Table 4.10 [85].

Ultrasound performs as well as magnetic resonance imaging (MRI) for anterior placentation, but MRI may have applications for posterior placentas and those in which percreta is suspected [83].

The SMFM released an obstetric care consensus in 2018 endorsed by the ACOG and Society of Gynecologic Oncology (SGO) regarding the diagnosis and management of PAS [84]. Their recommendations include:

- Using risk factors and prenatal imaging to suspect PAS.
- Preparing for delivery with a multidisciplinary team.
- Prenatally diagnosed PAS should be managed at a center with surgical experience and rapid access to blood products.
- If PAS is encountered during a case prior to hysterotomy and fetal well-being is not imminently compromised, the case should be paused in order to gather optimal resources and expertise prior to proceeding.
- Conservative management of PAS (leaving the placenta in situ) should only be undertaken under investigational protocols with thorough patient counseling and shared decision-making.

TABLE 4.10: Criteria to Consider Referral for Imaging of Suspected PAS

Clinical Risk Factors
Prior cesarean delivery (especially multiple cesareans)
Placenta previa
History of endometrial ablation
Previous uterine surgery
First- or second-trimester bleeding with other risk factors for placenta accreta
Sonographic Risk Factors
Abnormal placenta appearance
Abnormal uterine shape
Abnormal vascularity of myometrial wall
Current or previous cesarean scar ectopic

Source: Adapted from Ref. [85].

In summary, PAS is an entity that can be suspected by history and ultrasound findings and is best managed in centers of excellence to decrease maternal and fetal morbidity (see Chap 29).

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5

PRENATAL DIAGNOSIS AND SCREENING FOR ANEUPLOIDY

Sarah Harris, Angie Jelin, and Neeta Vora

Key points

- **All women, regardless of maternal age, should be counseled in regard to screening and diagnostic testing for aneuploidy**, ideally in the first trimester.
- Genetic **counseling should include comprehensive information on** all modalities, advantages, disadvantages, and the gestational age for each test prior to screening. All women should receive pre- and post-test counseling, particularly for an "abnormal" result.
- Issues of **sensitivity, specificity, and positive and negative predictive values** are vital to the interpretation of a screening test.
- The positive predictive value of a screening test is greatly influenced by **prevalence** rates in the population tested.
- The difference between a screening and a diagnostic test should be clearly explained prior to any testing. There is **no definitive noninvasive prenatal diagnostic test. The only diagnostic tests are invasive (i.e. chorionic villus sampling [CVS] and amniocentesis)**.
- **Cell-free DNA screening is the most sensitive and specific screening test for fetal aneuploidy, in particular trisomy 21, and should be offered regardless of maternal age. The detection rate for trisomy 21 is over 99%, with a false-positive rate of <1%**.
- **First-trimester screening (FTS) includes NT, PAPP-A, and B-HCG and is performed from $10^{3/7}$ to $13^{6/7}$ weeks.** The overall detection rate (sensitivity) is **84%–87%** (false positive rate [FPR]: 5%) for trisomy 21.
- Second-trimester maternal analyte screening (**quad screen**) **detects approximately 70%–81%** of pregnancies with trisomy 21 **(FPR 5%)**.
- **Integrated screening** has a **detection rate of 95% for trisomy 21, with a low (1%–4%) FPR**, but **results** are not provided until **the second trimester**. **Step-wise or contingent sequential screening** offers **the same 95% detection rate, a reasonable 5% FPR**, and **initial results are provided in the first trimester**.
- **Second-trimester "genetic" ultrasound** is an important screening modality for aneuploidy and anomalies. In addition to detecting major anomalies (e.g. congenital cardiac defects and duodenal atresia), it can identify soft markers (especially nuchal thickening, short humerus or femur, and echogenic bowel) that are associated with trisomy 21.
- **Amniocentesis for the diagnosis of fetal aneuploidy is typically performed between 15 and 20 weeks' gestation. It is associated with a 0.11% (1 in 900) procedure-related risk of pregnancy loss. Early amniocentesis prior to 15 weeks' gestation is not recommended**.
- **CVS can be performed between 10 and 13 weeks' gestation and is associated with a 0.22% (1 in 455) procedure-related risk of pregnancy loss. Higher background pregnancy loss rates in the first trimester contribute to the high-risk estimates**.
- Chromosomal microarray **(CMA) analysis should be recommended as the primary test (replacing conventional karyotype) to patients undergoing prenatal diagnosis in whom a structural abnormality is detected by ultrasound**.
- When CMA is normal, **targeted gene panels** can be considered if the phenotype is sufficiently defined to select an appropriate panel of genes to sequence.
- **Exome sequencing** of both parents and fetus (trio) shows an increased diagnostic yield, especially in fetuses with multiple abnormalities or nonimmune hydrops fetalis.
- Trisomy 21 is the most common trisomy at birth. Its incidence increases with increasing maternal age.

Screening versus diagnostic tests

The aim of a screening test is to identify pregnancies at increased risk of being affected by a particular condition. Prenatal genetic diagnostic testing is able to definitively identify affected pregnancies. Prenatal screening tests use noninvasive techniques, such as maternal blood sampling or ultrasound measurements, to determine risk. Prenatal diagnostic testing requires an invasive procedure, such as amniocentesis or chorionic villus sampling (CVS), to obtain a sample from the pregnancy to perform genetic testing.

Issues of prevalence, sensitivity, specificity, and positive and negative predictive values are vital to the interpretation of a screening test and are critical for interpreting the value of a test. Table 5.1 lists the characteristics of an ideal perinatal screening test.

Sensitivity and specificity

The sensitivity of a screening test, which can also be called the detection rate, describes the test's performance in correctly identifying individuals affected by the condition (true positive). For example, if a screening test for trisomy 21 has a detection rate of 80%, then 80% of fetuses with trisomy 21 will have a positive test result. Importantly, this also means that 20% of fetuses with trisomy 21 would not be detected with this particular screening test. The specificity of a test describes the test's ability to correct identify individuals without the condition (true negative).

Prevalence, positive predictive value, and negative predictive value

High sensitivity and specificity are preferable; however, the prevalence of a condition (based upon the population tested) will ultimately determine the value of a positive or negative result (Figure 5.1). With lower prevalence, the chance of a particular "positive" test to be a true finding is much less. For example, based upon the numbers from Figure 5.1, if all the women with a positive test from group "A" had CVS, there would be 1 positive

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TABLE 5.1: Ideal Prenatal Screening Test

Identify common or important fetal disorder
Be cost-effective
High detection rate; low false-positive rate
Be reliable and reproducible
Diagnostic test exists
Be positive early in pregnancy
Possible intervention if screening test is positive

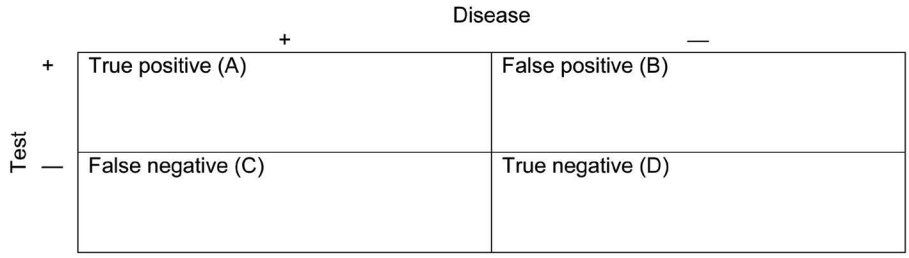
result for every 55 CVSs performed. If all the women in "B" had a CVS, 1 out of every 2.4 tests would yield a positive result.

While complicated, discussion of sensitivity (detection rates) and the 5% screen positive rate of screening tests (highlighted in Table 5.2) is necessary. Specific resources, including time, expertise, and the availability of genetic counseling, are paramount. Continuing education of health care providers is necessary. Some couples might prefer a screening approach with the earliest detection even with a higher—for example, 5%—false-positive rate (FPR) (e.g. first-trimester screening), and some prefer the highest detection with the lowest FPR (e.g. cell-free DNA screening, integrative screening).

No matter the sensitivity of available tests, for women undergoing screening, **detailed discussions regarding the advantages and disadvantages of screening versus diagnostic testing should occur**. After such counseling, each woman can make the most informed and best choice for their situation. **Since screening tests will never detect 100% of disease, the option of diagnostic testing should be offered to all pregnant women** [1]. Several studies have shown that **most pregnant women prefer early (vs. later) screening** for trisomy 21.

Pretest and posttest counseling

The decision to proceed with prenatal screening or testing is personal and based on an individual woman's reproductive goals and desires. Pretest counseling should include a discussion of the conditions being tested for, the expected performance of the test, and the risks and benefits of testing. Counseling should be



Sensitivity = A/A+C

Specificity = D/B+D

Positive predictive value (PPV)= A/A+B

Negative predictive value (NPV) = D/C+D

Effect of prevalence

N=100,000

Sensitivity 90%

False positive= 5%

Prevalence= 0.1%

90	5000
10	94900

PPV= 1.8%

NPV= 99.9%

Prevalence=4%

3600	5000
400	91000

PPV=41.9%

NPV= 99.5%

FIGURE 5.1 Screening test concepts and effect of prevalence.

TABLE 5.2: Comparison of Aneuploidy Testing Options

	>10 Weeks	First Trimester[a]			Second Trimester[b]				
	Screening Test	Screening Test		Diagnostic Test	Screening Test				Diagnostic Test
Name	Cell-free fetal DNA screening	NT	FTS (NT, PAPP-A, hCG)	CVS	Quad screen (AFP, hCG, uE3, inhibin)	Integrated screen (FTS, followed by QS)	Sequential screen (FTS followed by QS)	Genetic ultrasound	Amniocentesis
Detection rates for trisomy 21	>99%	65%–80%	80%	>99% accuracy for chromosome abnormalities	70%–81%	95%	Stepwise: 95% Contingent: 88%–94%	50%	>99% accuracy for chromosome abnormalities
Detection rate for other chromosome anomalies	T18: 98% T13: 99% SCA: Unknown	70%	74%	>99% accuracy for chromosome abnormalities	72%	60%–80%	50%–80%	Variable	>99% accuracy for chromosome abnormalities
Risk of pregnancy loss	N/A	N/A	N/A	1 in 455 procedure-related risk for pregnancy loss	N/A	N/A	N/A	N/A	1 in 900 procedure-related risk for pregnancy loss

[a] Usually 11–13 weeks.

[b] Usually 15–22 weeks.

Abbreviations: NT, nuchal translucency; FTS, first trimester screening; PAPP-A, pregnancy associated plasma protein-A; HCG, human chorionic gonadotropin; CVS, chorionic villus sampling; AFP, alpha fetoprotein; uE_3, unconjugated estriol; FTS, first trimester screening; QS, quad screen; T18, trisomy 18; T13, trisomy 13; SCA, sex chromosome aneuploidy; N/A, not applicable (no risk of pregnancy loss).

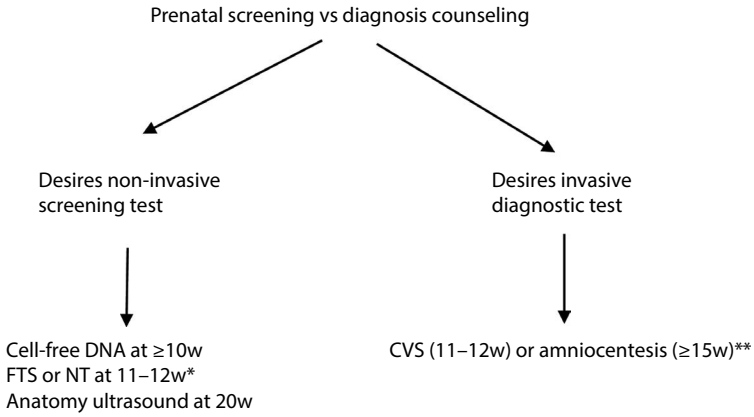


FIGURE 5.2 General approach to prenatal screening for aneuploidy. *Noninvasive screening test based on patient/provider preferences. **Test for karyotype and CMA. *Abbreviations:* FTS, first trimester screening; NT, nuchal translucency; w, weeks.

nondirective and stress that prenatal testing is not mandatory. Ideally, this counseling should be performed by a certified genetic counselor or an obstetric provider with expertise in screening and testing.

Pretest counseling should include:

- A discussion of all testing options, including screening tests (cell-free DNA screening, first- and second-trimester serum screening, ultrasound) versus diagnostic testing (CVS and amniocentesis); a discussion that all testing is optional and that it is acceptable to decline any additional testing.
- Review of possible results, including false-positive screening results, false-negative screening results, aneuploidy, copy number variants, incidental findings, false paternity, consanguinity, and normal results.
- A review of the patient's goals and values, including a discussion of her general attitude toward testing and screening, views and availability of pregnancy termination, and views on parenting a child with disabilities.
- Pregnancy and postpartum management options in the event of an abnormal result, including pregnancy termination versus continuation.

Posttest counseling should be provided to patients with negative or positive results. It is important for patients to understand that normal testing results do not eliminate the possibility of an underlying genetic condition in the pregnancy. For patients with abnormal results, referral to a genetic counselor or provider with expertise in the condition is recommended [2].

The **main aims of prenatal aneuploidy screening and testing are to identify pregnancies at risk for genetic conditions and to allow women to make informed decisions regarding the outcome of the pregnancy**. Some women may elect to proceed with pregnancy termination, whereas others may use the information to prepare for the birth of an affected child.

Many still believe that the rationale behind screening for aneuploidy is to provide the option for termination of the pregnancy prior to viability. While couples faced with the reality of an aneuploid pregnancy may opt for termination, **the purpose of prenatal diagnosis and screening is to provide information**. If an abnormality is identified, the patient can be provided with information specific to her situation. When a patient decides to carry an affected pregnancy to term, the antenatal, intrapartum, and postpartum care can be performed under more ideal circumstances, hopefully altering the outcome and informing care in the immediate newborn period. A general current approach to prenatal screening for fetal aneuploidy is shown in Figure 5.2.

Antenatal noninvasive aneuploidy screening (Table 5.2)

History

Langdon Down, in 1866, reported that the skin of individuals with trisomy 21 appeared enlarged. In the 1970s data became available on the relationship between maternal age and increased risk for aneuploidy. A statistically relevant difference was seen between the 30- to 34 years old group and the 35- to 39 years old group, so that this difference led to the offering of women 35 years of age diagnostic evaluation for karyotype. Maternal serum alpha-fetoprotein (MSAFP) was originally found to be elevated in women carrying fetuses with neural tube defects (NTDs); this led to the realization in 1984 that a low MSAFP was associated with a higher risk of trisomy 21 [3]. Nuchal translucency (NT) first-trimester ultrasound screening was introduced in the early 1990s [4].

Principles

All women should be offered aneuploidy screening, ideally in the first trimester [3]

Historically, the cutoff level for aneuploidy diagnosis and subsequent public policy was determined over 30 years ago and was based on a maternal age risk of 35 years at delivery equivalent to a second-trimester risk of 1:270 or higher (liveborn risk of 1:380). Factors considered in determining this value included the prevalence of disease, a perceived significant increase in the trisomy 21 risk after this age, the risk of invasive testing, the availability of resources, and a cost–benefit analysis. Since that time, a number of additional screening tests for trisomy 21 have become available that challenge the validity of maternal age as a single indication for invasive testing. The American Congress of Obstetricians and

TABLE 5.3: Risk for Down Syndrome Based upon Maternal and Gestational Age

	Gestational Age (weeks)			
Maternal Age	12	16	20	Liveborn
20	1/1068	1/1200	1/1295	1/1527
25	1/946	1/1062	1/1147	1/1352
30	1/626	1/703	1/759	1/895
31	1/543	1/610	1/658	1/776
32	1/461	1/518	1/559	1/659
33	1/383	1/430	1/464	1/547
34	1/312	1/350	1/378	1/446
35	1/249	1/280	1/302	1/356
36	1/196	1/220	1/238	1/280
37	1/152	1/171	1/185	1/218
38	1/117	1/131	1/142	1/167
39	1/89	1/100	1/108	1/128
40	1/68	1/76	1/82	1/97
42	1/38	1/43	1/46	1/55
44	1/21	1/24	1/26	1/30
45	1/16	1/18	1/19	1/23

Gynecologists (ACOG) now recommend that **diagnostic testing for aneuploidy be offered to all women, regardless of their personal risk factors** [1].

Age

The risk of fetal aneuploidy increases with maternal age, but decreases with the gestational age at assessment in determining the risk, secondary to in utero death rates (Table 5.3) [5].

Women older than 35 years of age have a higher individual risk than younger women; however, the vast majority of trisomy 21 pregnancies are born to the <35-year-old age group. Screening programs have been developed to try and detect affected pregnancies in both the "higher" and "lower" risk groups.

Screening in any trimester

Cell-free DNA screening

The discovery of cell-free DNA of fetal origin in maternal plasma opened up new possibilities for noninvasive maternal prenatal screening for fetal chromosomal aneuploidy. The methods utilized for detecting fetal aneuploidy differ based on whether amplified regions throughout the genome, chromosome-specific regions, or single nucleotide polymorphisms are the targets for sequencing used [6–10].

Cell-free DNA screening can be used to screen for fetal trisomy 21, trisomy 18, trisomy 13, and sex chromosome abnormalities. This screening can be completed between 10 weeks' gestation and term. On average, a pregnant woman will have approximately 3%–13% cell-free DNA of fetal origin in a blood sample [11]. The fetal fraction is derived from placental trophoblast cells.

Different factors, including gestational age, maternal weight, medication exposure, maternal race, fetal aneuploidy, and multiple gestations, have been shown to influence the fetal fraction [11–13]. Low fetal fraction is also associated with test failures or uninterpretable results. Due to the increased risk for aneuploidy in this group, referral to genetic counseling is recommended and diagnostic testing should be offered [13].

In high-risk populations who have undergone prenatal diagnosis, the sensitivity of cell-free DNA screening for trisomy 21 is greater than 99%, for trisomy 18 greater than 99%, and for trisomy 13 greater than 90% [14–17]. In a mixed population of low- and high-risk women, the sensitivity of cell-free DNA screening for trisomy 21 was reported between 99% and 100%, for trisomy 18 between 90% and 99%, and for trisomy 13 greater than 99% [18–20]. A recent meta-analysis for cell-free DNA screening reported a greater than 99% detection range for trisomy 21, 98% detection rate for trisomy 18, and 99% detection rate for trisomy 13 with a combined false-positive rate of 0.13%. The detection rate of sex chromosome aneuploidy could not be determined due to the small sample size [21].

Cell-free DNA screening is the most sensitive and specific test for screening for aneuploidies. However, it is important that patients understand the importance of positive predictive value (PPV) when it relates to a positive result. Understanding the patient's a priori risk is essential for helping patients interpret their results. For example:

- A 45-year-old woman with a 1 in 22 risk for trisomy 21 has a positive cell-free DNA screening result. The PPV of the screening test is 98%.
- A 20-year-old-woman with a 1 in 1177 risk for trisomy 21 has a positive cell-free DNA screening result. The PPV of the screening test is 48%.

Online calculators have been developed to assist with patient counseling (https://www.med.unc.edu/mfm/nips-calc/; https://www.perinatalquality.org/vendors/nsgc/nipt/). However, these calculators have limitations, and providing individual posttest risks may be less useful for some patients. It is critical that patients have comprehensive genetic counseling after an abnormal result, so that they can understand the implications and make informed decisions regarding additional testing options.

Some laboratories also offer screening using cell-free DNA for less common microdeletion syndromes. However, this testing is not recommended by ACOG, as it has not been validated, and because the conditions are so rare, the PPV of this testing is much lower [3].

First-trimester screening

Nuchal translucency

The NT is a fluid-filled space on the back of the fetal neck. The NT can be enlarged in fetuses with aneuploidy and structural anomalies at **$10^{3/7}$–$13^{6/7}$ weeks** (crown–rump length [CRL] about 36–86 mm) [22]. The NT measurement is obtained in a midsagittal plane with the neck of the fetus in a neutral position. The amnion should be seen separately from the neck. The image should be enlarged >75% of the screen. The measurement is obtained by placing the calipers in the inner edges of the nuchal translucency, and multiples of the medians are used to calculate the risk of Down syndrome via computer software. An increased NT is >70% sensitive for trisomy 21, trisomy 18, and trisomy 13 (Table 5.2) [3]. Rigorous training, certification, and ongoing quality control are necessary to achieve the detection rates published in the literature (www.fetalmedicine.com; www.ntqr.org). The optimal time to perform NT for aneuploidy screening is about 11 weeks.

Compared to a screening policy of amniocentesis for age ≥35 years and ultrasound at 18 weeks, a policy of NT screening is associated with similar numbers of births of infants

with trisomy 21 (a nonsignificant 37.5% decrease) and **a significant 82% decrease in invasive tests** [23].

Biochemistry

The maternal serum analytes measured in the first trimester are beta–human chorionic gonadotropin (B-hCG) and pregnancy-associated plasma protein-A (PAPP-A). **B-hCG** normally decreases in pregnancy, but is *increased* in fetuses affected with trisomy 21. **Free** B-hCG performs better than **total hCG** as an independent marker, but there does not appear to be a clinically significant difference in sensitivity when either is combined with NT and PAPPA-A for first-trimester screening (FTS) [24]. **PAPP-A** normally increases in pregnancy, but is *decreased* in fetuses affected with trisomy 21. hCG discrimination is greatest at 13 weeks, while PAPP-A discrimination is greatest at 10 weeks, making 11 weeks the optimal time for first-trimester analyte screening.

First-trimester screening

FTS consists of measuring the **NT** combined with maternal serum screening (**PAPP-A** and **B-hCG**). Over 20 studies in more than 200,000 women have been performed to assess the sensitivity of this screening test [24–28].

The gestational age for FTS is about **$10^{3/7}$–$13^{6/7}$ weeks** (about 73–98 days; CRL about 36–86 mm). The usual cutoff risk is 1:270. The detection rate (sensitivity) is about **84%–87%** (95% CI 80%–90%) for trisomy 21. For non–trisomy 21 there is an estimated detection rate of 74% [28]. **The best detection rate is achieved at 11 weeks**.

FTS should be offered only if the following criteria can be met [24–27]:

1. Appropriate training and ongoing quality monitoring programs are in place for both ultrasound (NT) and laboratory assays of analytes.
2. Sufficient information and resources are available to provide comprehensive counseling to women regarding the different options and limitations of these tests.
3. Access to an appropriate diagnostic test (i.e. CVS) is available when screening results are positive.

The Maternal Fetal Medicine Foundation (www.mfmf.org) and the Fetal Medicine Foundation (www.fetalmedicine.com) both provide NT education and quality review programs. There is sufficient evidence to support implementing FTS for Down syndrome provided the previous three requirements are met. Almost 85% of women in the United States present for care within 12 weeks and can be offered FTS. FTS can provide high detection, early reassurance, more time/diagnostic options, and earlier completion of aneuploidy screening.

Compared to screening programs using second-trimester screening (STS), the use of FTS is also associated with a significant reduction in induction for postterm pregnancy because of better dating with first-trimester ultrasound [29].

Other first-trimester ultrasound markers

An absent nasal bone has also been associated with trisomy 21. When added to FTS (NT, PAPP-A, and B-HCG), an absent nasal bone may increase the detection rate and decrease the FPR [30]. Possibly because of the difficulty of this exam, these data have not been confirmed in all studies. Abnormal ductus venosus Doppler flow and tricuspid regurgitation have also been found to be >70% sensitive for trisomy 21, but there are insufficient prospective data for any increase in accuracy over FTS alone [31].

Second-trimester screening

Maternal analyte screening had the first reported association with trisomy 21 with low **MSAFP** (MoM 0.75), followed by the association of high **hCG** (MoM 2.3) and a low **unconjugated estriol** (MoM 0.7) to form the "**triple screen**." The detection rate for women under 35 with a triple screen ranges between 57% and 74%, with a constant 5% FPR [23–25]. For women above 35 using similar cutoff values, the sensitivity increases to 87%, but the FPR also balloons to 25% [32]. **Inhibin** was added to analyte screening (**quad screen**), but since levels correlate somewhat with hCG, it is not an independent predictor like the other markers, and the increase in detection is more limited (7–11 percentage points). Approximately 70%–81% of cases of trisomy 21 are detected in the majority of studies, holding the FPR at 5% [24–26]. The detection rate for non–trisomy 21 aneuploidies has been estimated at 72% [28]. This screening test can be performed between 15 and 22 weeks, with best results obtained at 16–18 weeks. Values need to be adjusted, as needed, for diabetes, obesity, and other factors.

Other combinations of markers have been assessed; however, with the addition of extra markers, the potential benefit versus the cost must be balanced. With each additional marker, costs to society reach into the millions secondary to the numbers of pregnancies tested each year. The relative cost and value of raising the sensitivity or lowering the FPR a few percentage points is an ongoing debate.

Combined first- and second-trimester tests

Combined screening programs in the first trimester (using both ultrasound assessments of the NT as well as maternal analytes) and the second trimester (using maternal analytes) have been described. Patterns of testing include sequential testing (results given after each test) and integrated testing (delaying reporting until both tests have been completed).

Integrated screening

Integrated screening refers to performing screening tests at different times during pregnancy with a single result provided to the patient only after all tests have been completed. A protocol for integrated screening for trisomy 21 is based upon tests performed during the first and second trimester (NT, PAPP-A, MSAFP, hCG, estriol, and inhibin). Mathematical models calculated that >85% of affected pregnancies would be detected with an FPR of only 0.9%. The FASTER trial (First- And Second-Trimester Evaluation of Risk) performed integrated screening in 33,557 women (84 with trisomy 21) [26]. Cutoff values for the different tests varied (first-trimester combined test cutoff 1:150, second-trimester "quad screen": 1:300). The authors report a sensitivity of 86% with FTS (FPR 5%), 85% with second-trimester (FPR high at 8.5%), and, when combined, a 94% detection of trisomy 21 cases. If results are revealed after STS, the FPR is only 4.9%, with the **best sensitivity**. If NT is not available, an "integrated serum screening test" has a detection rate of 85% with 3.9% FPR [24]. Disadvantages of integrative screening include the lack of early diagnosis, the physical and psychological ramifications created if an abnormality is found and the woman opts for termination (compared to the first trimester), the increase in costs (compared to either FTS or STS), the perception of "hiding" abnormal results, and the limitations it places on multiple gestations if discordant karyotypes are found.

Sequential screening

Sequential screening involves performing different screening tests at different times during pregnancy with the results provided to the patient after each test. There are three approaches to sequential testing: Independent, stepwise, and contingent.

Independent

This approach involves the independent interpretation of FTS and STS. While the sensitivity is as exemplary with this approach as with integrative screening (94%–95%), combining screening tests and revealing the results after each increases the chance for false-positive results. The FASTER trial's FPR was 10.8% with sequential independent screening [26], far too high for population-based usage. As a high FPR means higher loss rates due to more invasive testing, independent sequential screening is the least efficient risk assessment strategy and should NOT be used.

Stepwise

With this method, both FTS and STS are performed with results revealed after FTS. If FTS risk is above a certain cutoff, invasive testing (i.e. CVS) is offered; if FTS is below a certain cutoff, STS is recommended with a final risk revealed at that point. In the FASTER trial, such an approach (low cutoff 1:150; high cutoff 1:300) had a **detection rate of 95% with an FPR of 4.9%** [26]. The advantages of this approach are a very high detection rate (as with integrative screening), with the option of early results in the first trimester for the highest-risk women.

Contingent

In contingent testing, both FTS and STS are performed, with results revealed after FTS. If FTS risk is above a certain cutoff (e.g. 1/150), invasive testing (i.e. CVS) is offered; if FTS is below a certain cutoff (e.g. 1/300), no further screening is necessary; if FTS is in between, STS is recommended with a final risk revealed at that point. Careful determination of risk cutoffs is necessary. This strategy has not been studied prospectively.

"Genetic" ultrasound screening for trisomy 21

An ultrasound of the fetus performed at **18–24 weeks** is associated with several important benefits and should be offered to all pregnant women (see Chap. 4). One of the benefits is the antenatal detection of anomalies. The identification of a fetus with an issue allows for directed counseling and optimization of antepartum, intrapartum, and postpartum care. Whether routine or targeted anatomic assessment is being performed, it should be done by experienced centers with ongoing quality assessment to increase detection of anomalies and limit false-positive results.

The in utero diagnosis of trisomy 21 can be suspected when anomalies or physical features that occur more frequently in fetuses with trisomy 21 than in the general population are noted on an ultrasound examination. Some of these major structural congenital anomalies, such as atrioventricular canal or duodenal atresia, strongly suggest the possibility of trisomy 21 and are independent indications to offer invasive testing. Although, when present, there is a high risk of trisomy 21, these anomalies have low sensitivity and thus are not useful in screening. For example, when **duodenal atresia** is identified, there is approximately a 40% risk of trisomy 21, yet it is seen in only 8% of affected fetuses. About 50% of fetuses with Down syndrome have **congenital heart defects**.

Physical characteristics that are not structural anomalies but occur more commonly in fetuses with trisomy 21 are called **markers**. By comparing the prevalence of markers in trisomy 21 fetuses to their prevalence in the normal population, a likelihood ratio (LR) can be calculated, which can be used to modify risk. This is the basis for ultrasound screening for trisomy 21. In order for a marker to be useful for trisomy 21 screening, it should be sensitive (i.e. present in a high proportion of trisomy 21 pregnancies), specific (i.e. not commonly seen in normal fetuses), easily imaged in standard sonographic examination, and present early enough in the second trimester that diagnostic testing can be performed so that results are available when pregnancy termination remains an option. A list of markers and likelihood ratios are seen in Tables 5.4 and 5.5, respectively [33–35]. Markers commonly sought to assess the risk of trisomy 21 are discussed in the following sections.

TABLE 5.4: Selected Ultrasound Findings Associated with Down Syndrome

Major Anomalies
Congenital heart defects
Duodenal atresia
Major Markers
Increased nuchal thickness
Hyperechoic bowel
Shortened humerus
Shortened femur
Echogenic intracardiac focus
Renal pyelectasis
Minor Markers
Shortened or absent nasal bone
Foot length
"Sandal gap" of the foot
Widened ischial spine angle
Hypoplasia of the midphalanx of the fifth digit
Brachycephaly

TABLE 5.5: Likelihood Ratios and 95% Confidence Limits for Isolated Ultrasound Markers

Isolated Sonographic Marker	Nyberg et al. [10] LR (95% CI)	Smith-Bindman et al. [11] LR (95% CI)	Nicolaides et al. [12] LR
Nuchal fold/thickening	11 (5.2–22)	17 (8–38)	9.8
Hyperechoic bowel	6.7 (2.7–16.8)	6.1 (3–12.6)	3.0
Short humerus	5.1 (1.6–16.5)	7.5 (4.7–12)	4.1
Short femur	1.5 (0.8–2.8)	2.7 (1.2–6)	1.6
EIF	1.8 (1.0–3)	2.8 (1.5–5.5)	1.1
Pyelectasis	1.5 (0.6–3.6)	1.9 (0.7–5.1)	1.0

Increased nuchal fold

About 35% of trisomy 21 fetuses, but only 0.7% of normal fetuses, have a nuchal skin fold measurement ≥6 mm (some studies use ≥5 mm). When an increased nuchal fold is an isolated finding, the LR is strong, at 10–17. Thus the presence of an increased nuchal fold alone is usually an indication to offer invasive testing.

Increased echogenicity of the fetal bowel

When brighter than the surrounding bone, this marker has a trisomy 21 LR of 3.0–6.7. This finding can also be seen with fetal cystic fibrosis, congenital cytomegalovirus (CMV) infection, swallowed bloody amniotic fluid, and fetal growth restriction.

Short long bones

These markers in the second trimester are associated with trisomy 21 relative to the length expected from their biparietal diameter. This can be used to identify at-risk pregnancies by calculating a ratio of observed to expected (O/E) femur/humerus length based on the fetus's biparietal diameter (BPD). An O/E ratio for femur length of <0.91 has a reported LR of 1.5–2.7 when present as an isolated finding. A short humerus is more strongly related to trisomy 21, with reported LRs ranging from 4.1 to 7.5.

Pyelectasis

This marker is defined as a renal anteroposterior (AP) diameter of ≥4–5 mm and has an LR that ranges from 1.1 to 1.9 as an isolated marker. This has been found by some not to be significantly more frequent in fetuses with trisomy 21 than in euploid fetuses (low specificity).

Echogenic intracardiac foci

This marker occurs in up to 5% of normal pregnancies and in approximately 13%–18% of trisomy 21 gestations. The LR for trisomy 21 when an echogenic focus is present as an isolated marker has ranged from 1.0 to 2.8. This has been found by most investigators not to be significantly more frequent in trisomy 21 pregnancies than in unaffected pregnancies (low specificity). The risk does not seem to vary if the focus is in the right or left ventricle or if it is unilateral or bilateral, but may be affected by ethnicity.

Other ultrasound markers

Other markers described include a hypoplastic fifth middle phalanx of the hand, short ears, a sandal gap between the first and second toes, an abnormal iliac wing angle, an altered foot to femur ratio, short or absent nasal bone, and others. These markers are inconsistently used because of the time and expertise required to obtain them. Mild ventriculomegaly (10–15 mm) can be an indication for invasive prenatal diagnosis, since it is associated with a 1%–2% risk of aneuploidy if isolated. If the karyotype is normal, mild ventriculomegaly is still associated with about 8% of structural anomalies, 3% of perinatal deaths, and 10%–20% of abnormal neurodevelopment.

Except for major anomalies and increased nuchal thickness, isolated "genetic ultrasound" markers should, in general, not be used as the sole indication for invasive testing. As with other screening modalities, "genetic" ultrasound can be used to alter the a priori risk in either direction. A positive LR can be used to increase estimated risk. The magnitude of the increase depends upon the marker(s) or anomalies seen. While most of the clinical prospective data justifying this approach have come from a baseline age-related risk, some have advocated using these LRs to adjust whichever baseline risk, even that derived by other screening tests (e.g. FTS and/or unconjugated estriol and inhibin [QS], or even integrative or consecutive approaches). A benign second-trimester scan having none of the known markers and no anomalies has been suggested to have an LR of 0.4–0.5, assuming the image quality is satisfactory when the "genetic ultrasound" is normal. It is doubtful that the same sensitivity can be achieved in every center.

Ultrasound screening for other chromosomal abnormalities

Fetal aneuploidy other than trisomy 21 can be suspected based on ultrasound findings [36]. The rates reported are usually in high-risk populations and may overestimate the strength of the association when such findings are noted on a screening examination.

Trisomy 18

FTS and STS with MSAFP, hCG, and QS have a high detection rate for trisomy 18. Second-trimester ultrasound also has a high detection rate for trisomy 18.

Choroid plexus cysts (CPCs) have a very weak association with trisomy 18 and should not be the sole indication for invasive testing if isolated. The presence of CPC should be an indication for a detailed second-trimester ultrasound for trisomy 18 major anomalies, such as cardiac, central nervous system (CNS), hand defects, etc.

Positive screening for aneuploidy but normal karyotype

Nuchal translucency

An NT above the 95% percentile for gestational age, and especially ≥3.5 mm at $10^{3/7}$–$13^{6/7}$ weeks, is associated with an increased risk of other anomalies and syndromes, with the risk directly proportional to the increase in NT (Table 5.6) [37]. The list of anomalies

TABLE 5.6: Risk of Chromosome Abnormalities and (If Normal Karyotype) of Fetal Death or Anomalies According to Nuchal Translucency

		Normal Karyotype			
NT	Chromosomal Defects (%)	Fetal Death (%)	Major Fetal Anomalies (%)	Alive and Well (%)	Cardiac Defects (%)
<95th centile	0.2	1.3	1.6	97	0.6
95th–99th centiles	3.7	1.3	2.5	93	0.6
3.5–4.4	21.1	2.7	10.0	70	3.7
4.5–5.4	33	3.4	18.5	50	6.7
5.5–6.4	50	10	24	30	13
≥6.5	65	19	46	15	20

Abbreviation: NT, nuchal translucency.

is long and a detailed second trimester ultrasound is recommended. The incidence of cardiac anomalies is ≥3.7% for NT ≥3.5 mm, so that a fetal cardiac ultrasound by an experienced operator is recommended.

First-trimester PAPP-A and B-hCG

Low PAPP-A in FTS in the presence of a normal karyotype is associated with several adverse pregnancy outcomes, including fetal loss, premature birth (PTB), and fetal growth restriction (FGR). Low free hCG is associated with fetal loss. There are no randomized trials assessing any type of intervention or treatment for patients with abnormal serum markers [38].

Second-trimester screening

High MSAFP is associated with NTDs, as well as abdominal wall defects and several other fetal abnormalities. High MSAFP, negative acetylcholinesterase (AChE), and normal ultrasound can be associated with congenital nephrosis or other syndromes, or a normal pregnancy. Unexplained high MSAFP is associated with mild increases in the incidence of preeclampsia, abruption, placental ischemia, preterm birth, fetal demise, low birth weight, and sudden infant death syndrome (SIDS). No trials have assessed specific management to prevent these complications [38].

Low unconjugated estriol is associated with steroid sulfatase deficiency, Smith-Lemli-Optitz, or other conditions when very low, usually <0.3 MOM [38].

MSAFP screening for NTD

Elevated (usually ≥2.5 MOM) MSAFP between 14 and 21 weeks is associated with a ≥90%–95% sensitivity for NTDs (false-negative rate 5%). Given that ultrasound is also ≥95% sensitive for NTDs, the routine use of MSAFP screening is most important for pregnancies that will not have a detailed second-trimester ultrasound.

Screening for aneuploidies in twins

NT is accurate in estimating risk for fetal aneuploidy in dizygotic twins, using each NT separately for each fetus. In monochorionic twins, the average NT is the most effective screening method. Detection rates comparable to singletons can be achieved.

Cell-free DNA screening can be used in twin gestations [39]. **Detection rates for trisomy 21 are similar to singleton gestations**; however, due to the small number of cases, it is not possible to accurately estimate detection rates for trisomy 18 and trisomy 13 [40].

Detection rates of FTS or STS tests are usually lower than in singletons, with higher rates of false-positive and false-negative results. Chorionicity does not seem to affect serum analytes in FTS or STS (see Chap. 44 in *Maternal-Fetal Evidence Based Guidelines*).

Diagnostic testing

Chorionic villus sampling and amniocentesis

Selected common indications for invasive prenatal diagnosis of fetal aneuploidy are listed in Table 5.7. Both CVS and amniocentesis have been performed for many years and can fairly safely diagnose a karyotypic or genetic abnormality. Both procedures have been studied extensively. Differences in technique, as well as timing of the procedure, affect loss rates. To fairly compare procedure-induced loss rates between the two procedures, adjustments must be made for the higher background frequency of pregnancy loss earlier in gestation.

TABLE 5.7: Selected Common Indications for Invasive Prenatal Diagnosis

- Abnormal first- or second-trimester aneuploidy screen
- Abnormal ultrasound findings
- Parental concern/anxiety
- Parental desire for diagnostic testing

CVS

CVS is typically performed between 10 and 13 weeks' gestation. The procedure should not be completed prior to 10 weeks, due to an unacceptably high incidence of limb deficiencies. The chorionic villi are sampled using ultrasound guidance and a special catheter to aspirate a sample of the placental cells. The placenta can be accessed through **either a transcervical or transabdominal approach**. There are no significant differences in pregnancy loss between transabdominal and transcervical CVS, with significant heterogeneity between studies [30, 41].

A systematic review of procedure-related losses for CVS and amniocentesis revealed pooled loss rates for CVS at 14 days, 30 days, and prior to 24 weeks of 0.7%, 1.3%, and 1.3%, respectively. The pooled loss rates for amniocentesis for the same period were 0.6%, 0.8%, and 0.9%, respectively [42]. In a recent meta-analysis, the procedure-related risk of miscarriage following CVS has been reported to be about 2/1000 [43]. Since CVS and amniocentesis are performed at different times, it is difficult to compare these procedures due to the higher background loss rate for the period when CVS is performed. The benefit of earliest diagnosis with CVS compared to amniocentesis should not be underestimated. With the advent of FTS, prenatal diagnosis has moved more to the first trimester. While the total miscarriage rate is higher following first-trimester CVS because of the higher background rate in early pregnancy, **for experienced centers, the rates of procedure-induced losses secondary to CVS are similar to those of second-trimester amniocentesis** [43]. In a recent meta-analysis, the weighted-pooled **procedure-related risk for pregnancy loss associated with CVS was 0.22%** (1 in 455) [44].

The learning curve for CVS has been estimated to exceed 400 cases, with postprocedure loss rates for operators having performed fewer than 100 cases being two to three times higher when compared to more experienced operators. **The importance of operator experience cannot be overemphasized**, particularly for the route of CVS, with transcervical CVS requiring more experience.

Second-trimester amniocentesis

For the purpose of genetic testing, amniocentesis is typically completed between 15 and 20 weeks of pregnancy. The procedure is performed using a 22-guage needle and direct ultrasound guidance to obtain a sample of amniotic fluid.

Second-trimester amniocentesis is associated with a 0.8% increase in spontaneous miscarriage (2.1% versus 1.3%; relative risk [RR] 1.60; 95% confidence interval [CI] 1.02–2.52), but similar incidence of perinatal deaths (0.4 vs. 0.7%) [29, 30]. In a meta-analysis, the procedure-related risk of miscarriage following amniocentesis was reported to be about **0.11% (1 in 900)** [44]. Amniocentesis is also associated with vaginal spotting and leakage of amniotic fluid. Rarely, injury to the fetus from the needle can occur.

Early amniocentesis

Early amniocentesis (<15 weeks) is not a safe early alternative to second-trimester amniocentesis because it is associated with

increased pregnancy loss when compared to traditional amniocentesis (2.5% vs. 0.7%), and higher incidence of talipes equinovarus (1.8% vs. 0.2%) compared to CVS [44]. Additionally, there is an increased rate of culture failure, which may require additional invasive procedures [45]. As a result, early amniocentesis is not currently recommended [1].

Genetic testing options for aneuploidy

Fluorescent in situ hybridization

Fluorescent in situ hybridization (FISH) allows for the rapid and accurate detection of trisomies 21, 18, and 13, as well as sex chromosome aneuploidy and triploidy. These common aneuploidies account for 80% of clinically significant chromosome conditions detected prenatally [46]. In the event of an abnormal FISH result, confirmatory testing should be completed using a conventional karyotype to determine if a chromosomal translocation is present. If FISH results are normal, then additional testing with conventional karyotype or chromosomal microarray (CMA) analysis should be considered to rule out less common aneuploidies or to identify smaller deletions or duplications that would be missed using FISH alone.

Conventional karyotype

Traditionally, conventional karyotyping has been the standard for prenatal diagnosis of fetal aneuploidy. Karyotype analysis allows for the detection of whole chromosomal aneuploidies, balanced and unbalanced translocation, and large deletions or duplications. Conventional karyotype has a resolution of 5–10 Mb. Karyotype analysis requires cell culturing, which can delay results and result in test failures.

Chromosomal microarray

CMA can query the entire human genome for copy number changes such as aneuploidy, deletions, duplications, and unbalanced translocations. Unlike traditional cytogenetics, which requires dividing cells, CMA does not require cell culture and can be completed on nondividing cells [47–52]. It can be particularly useful in cases of intrauterine fetal demise with congenital anomalies and culture failure with conventional karyotype [53].

In a high-risk population referred for prenatal diagnosis, CMA was compared to conventional karyotyping. The indications for prenatal diagnosis were ultrasound abnormalities, advanced maternal age, or a positive result on prenatal screening. CMA was similar to conventional karyotyping in detecting common chromosomal aneuploidy, but was able to detect clinically significant aneuploidies not detected by karyotype [54]. Another study demonstrated that CMA was more likely to provide genetic results after stillbirth when compared to conventional karyotype [55]. When structural abnormalities are detected by prenatal ultrasound, CMA can identify clinically significant chromosomal abnormalities in approximately 6% of the fetuses that have a normal karyotype [54]. For this reason, **CMA should be recommended as the primary test (replacing conventional karyotype) to patients undergoing prenatal diagnosis in whom a structural abnormality is detected by ultrasound**. Given its improved detection rates for clinically significant abnormalities, ACOG also recommends that CMA be made available to any patient electing to proceed with an invasive prenatal diagnostic test [56].

Targeted gene sequencing

In the event of normal karyotype or CMA testing results, additional genetic testing can be considered. Targeted panels can be considered if the phenotype is sufficiently defined to select an appropriate panel of genes to sequence.

Exome sequencing

Exome sequencing (ES) represents the next generation of prenatal genetic testing. ES uses massively parallel sequencings to sequence the entire coding regions of the genome, or the exons, which contains the majority of disease-causing mutations. Testing typically involves a trio approach, with testing of the fetus, the mother, and the father, to assist with categorization of variants as inherited or de novo.

In fetuses with anomalies, it has been estimated to have diagnostic rates between 6.2% and 80% [57]. Two large prospective cohort studies using ES in anomalous fetuses with normal karyotype and CMA showed an overall detection rate for diagnostic genetic variants in 9%–10% of fetuses and approximately 15%–20% of fetuses with two or more anomalies [58, 59]. In the case of nonimmune hydrops fetalis, ES was able to provide a genetic etiology in approximately 30% of cases [60].

Although promising, this new technology has many challenges that are still being uncovered, including long turnaround time for results, incomplete data on prenatal phenotypes and sequence variants, ethical issues related to incidental findings, the large amount of data and need for reanalysis, and a high cost associated with extensive DNA sequencing [61].

The decision to proceed with more advanced genetic testing should be made in consultation with a certified genetic counselor or medical geneticist.

Common karyotype abnormalities

Trisomy 21 (Down syndrome)

Historic notes

First complete description in 1846 by Seguin. Report by Down in 1866 established the name of the syndrome. In 1959 LeJeune and Jacobs independently described that Down syndrome was caused by trisomy 21.

Definition

Down syndrome is **trisomy 21**, or the presence of an extra chromosome number 21, either as three number 21s or as a translocation between 21 and another chromosome, usually an acrocentric in a Robertsonian translocation.

Epidemiology/Incidence

About **1 in 800 live births**. This is the most common trisomy at birth. Incidence increases with maternal age.

Embryology

The Down syndrome critical region on chromosome 21 is being studied extensively to identify the genes involved in the Down **syndrome phenotype**. However, this region is not one small, isolated spot, but most likely several areas on chromosome 21 that are not necessarily side by side.

Genetics/Inheritance

Error in cell division at the time of conception (**nondisjunction**) is responsible for 92% of Down syndrome cases resulting in **full trisomy 21**. Approximately 90% of nondisjunction occurs in the eggs. The cause of the nondisjunction error is not known, but there is a known association with maternal age. The recurrence risk is empirically 1% or the age-related risk as a woman

gets older. Three to four percent of all cases of trisomy 21 are due to a **Robertsonian translocation, most commonly** between chromosomes 14 and 21. In the balanced state, the individual is healthy and has 45 chromosomes with fusion of the entire long arm of chromosome 21 and another acrocentric chromosome (13, 14, 15, or 22). An individual with Down syndrome due to a Robertsonian translocation has 46 chromosomes with an unbalanced derivative chromosome. Translocations resulting in trisomy 21 may be inherited, so parental chromosomes must be checked. A female carrier of a balanced Robertsonian translocation has about a 12% risk of recurrence of trisomy 21 in future pregnancies, while a male carrier has approximately a 3% risk of recurrence. **Mosaic trisomy 21** occurs when there is a mixture of cell lines, some of which have normal chromosomes and another cell line with trisomy 21. It is impossible to know how the normal and trisomy 21 cells are distributed in the different organs; therefore, the percentage of mosaic to normal cells in the peripheral blood cannot be used to predict outcome. Another tissue can be examined to help determine the level of mosaicism, usually skin.

Teratology
None.

Classification
Full trisomy 21, translocation trisomy 21, and mosaic trisomy 21.

Risk factors/Associations
Advanced maternal age. Individuals who are carriers of balanced Robertsonian translocations involving chromosome 21 have an increased risk unrelated to age.

Pregnancy management
Screening (nonultrasound and/or ultrasound)
First- and second-trimester ultrasound, cell-free DNA screening, FTS, STS.

Ultrasound findings in fetus

- Thickened nuchal translucency at 11–14 weeks (80%) (at times cystic hygroma: 10%)
- Thickened nuchal fold (≥6 mm) at 16–23 weeks
- Congenital heart disease (CHD) (40%–50%)
- Duodenal atresia (2%)
- Omphalocele (2%)
- Ventriculomegaly
- Hydrops or some hydropic changes (pleural effusion, ascites)
- Several "soft markers," such as short humerus and femur, echogenic bowel, renal pyelectasis, cardiac (usually left ventricular) echogenic focus, short middle phalanx fifth digit, "sandal foot," iliac crest >90 degree angle, short ear length
- Biometry may reveal symmetric FGR by the third trimester
- Amniotic fluid: Polyhydramnios (if gastrointestinal [GI] obstruction or macroglossia present)
- Placenta: Normal
- Ultrasound after 14 weeks only detects ~50% of fetuses with trisomy 21. CPCs do not increase the risk. Screening provides the mother and family with a risk for trisomy 21, but diagnosis can only be achieved with CVS or amniocentesis.

Diagnosis
CVS or amniocentesis achieves the diagnosis by a study of the fetal chromosomes, which reveal trisomy 21. In the neonate, usually peripheral blood is cultured and karyotyped.

Counseling
The major abnormalities are increased risk of FGR, congenital heart defects, fetal and postnatal death, and developmental delay, with average IQ 50–75. Congenital heart defects are major contributors to mortality.

Workup/Investigations and consultations
A **fetal echocardiogram** is recommended. Depending on the lesions detected, specific pediatric subspecialty consultation can be offered. Genetic counseling can be offered as well. Care in a tertiary care center is indicated if there are significant associated anomalies or if they cannot be ruled out adequately.

Fetal intervention
None available

Termination issues
Termination can be offered as a sole intervention as regulated by local law (usually legal <24 weeks)

Fetal monitoring/Testing
No specific trials. NSTs weekly at ≥32 weeks can be offered. Nonreassuring fetal heart rate (NRFHR) is common.

Delivery/Anesthesia
Mode and management of delivery should not be affected by the diagnosis of trisomy 21. NRFHT is common.

Neonatology management
Resuscitation
Providing life support as needed, as in any other infant, is generally appropriate.

Transport
Indicated if counseling, general care, and/or major anomalies cannot be assessed and treated adequately at the birth institution.

Testing and confirmation
Karyotype is usually confirmed by blood lymphocyte culture.

Nursery management
Neonatal echocardiogram and physical exam to assess any anomaly. **Surgery** may need to be scheduled for GI or cardiac anomalies. Down syndrome presents with a wide variety of features and characteristics. A wide range of intellectual disability and developmental delay is noted among children with Down syndrome. There is a great deal of variability in the presence of other anomalies such as CHD, GI, and hematologic problems in these children. Hypothyroidism occurs in a high percentage of individuals with Down syndrome and should be monitored closely for their lifetime. **Early intervention** and specialized help with education and home rearing have improved the outcome in children with this condition. Many young adults with Down syndrome move in to community living arrangements and work regular jobs or in sheltered workshops.

Future pregnancy preconception counseling
With full trisomy 21, the recurrence risk is empirically 1% or the age-related risk. With Robertsonian translocation, parental

chromosomes should be checked, with genetic counseling regarding specific future risks. A Robertsonian translocation between two chromosomes 21, t(21;21) has a 100% risk for trisomy 21 when transmitted by a carrier parent. Also rare is a non-Robertsonian translocation formed by the union of two 21s such that the translocation forms a mirror image of the normal 21. Some literature suggests that in some families where there have been recurrent trisomies, a relationship exists with their MTHFR status. This has not been proven in large studies.

Helpful websites

- **General:** http://www.ds-health.com/
- **Health care guidelines for the care of individuals with Down syndrome:** http://www.denison.edu/collaborations/dsq/health96.html
- **Risk and recurrence risk of Down syndrome:** http://www.nas.com/downsyn/benke.html

Trisomy 18 (Edward syndrome)

Historic notes

Trisomy 18 was independently described by Edwards et al. and Smith et al. in 1960.

Definition

Edward syndrome is **trisomy 18**, or the presence of an extra chromosome number 18.

Epidemiology/Incidence

Incidence of 1 in 6600 live births in the United States and the United Kingdom. This is the second most common trisomy at birth. Incidence increases with increasing maternal age.

Embryology

The presence of three copies of chromosome 18 affects development of all organs.

Genetics/Inheritance/Recurrence

Extra chromosome 18 is usually (95%) secondary to de novo **meiotic nondisjunction** associated with advanced maternal age. In approximately 90% of cases, the extra chromosome is maternal in origin, with meiosis II errors occurring twice as frequently as meiosis I errors. Other human trisomies have a higher frequency of nondisjunction in maternal meiosis I. Approximately 80% of nondisjunctions occurs in females. **Mosaicism** occurs in approximately 10% and is due to postzygotic nondisjunction or anaphase lag. The causes of meiotic and mitotic nondisjunction are unknown. **Translocations** may also result in trisomy or partial trisomy 18 with varying phenotype due to monosomy of another chromosome and the variable size of the piece of chromosome 18 involved. The smallest extra region necessary for expression of serious anomalies of trisomy 18 appears to be 18q11-q12.

Teratology

None.

Classification

Trisomy 18 (95%), mosaic trisomy 18, and variable partial trisomy 18 related to translocations.

Risk factors/Associations

Advanced maternal age and translocation carriers have increased risk. Recurrence risk approximately 1% for full trisomy 18.

Pregnancy management

Screening

NT has a sensitivity of >80%; cell-free DNA screening and FTS have a sensitivity of >90%, STS is typically low alpha fetoprotein (AFP), low HCG, and low estriol with a sensitivity of about >80%. Accurate ultrasound is usually >90% sensitive for trisomy 18.

Ultrasound findings in fetus

- Thickened NT at 11–14 weeks (80%) (at times cystic hygroma: 15%)
- Thickened nuchal fold (≥6 mm) at 16–23 weeks
- CHD (90%)
- Omphalocele (25%)
- NTDs (20%)
- Clenched hands with overlapping fingers
- Clubbed or rocker-bottom feet
- CPCs (25%; most commonly isolated and seen in normal fetuses; karyotyping probably not indicated if isolated)
- Enlarged (>1 cm) cisterna magna
- Single umbilical artery
- Micrognathia
- Cleft lip or palate
- Hydrops or some hydropic changes (pleural effusion, ascites)
- Biometry may reveal FGR by the third trimester
- Amniotic fluid: Polyhydramnios (25%)
- Placenta: Normal

Diagnosis

CVS or amniocentesis

Counseling

Approximately 95% of concept uses with trisomy 18 die in embryonic or fetal life. Five to ten percent of affected children born alive survive beyond the first year of life. In utero, there are decreased fetal movements. Clinical findings the parents should be informed about include severe psychomotor and growth delay, microcephaly, microphthalmia, malformed ears, micrognathia or retrognathia, microstomia, distinctively clenched fingers, rocker-bottom feet, and other congenital malformations. **CHD occurs in 90%**, with ventricular septal defect (VSD) and polyvalvular heart disease (pulmonary and aortic valve defects) common. Renal anomalies and GI and brain malformations are common. Classical dermatoglyphics with digital arch patterns on finger and toe tips and distal palmar triradius with hypoplastic finger tips and small nails. Central apnea is a frequent cause of death, along with cardiac, CNS, and renal malformations [62].

If diagnosed prenatally, recommend discussion with parents about how to proceed in labor and delivery, including option to labor without monitoring, level of intervention desired by parents, and extent of resuscitation after delivery. Indication for C-section for fetal indications may be futile. **Parents need to be counseled that some children with trisomy 18 do survive and require lifelong complete care** but never achieve any independence. Few milestones are reached. There is an increased incidence of Wilms tumor in trisomy 18 children who survive. Cardiac surgery is controversial. In the first weeks, it may be considered a heroic measure, but if the child is surviving, it may make life more comfortable (comfort care). Apnea is a common cause of death.

Workup/Investigations and consultations required
A fetal echocardiogram is recommended. Genetic counseling can be offered. **Neonatal consultation** is extremely important to help the couple decide regarding neonatal management; usually just comfort care for the baby and psychological support for the parents are most appropriate.

Fetal intervention: None available.

Termination issues
Termination can be offered as the sole intervention as regulated by local law (usually legal <24 weeks).

Antepartum testing
As NRFHT is very common and the prognosis poor, fetal testing is not recommended. Many pregnancies continue without spontaneous labor until postterm (>42 weeks).

Delivery/Anesthesia
Fetal heart monitoring is usually declined and not indicated. Every attempt should be made to maximize the chances of vaginal delivery to minimize maternal morbidity, given the frequently fatal neonatal prognosis. Cesarean delivery for fetal indications is not recommended and should be discussed.

Neonatology management
Resuscitation
Comfort care only. Allow parents to grieve appropriately. Providing life support is usually not appropriate.

Transport
Not indicated.

Testing and confirmation
Karyotype is usually confirmed by blood lymphocyte culture.

Future pregnancy preconception counseling
With full trisomy 18, the recurrence risk is empirically 1% or the maternal age-related risk. With Robertsonian translocation, parental chromosomes should be analyzed, with genetic counseling regarding specific future risks. There are other rare translocations leading to trisomy 18.

Helpful website
https://rarediseases.info.nih.gov/diseases/6321/trisomy-18

Trisomy 13 (Patau syndrome)
Historic notes
Patau first identified in a laboratory in 1960 noting three of the group 13–15 chromosomes

Definition
Patau syndrome is **trisomy 13**, or the presence of an extra chromosome number 13.

Epidemiology/Incidence
1/10,000 live births. Incidence increases with increasing maternal age. Approximately 1% of all first-trimester spontaneous losses are due to trisomy 13.

Embryology
Extra chromosome 13 affects development of all organs.

Genetics/Inheritance
Extra chromosome # 13 resulting in **full trisomy 13** (80% of cases). This is due to maternal nondisjunction, usually in meiosis I. About 15% of cases are due to **translocation**, mostly Robertsonian translocation t(13q14). In 5% of cases, translocation is familial with a recurrence risk of 5% and risk of spontaneous abortion of 20%. The other cases are due to **mosaicism** (5%) with trisomy 13 and a normal cell line. Mosaicism cases may have a milder phenotype.

Teratology
None.

Classification
Trisomy 13, mosaic trisomy 13, and translocation trisomy or partial trisomy 13.

Risk factors/Associations
Advanced maternal age. Individuals who are carriers of balanced Robertsonian translocations involving chromosome 13 have an increased risk.

Pregnancy management
Screening
First-trimester ultrasound (with NT). Cell-free fetal DNA screening. First- or second-trimester multiple marker screening is not sensitive nor clinically useful for detecting trisomy 13. Accurate ultrasound is usually 90% sensitive for trisomy 13.

Ultrasound findings in fetus

- Thickened NT at 11–14 weeks (>70%) (at times cystic hygroma: 20%)
- Thickened nuchal fold (≥6 mm) at 16–23 weeks
- CHD (80%) (atrial septal defect [ASD] and VSD most common, but also often complex CHD)
- Holoprosencephaly (40%)
- Cleft lip and palate (45%)
- Hypotelorism/microphthalmia
- Polydactyly
- Rocker-bottom feet
- Omphalocele (10%)
- Polycystic kidneys (30%)
- Enlarged (>1 cm) cisterna magna (15%)
- NTDs
- Hydrops or some hydropic changes (pleural effusion, ascites)
- Biometry may reveal symmetric FGR by the third trimester
- Amniotic fluid: Polyhydramnios or oligohydramnios
- Placenta: Normal

Diagnosis
CVS or amniocentesis achieves the diagnosis by a study of the fetal chromosomes, which reveals trisomy 13. In the neonate, usually peripheral blood is cultured and karyotyped.

Counseling
Most trisomy 13 conceptions result in spontaneous abortions (SABs). Median survival is less than 3 days. Mean life expectancy is 130 days, with most dying in first month of life—95% die within 6 months. Apnea is a common cause of death and can happen at

home. The family needs to be prepared for intense care needs and possible sudden death. The most common causes of death are cardiopulmonary arrest, 69%; CHD, 13%; and pneumonia, 4%.

Some infants do survive, and those need complete care and achieve few milestones. Survival depends on associated medical problems. Survivors with trisomy 13 have severe intellectual disability and developmental delays. For survivors, specific growth charts are available for monitoring growth. Children with trisomy 13 are irritable, do not achieve milestones beyond smiling, and most need to be fed by tube.

If diagnosed prenatally, recommend discussion with parents about how to proceed in labor and delivery, including option to labor without monitoring, level of intervention desired by parents, and extent of resuscitation after delivery. Parents need to be counseled that some children with trisomy 13 do survive and require lifelong complete care and never achieve any independence

Workup/Investigations and consultations

A fetal echocardiogram is recommended. Genetic counseling can be offered. **Neonatal consultation** is extremely important to help the couple decide regarding neonatal management; usually just comfort care for the baby and psychological support for the parents are most appropriate.

Fetal intervention

None available.

Termination issues

Termination can be offered as the sole intervention as regulated by local law (usually legal <24 weeks).

Antepartum testing

As NRFHT is very common and the prognosis poor, fetal testing is not recommended. Many pregnancies continue without spontaneous labor until postterm (>42 weeks).

Delivery/Anesthesia

Fetal heart monitoring is usually declined and not indicated. Every attempt should be made to maximize the chances of vaginal delivery to minimize maternal morbidity, given the almost universally fatal neonatal prognosis.

Cesarean delivery for fetal indications is not recommended and should be discussed.

Neonatology management

Resuscitation

Comfort care only. Allow parents to grieve appropriately. Providing life support is usually not appropriate.

Transport

Not indicated.

Testing and confirmation

Karyotype is usually confirmed by blood lymphocyte culture.

Long-term care

Feeding issues, gastrostomy; irritability; chronic infections, aspiration pneumonia; heart failure; frequent hospitalizations; seizures; blindness and hearing loss; few milestones achieved (smile, laugh); parental stress.

Future pregnancy preconception counseling

With full trisomy 13, the recurrence risk is empirically 1% or the maternal age-related risk. With Robertsonian translocation, parental chromosomes should be checked, with genetic counseling regarding specific future risks. There are other rare translocations leading to trisomy 13. With rare translocation of t(13q13q), the risk of recurrence or SAB is 100%.

Helpful website

https://rarediseases.info.nih.gov/diseases/7341/trisomy-13

Turner syndrome

Historic notes

In 1938 Turner described the combination of sexual infantilism, webbed neck, and cubitus valgus. Ford showed in 1959 that this combination of findings was associated with a missing X chromosome.

Definition

Turner syndrome is the **presence of single X chromosome,** or **any karyotype with Xp missing** such as isochromosome Xq, ring X, or deletion Xp. Also called 45X0 or 45X syndrome.

Epidemiology/Incidence

1/2500 female births (**1/5000** total births). Ninety-eight to ninety-nine percent of Turner fetuses are spontaneously aborted; about 20% of all SABs are due to Turner syndrome.

Embryology

Lymphedema usually due to congenital hypoplasia of lymphatic channels.

Genetics/Inheritance

The **presence of a single X chromosome** or **any karyotype with Xp missing**, such as isochromosome Xq, ring X, or deletion Xp. The presence of a single X chromosome results from chromosomal nondisjunction. **Mosaicism** is common (40%) and may include a 46,XY karyotype associated with ambiguous genitalia. Since features of Turner syndrome are seen in other syndromes, karyotype is essential to make the diagnosis. Chromosome studies on more than one tissue may be needed to detect mosaicism. Not associated with advanced maternal age.

Teratology

None.

Classification

45,X in 50%. 46,X,i(Xq) in 17%, mosaicism in 40%.

Risk factors/Associations

Not associated with advanced maternal age. Differentiate from Noonan syndrome by karyotype, which is normal in Noonan syndrome.

Pregnancy management

Screening

FTS with NT measurement. Cell-free DNA screening, although detection rates are unknown.

Ultrasound findings in fetus

- Cystic hygroma
- Thickened nuchal fold (≥6 mm) at 16–23 weeks
- CHD (20%; usually left side: Coarctation, aortic stenosis, bicuspid aortic valve, left hypoplastic heart)
- Renal anomalies (60%)
- Hydrops or some hydropic changes (pleural effusion, ascites)

- Amniotic fluid: Occasionally oligohydramnios
- Placenta: Normal

Diagnosis
CVS or amniocentesis achieves the diagnosis with a study of the fetal chromosomes, which reveals 45,X or missing Xp. In the neonate, usually peripheral blood is cultured and karyotyped.

Counseling
45,X conceptions frequently (>95%) end in SAB. **The presence of a cystic hygroma with the diagnosis of Turner syndrome is associated with an estimated live birth rate of 2.6%, with only 1% surviving to infancy** [63]. If cystic hygroma is not present or resolves and the fetus is still alive >20 weeks, many survive until birth. Female infants with Turner syndrome have excess nuchal skin and edema of the hands and feet (80%) due to lymphedema. CHD, if present, usually most affects the prognosis and requires surgery and long-term care. In childhood, short stature is apparent. Teenagers have delayed puberty and primary amenorrhea (>90%) with infertility (>99%). Other clinical findings include shield-shaped chest with widely spaced nipples; low posterior hairline with webbing or shortness of neck; renal anomalies (60%); cubitus valgus; short fourth metacarpal; narrow, hyperconvex, and deep-set nails; hearing loss; and thyroid dysfunction. Some girls with Turner syndrome have learning difficulties, including difficulty with math and reading maps, related to a deficit in spatial ability. Intelligence and verbal skills are usually within the normal range. Mosaicism with a normal female cell line may result in a milder phenotype and spontaneous puberty with fertility but often early menopause. If there is a deleted X but the XIST locus is intact, normal random X-inactivation may occur, and the phenotype may be milder. If XIST is not present in a small X chromosome marker, the phenotype may be more severe. In mosaic 45,X/46,XY individuals clitoral enlargement may be present and virilization may occur. In these cases there is an increased risk of gonadoblastoma, and the gonad should be removed. Psychological impact of short stature, infertility, and learning difficulties needs to be discussed.

Workup/Investigations and consultations
A **fetal echocardiogram** is recommended. Depending on the lesions detected, specific pediatric subspecialty (in particular for cardiac anomalies) consultation can be offered. Genetic counseling can be offered as well. Care in a tertiary care center is indicated if there are significant associated anomalies or if they cannot be ruled out adequately. Endocrine follow-up is indicated.

Fetal intervention
None available.

Termination issues
Termination can be offered as the sole intervention as regulated by local law (usually legal <24 weeks).

Fetal monitoring/Testing
No specific trials. NSTs weekly at ≥32 weeks can be offered.

Delivery/Anesthesia
Mode and management of delivery should not be affected by the diagnosis of Turner syndrome.

Neonatology management
Resuscitation
Providing life support as needed, as in any other infant, is generally appropriate.

Transport
Indicated if counseling, general care, and/or major anomalies cannot be assessed and treated adequately at the birth institution.

Testing and confirmation
Karyotype is usually confirmed by blood lymphocyte culture.

Nursery management
Neonatal echocardiogram, **renal ultrasound**, and physical exam are indicated to assess any anomaly. **Surgery** may need to be scheduled for cardiac anomalies. **Early intervention** and specialized help with education have improved the outcome in children with Turner syndrome.

Long-term care
Thyroid studies annually; hearing test if otitis and not done before; speech evaluation, if needed; blood pressure checks routinely (hypertension a complication); annual echocardiogram to measure aortic root; annual urinalysis and culture if renal anomaly; use Turner growth curve after 2 years old; monitor diet (calories and calcium); ophthalmology follow-up as indicated; psychological support; individual education plan (IEP) at school if indicated; refer to endocrinologist in infancy, discuss growth hormone (GH) and hormone replacement therapy (HRT): GH treatment can improve growth and influence a girl's final adult height. HRT helps the girl with Turner syndrome develop the physical changes of puberty. In vitro fertilization can make it possible for some women with Turner syndrome to become pregnant using a donor egg. It is important to discuss at what age to inform the child of her diagnosis and its implications.

Future pregnancy preconception counseling
Recurrence risk in 45,X is not increased over population risk. There is an increased risk if associated with a translocation.

Klinefelter syndrome
Historic notes
In 1942, Dr. Harry Klinefelter described males who had enlarged breasts, sparse facial and body hair, small testes, and azoospermia. By the late 1950s these findings were associated initially with an extra Barr body, and later the extra X chromosome was identified with the karyotype 47,XXY.

Diagnosis/Definition
Chromosome study for 47,XXY. There are no specific phenotypic features to identify Klinefelter syndrome in an infant.

Epidemiology/Incidence
1 in 500 to 1 in 1000 male births.

Genetics/Inheritance/Recurrence/Future prevention
Advanced maternal age slightly increases the risk for XXY. Recent studies have shown that half the time, the extra chromosome comes from the father.

Risk factors/Associations
Advanced maternal age.

Screening
The prenatal phenotype is not well defined. Cell-free DNA screening, although detection rates are unknown.

Clinical features
Occasional breast enlargement, lack of facial and body hair, and a female-type body configuration. Small testes. Taller than others in their family. Delayed speech occurs in >50%. Poor gross motor coordination is present in ~27%. School difficulties are relatively common, and many boys with 47,XXY need assistance at school. Many are shy and somewhat passive and easy babies to care for. The average IQ is 90, with verbal IQ higher than performance IQ. XXY boys enter puberty normally, without any delay of physical maturity. But as puberty progresses, they fail to keep pace with other males. Most XXY boys benefit from receiving an injection of testosterone every 2 weeks, beginning at puberty.

Counseling
Regular injections of the male hormone testosterone, beginning at puberty, can promote strength and facial hair growth, as well as bring about a more muscular body type.

Psychological support and therapy can help with self-esteem issues and interaction with peers. Depression also may be a problem in adults.

Boys with 47,XXY have a slightly increased risk of autoimmune disorders such as type 1 (insulin dependent) diabetes, autoimmune thyroiditis, and lupus erythematosus. XXY males with enlarged breasts have the same risk of breast cancer as do women—roughly 50 times the risk of XY males. XXY males who do not receive testosterone injections may have an increased risk of developing osteoporosis in later life.

It is unnecessary to share this diagnosis outside of medical providers, as the diagnosis may be misunderstood.

Rare/Related
Variations include the XY/XXY mosaic, who may have enough normally functioning cells in the testes to allow them to father children. Males with two or even three additional X chromosomes have also been reported in the medical literature. In these individuals, the classic features of Klinefelter syndrome may be exaggerated, with low IQ or moderate to severe mental retardation also occurring. Testosterone injections may not be appropriate for all of them.

Helpful website
https://rarediseases.info.nih.gov/diseases/8705/klinefelter-syndrome

47,XXX
Diagnosis/Definition
Karyotype shows 47,XXX.

Epidemiology/Incidence
1:1000 newborn females.

Genetics/Inheritance/Recurrence
Sporadic, increased by advanced maternal age.

Risk factors/Associations
Advanced maternal age.

Screening
No identifying physical features in the fetus. Cell-free DNA screening, although detection rates are unknown.

Clinical features
Girls with 47,XXX are usually tall. Pubertal development is usually normal, and fertility is probably normal, but there may be an increased incidence of offspring with chromosome abnormalities.

Counseling
Girls with 47,XXX are shy and may demonstrate immaturity. The support of a loving and understanding family can improve the outcome for these girls. Many have learning difficulties (math and reading), but they are not intellectually disabled. The IQ of a girl with 47,XXX may be a few points lower than that of her siblings. Those diagnosed on amniocentesis or CVS with normal ultrasound, where the indication is Advanced maternal age (AMA), have a better prognosis than those diagnosed postnatally because a problem has been noted.

Selected microdeletions and duplications

DiGeorge syndrome (22q11.2 deletion syndrome)
Historic notes
DiGeorge syndrome, described in 1965, and velo-cardio-facial syndrome, described in 1978, are different manifestations of the same deletion of chromosome 22q11.2.

Diagnosis/Definition
FISH study reveals an interstitial deletion of chromosome 22 p11.2. Can be detected on microarray.

Epidemiology/Incidence
1 in 2000–4000 births

Embryology
Defects occur in the third and fourth pharyngeal pouches, which later develop into the thymus and parathyroid glands. Developmental abnormalities may also occur in the fourth branchial arch.

Genetics/Inheritance/Recurrence/Future prevention
Autosomal dominant inheritance. In 6% of affected individuals, one of the parents is affected. Expression is very variable, so both parents of an affected child should be tested for the deletion.

Risk factors/Associations
Other conditions have been noted to be associated with deleted 22q11.2, including conotruncal anomaly face syndrome (CAFS) (Japan) and sometimes Opitz G/BBB syndrome, CHARGE association, and Cayler cardiofacial syndrome.

Screening
All women with a fetus or neonate with a diagnosis of congenital heart defect, especially if conotruncal, can be offered testing (usually FISH) for this deletion. Testing is available from amniocytes or chorionic villi.

Clinical features
Characteristic facies, cardiovascular defects in 85%, most are VSD. Cleft of secondary palate, may be submucous cleft or velopharyngeal incompetence. Nasal reflux in infants. Transient neonatal hypocalcemia. Hypotonia. Immune system dysfunction. Postnatal growth delay. Developmental delay, learning disability, and psychological problems, especially in adolescence. Hypernasal speech.

Counseling (prognosis, complications, pregnancy considerations)

Clinical features should be reviewed. Early death due to CHDs before 6 months of age in 8%. Early intervention for speech and motor delays. Special education for older children. Chance of psychiatric disorders in 10%. Very variable phenotype, not predictable from laboratory result.

5p- (cri-du-chat syndrome)

Historic notes

In 1963, Lejeune et al. described a syndrome of multiple congenital anomalies; developmental delay; microcephaly; dysmorphic features; and a high-pitched, catlike cry in infants with deletion of a B group chromosome (Bp-), later identified as 5p-.

Diagnosis/Definition

5p- syndrome is characterized at birth by a high-pitched, catlike cry; low birth weight; poor muscle tone; and microcephaly. The cry is caused by abnormal laryngeal development. The cry disappears by age 2 years in about one-third of children with 5p-.

A karyotype is needed for the diagnosis. The size of the deletion of the short arm of chromosome 5 is variable, and a very small deletion may be missed using conventional G-banding. High-resolution studies may be needed or a FISH study using a specific probe for the small, deleted area of 5p that is essential for this diagnosis. Microarray would identify this deletion.

Epidemiology/Incidence

Estimated prevalence is about 1 in 50,000 live births. Up to 1% of profoundly retarded individuals have 5p-.

Genetics/Inheritance/Recurrence/Future prevention

May be sporadic (80%–85%) if both parents have normal chromosomes with a recurrence risk of less than 1%. In rare cases, gonadal mosaicism in one parent may result in a recurrence. If one parent carries a balanced translocation (10%–15%) involving 5p, the recurrence risk is substantially higher.

Most cases have a terminal deletion of 5p. The catlike cry maps to 5p15.3, and the cri-du-chat critical region is 5p15.2, which is associated with all the clinical features of the syndrome. The deletion is paternal in origin in 80% of cases.

Affected females are fertile and have a 50% chance of passing on the deletion to their offspring, although none is documented to have reproduced.

Risk factors/Associations

Increased risk if translocation carrier involving 5p.

Screening

Amniocentesis, CVS, ultrasound.

Counseling

Early feeding problems are common because of swallowing difficulties; poor suck with resultant failure to thrive. Death occurs in 6%–8% of the overall population with cri-du-chat due to pneumonia, aspiration pneumonia, and CHDs. Survival to adulthood is possible. Children who are raised at home with early intervention and schooling do better than those described in the early literature. Almost all individuals with 5p- have significant cognitive, speech, and motor delays (IQ rarely above 35). Many children can develop some language and motor skills. They may also become independent in self-care skills. Physical features include microcephaly, growth retardation, hypertelorism, epicanthal folds, downslanting palpebral fissures, round face with full cheeks, flat nasal bridge, downturned corners of mouth, micrognathia, low-set ears, and variable cardiac defects. Renal anomalies have been described, as have cleft lip and palate, talipes equinovarus, and gut malrotation. Treatment is symptomatic.

Helpful website

http://www.emedicine.com/ped/topic504.htm

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6

CARRIER SCREENING FOR INHERITED GENETIC CONDITIONS

Whitney Bender and Lorraine Dugoff

Key points

- The primary goals of carrier screening are to identify individuals and couples who are carriers of disease-causing variants that place them at increased risk of having a child with a serious medical disorder and provide them with information to optimize pregnancy outcomes based on their personal values and preferences.
- **Preconception carrier screening is preferred to prenatal carrier screening**, as it enables couples to consider the most complete range of reproductive options. Information regarding the risk of having an affected child may influence a couple's decision to conceive or to consider the use of donor gametes, preimplantation genetic diagnosis, or prenatal genetic testing.
- **Information regarding genetic carrier screening should be provided to every pregnant woman**.
- Most inherited genetic conditions are autosomal recessive. Carriers for these conditions are usually asymptomatic, have no significant family history, and are unaware of their carrier status.
- Current professional guidelines by the American College of Obstetricians and Gynecologists (ACOG) and the American College of Medical Genetics and Genomics (ACMG) **recommend pan-ethnic carrier screening for cystic fibrosis** (CF) and **spinal muscular atrophy** (SMA).
- ACOG recommends that individuals of African, Southeast Asian, and Mediterranean ancestry should have screening for **hemoglobinopathies** with a complete blood count in combination with a **hemoglobin electrophoresis**.
- Prenatal testing for **fragile X syndrome** should be offered to known carriers of the fragile X premutation or full mutation. Women with a family history of fragile X–related disorders, unexplained intellectual disability or developmental delay, autism, or premature ovarian insufficiency are candidates for genetic counseling and fragile X premutation carrier screening.
- Carrier screening for Tay–Sachs disease, Canavan disease, CF, and familial dysautonomia should be offered to **Ashkenazi Jewish (one Jewish grandparent)** individuals before conception or during early pregnancy. The availability of genetic carrier screening for mucolipidosis IV, Niemann-Pick disease type A, Fanconi anemia group C, Bloom syndrome, and Gaucher disease should be discussed.
- **Patients with a positive family history of a genetic condition should be referred for genetic counseling** to review the family history, provide accurate information regarding risk, offer the appropriate genetic testing, and discuss reproductive options.
- Historically, professional practice guidelines recommended **targeted carrier screening** for individual conditions based on race or ethnicity, condition severity, carrier frequency, prevalence, detection rates, and residual risk. This approach is **limited due to inaccurate or unavailable information regarding ancestry, increased intermixing between different races/ethnicities, and the presence of carriers for genetic conditions in the nontargeted populations**.
- Technological advances in next-generation sequencing have made it possible to perform **expanded carrier screening**, which involves screening for variants associated with multiple genetic diseases simultaneously irrespective of ancestry (pan-ethnic screening). **Pan-ethnic screening can identify more carriers and narrow the equity gap inherent in ethnicity-based screening**. Although pan-ethnic screening is deemed acceptable by medical societies, it is currently not recommended.
- Professional practice guidelines and recommendations are needed regarding patient and provider education and the conditions that should be included on expanded carrier screening panels.
- **Appropriate pre- and posttest counseling regarding prognosis, possible complications, long-term issues, and follow-up should be provided to every couple with a pre- or postnatal diagnosis of genetic disorders**.

Background

Carrier screening for single-gene disorders, also known as Mendelian disorders, is an important component of preconception and prenatal care. Carrier screening enables identification of individuals and couples at risk of transmitting disease-causing genetic variants to their offspring at the time of fertilization. **Preconception carrier screening** can increase the reproductive autonomy of individuals and couples by providing them with knowledge that could lead to the broadest range of available options, including preimplantation genetic testing for monogenetic/single gene disorders (PGT-M), adoption, the use of gamete donors, and prenatal diagnostic testing.

Single-gene disorders result from a disease-causing variant at a single genetic locus. Although single-gene disorders are not very common individually, autosomal recessive and X-linked disorders collectively occur in up to 1/175 pregnancies [1]. Severe or profound single-gene disorders occur in 1 in 545 pregnancies and account for 20% of pediatric hospitalizations and 18% of pediatric deaths [2–4].

This chapter will review carrier screening approaches, current society guidelines, genetic counseling principles, and some of the more common genetic conditions currently included in society screening guidelines.

Carrier screening approaches

Ethnicity-based screening

Historically, screening approaches to identify pregnancies at risk for genetic disorders relied upon a patient's reported race

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or ethnicity. For example, individuals of African American race were offered screening for sickle cell disease, while individuals of Northern European ancestry were offered cystic fibrosis (CF) screening.

Ethnicity-based screening is limited by the fact that many individuals do not have accurate knowledge of their race or ethnic ancestry. In addition, increasing numbers of couples are of mixed race and ethnicity. A recent study of 93,419 individuals undergoing a 96-gene expanded carrier screen reported that 9% of individuals had greater than 50% of genetic ancestry from a lineage inconsistent with self-reported ethnicity. Limitations of self-reported ancestry led to missed carriers in at-risk populations. In addition, for 7 of the 16 conditions included in current screening guidelines, most carriers were not from the population the guideline aimed to serve [5]. Therefore, the perpetuation of ethnic or racial bias in carrier detection utilizing these approaches is a significant concern.

Pan-ethnic screening

In pan-ethnic screening, carrier screening for a panel of disorders is offered to all individuals regardless of ethnicity. This strategy encompasses screening for specific recommended conditions. This approach satisfies the **ethical principle of justice, as all individuals are offered the same screening panel regardless of race** [6].

Expanded carrier screening

Expanded carrier screening involves **simultaneous screening for multiple genetic conditions regardless of a patient's race/ethnicity (pan-ethnic screening)**. Technological advances in next-generation sequencing have made it possible to efficiently screen for a large number of conditions simultaneously for the same cost as one or two single-gene carrier tests. Screening panels offered by laboratories vary and may include options to screen for up to several hundred conditions.

Expanded carrier screening has a number of advantages

It can overcome the limitations associated with the targeted ethnicity-based screening approach, including inaccurate and unavailable information regarding ancestry, increased intermixing between different races/ethnicities, and the presence of carriers for genetic conditions in the nontargeted populations. Data from expanded carrier screening studies have demonstrated that diseases currently recommended for screening only in certain populations, such as Canavan disease and sickle cell disease, are widely distributed outside of their targeted populations [7, 5]. A modeling analysis based on data from expanded carrier screening in 346,790 individuals demonstrated that expanded carrier screening may increase the detection of carrier status for a variety of potentially serious genetic conditions [8]. Expanded carrier screening may be the preferred approach for consanguineous couples in which both members of the couple may be carriers of the same rare autosomal recessive disorder.

Data are emerging regarding the clinical use of expanded carrier screening. Among 391 at-risk couples who underwent expanded carrier screening and were found to be at risk of having an affected fetus, **77% of those diagnosed prior to pregnancy planned or pursued action to avoid having an affected offspring. Of those diagnosed in pregnancy, 37% elected to have prenatal diagnostic testing** [9].

Carrier screening guidelines

The American College of Obstetrics and Gynecology (ACOG) acknowledges that ethnic-specific, pan-ethnic, and expanded carrier screening are acceptable strategies for pre-pregnancy and prenatal carrier screening [10]. ACOG recommends that **all pregnant women or women considering pregnancy be offered screening for spinal muscular atrophy (SMA), CF, and hemoglobinopathies**. Screening for fragile X syndrome, Tay-Sachs disease (TSD), and other genetic conditions commonly affecting individuals of Jewish descent (Canavan disease and familial dysautonomia) are recommended on the basis of family history or background. ACOG recommends **that conditions included on an expanded carrier screening have a carrier frequency of 1 in 100 or greater** [10]. Of note, the recommendation does not provide guidance with respect to X-linked disorders, and it does not specify the ethnicities in which the 1 in 100 threshold should be applied.

The American College of Medical Genetics and Genomics (ACMG) also recommends pan-ethnic carrier screening for CF and SMA. **In addition to the conditions recommended by ACOG for individuals of Ashkenazi Jewish descent, ACMG recommends offering screening for Fanconi anemia group C, Niemann-Pick disease type A, Bloom syndrome, mucolipidosis type IV, and Gaucher disease**.

Genetic counseling

All individuals and couples considering pregnancy should have a basic screen for family history of genetic disorders, with a pedigree to at least the second prior generation (three-generation pedigree). Questions should also involve history of birth defects, stillbirth, intellectual disability, developmental delay, recurrent spontaneous pregnancy loss, history of a previous fetus or child who was affected by a genetic disorder, and cancer history. It is **optimal to offer carrier screening preconception** so that women and their partners have the option to consider how much genetic information they would like to have before starting a family. Carrier screening results in the preconception period may influence a couple's decision to conceive or to consider the use of donor gametes, preimplantation genetic diagnosis, or prenatal genetic testing. Additionally, genetic carrier screening should be performed on potential gamete donors.

Information regarding genetic carrier screening should be provided to every pregnant woman. As recommended by ACOG, screening for CF and SMA should be discussed with every pregnant woman. Those patients belonging to an ethnic group at increased risk for a recessive condition (e.g. sickle cell—African-American; TSD and others—Jewish; TSD in Irish, Cajun, and French Canadian; alpha-thalassemia—Southeast Asian; and beta-thalassemia—Mediterranean) should be offered specific screening.

Providers may also offer an expanded carrier screening panel. Individuals offered expanded carrier screening should have appropriate pretest counseling. Since expanded carrier screens can include over 100 conditions, it is not feasible to counsel patients regarding the specific conditions on the panel. It is important to discuss the concept of residual risk with patients undergoing carrier screening. While sequencing has significantly increased detection rates, the sensitivity is not 100% for any condition. Table 6.1 lists points to include in the pretest counseling and consent process [11].

TABLE 6.1: Discussion Points for Pretest Counseling and Consent Process for Expanded Carrier Screening

1. Carrier screening is voluntary. Patients can choose to participate or decline.
2. Genetic testing results are confidential and protected in employment and health insurance by the Genetic Information Non-Discrimination Act of 2008.
3. Expanded carrier screening panels include conditions that may vary in severity. The panels include many conditions that are associated with significant adverse outcomes, including decreased life expectancy, cognitive impairment, and the need for medical and/or surgical intervention.
4. Accurate knowledge of paternity is necessary to provide accurate information regarding risk. DNA (or blood) from the biologic father is necessary in order to provide risk assessments for autosomal recessive conditions.
5. There is a residual risk for having an affected offspring even if both partners screen negative. This risk may vary depending on ethnicity, the specific condition, and the laboratory performing the testing.
6. It is common to identify carriers for one or more conditions when using expanded screening panels. In most cases, being a carrier has no significant medical consequences for the individual. If two partners are carriers of different autosomal recessive conditions, offspring are not likely to be affected.
7. It is possible that carrier screening will determine that an individual has two pathogenic variants for a condition and thus has an autosomal recessive condition that might affect their health. Expanded carrier screening panels that include autosomal dominant and X-linked conditions may detect individuals affected with one of these conditions. In these situations, individuals should be referred for genetic counseling and appropriate medical management.

Source: From Ref. [9] under Creative Commons Attribution license.

In approximately 1.7%–2.5% of couples undergoing expanded carrier screening, both members will be identified as carriers of a pathogenic variant for the same condition [12–14]. If a patient and her partner both test positive as carriers for the same autosomal recessive genetic condition, or if a patient tests positive as a carrier for an X-linked condition, they should be referred to a certified genetics professional to discuss the implications and reproductive options.

In addition to implications for a potential fetus, patients undergoing expanded carrier screening should be counseled regarding the potential for results that have direct personal health consequences. Some of the genes associated with potential consequences in the carrier of a disease-causing variant are discussed briefly next.

FMR-1

Female carriers with the premutation of this FMRP translational regulator 1 gene (55-200 CGG repeats) have an increased risk of premature ovarian failure. Premature ovarian failure is defined as the development of hypergonadotropic hypogonadism prior to age 40. Male carriers of the premutation are at risk of fragile X–associated tremor/ataxia syndrome (FXTAS). This disease may develop in as many as 20%–33% of adult male permutation carriers, with increasing age and length of CGG repeats correlated with greater motor impairment [15]. FXTAS may also occur in female carriers due to X-inactivation.

DMD

Female carriers of mutations in the Duchene muscular dystrophy (DMD) gene may develop an abnormal skeletal or cardiac muscle phenotype. The muscle disease is quite variable and could include creatine–kinase elevation, exercise intolerance, muscle cramps, or muscle weakness and wasting [16]. Cardiac manifestations are also possible, although their frequency and features are variable. Myocardial fibrosis, electrocardiogram (ECG) abnormalities, systolic dysfunction, and dilated cardiomyopathy have been described [16]. A screening echocardiogram is recommended for known female carriers of DMD.

ATM

Carriers of pathogenic variants in the ataxia–telangiectasia mutated (ATM) gene are at an increased risk of breast cancer compared to noncarriers. These individuals are at a twofold higher risk of breast cancer with a cumulative lifetime risk of approximately 30% [17].

GBA

Carriers of mutations in the glucocerebrosidase (GBA) gene are at increased risk for Parkinson disease and other movement disorders. The risk of Parkinson disease among carriers is increased between twofold and sevenfold over noncarriers. Among patients ultimately diagnosed with Parkinson disease, those with a GBA mutation had younger onset; greater likelihood of cognitive impairment; and less prominent tremor, bradykinesia, and rigidity [18].

Women with a specific indication for genetic testing should be referred for genetic counseling and a discussion of options available for prenatal diagnosis. **Responsibilities of clinicians** (e.g. ob-gyns, family medicine specialists, and nurse midwives) caring for pregnant women regarding genetic screening are shown in Table 6.2 [19]. **Possible indications for genetic consultation** for preconception and prenatal patients are shown in Table 6.3 [20]. **Possible indications for genetic consultation for adult patients** are shown in Table 6.4 [20].

TABLE 6.2: Responsibilities of Clinicians Caring for Pregnant Women Regarding Genetic Screening

1. Clinicians should be able to identify patients within their practices who are candidates for genetic testing and should maintain competence in the face of increasing genetic knowledge.
2. Obstetrician-gynecologists should recognize that geneticists and genetic counselors are an important part of the health care team and should consult with them and refer as needed.
3. Discussions with patients about the importance of genetic information for their kindred, as well as a recommendation that information be shared with potentially affected family members as appropriate, should be a standard part of genetic counseling.
4. Obstetrician-gynecologists should be aware that genetic information has the potential to lead to discrimination in the workplace and to adversely affect an individual's insurability. In addition to including this information in counseling materials, physicians should recognize that their obligation to professionalism includes a mandate to prevent discrimination.

Source: From Ref. [19] with permission.

TABLE 6.3: Possible Indications for Genetic Consultation for Preconception and Prenatal Patients

Either Member of the Couple with	Reason to Consider Consultation
A positive carrier screening test for a genetic condition such as cystic fibrosis[a]	Discuss additional testing strategies and inheritance, testing of partner and siblings
A personal history of stillbirths, previous child with hydrops, recurrent pregnancy losses, or a child with sudden infant death syndrome (SIDS)	Rule out a chromosomal, metabolic, or syndromic diagnosis associated with an unexplained neonatal death or SIDS
A progressive neurologic condition known to be genetically determined, such as progressive ataxia	Discuss a potential diagnosis, the differential diagnosis, inheritance, and testing options
A statin-induced myopathy	Discuss a potential mitochondrial disorder, inheritance, and testing options
A birth defect such as cleft lip	Discuss recurrence risks and testing options
A chromosomal abnormality such as translocation	Discuss risks to the fetus and testing options
Significant hearing or vision loss thought to be genetically determined	Discuss risks to the fetus and testing options
Intellectual disability, developmental delay or autism	Discuss risks to the fetus and testing options

Source: From Ref. [20] with permission.

[a] If a patient tests positive as a carrier for an autosomal recessive condition, carrier testing should be offered to the patient's partner. This does not require consultation with a genetic counselor.

Abbreviation: SIDS, sudden infant death syndrome.

Common genetic disorders

Cystic fibrosis

CF is the most common life-limiting genetic disorder in Caucasians [21]. Faulty chloride transport leads to increased sweat chloride levels and increased viscosity of secretions in the lungs, pancreas, biliary tree, and intestines.

CF is an autosomal recessive disorder resulting from pathogenic variants in the cystic fibrosis transmembrane conductance regulator (CFTR) protein. The most common mutation is ΔF508, but >1700 other mutations have been described [21].

CF screening should be offered to all women of reproductive age [18, 21–23]. It is generally more cost-effective and practical to **initially perform CF carrier screening for the patient only** [21].

TABLE 6.4: Possible Indications for Genetic Consultation for Adult Patients

Personal History of	Reason to Consider Consultation
Abnormal sexual maturation or delayed puberty	Rule out an intersex condition, chromosomal abnormality, or syndromic diagnosis
Recurrent pregnancy losses (more than two)	Rule out a chromosomal rearrangement such as a balanced translocation with karyotype
Tall or short stature for genetic background	Rule out a skeletal dysplasia, chromosomal, or syndromic diagnosis
One or more birth defects	Rule out a chromosomal or syndromic diagnosis, and provide genetic counseling
Six or more cafe-au-lait macules >1.5 cm in diameter	Rule out neurofibromatosis type 1
Statin-induced myopathy	Rule out a mitochondrial disorder
A cancer or cancers known to be associated with specific genes or mutations in the context of a compelling family history: young age at onset, bilateral lesions, and familial clustering of related tumors	Rule out an identifiable mutation in a gene such as *BRCA1*; rule out a cancer syndrome (MEN2); discuss surveillance, treatment, testing options, and inheritance
Cardiovascular problems known to be associated with genetic factors such as cardiomyopathy	Rule out a mutation in a causative or contributory gene; discuss surveillance, treatment, testing options, and inheritance
Suspected genetic disorder affecting connective tissue	Rule out a syndromic diagnosis (Marfan syndrome); discuss surveillance, treatment, testing options, and inheritance
Hematologic condition associated with excessive bleeding or excessive clotting	Confirm or rule out genetic condition; discuss treatment, testing options, and inheritance
Progressive neurologic condition known to be genetically determined, such as unexplained myopathy	Confirm or rule out suspected diagnosis; discuss surveillance, treatment, testing options, and inheritance
Visual loss known to be associated with genetic factors, such as retinitis pigmentosa	Rule out a syndromic diagnosis (Stickler syndrome); discuss testing options, if applicable, and inheritance
Early-onset hearing loss	Rule out a syndromic or nonsyndromic genetic form of hearing loss; discuss surveillance, testing options, and inheritance
Recognized genetic disorder, including a chromosomal or single-gene disorder	Confirm the diagnosis; discuss prognosis, medical management, and inheritance
Mental illness such as schizophrenia	Rule out a genetic condition associated with this history
A close relative with a sudden, unexplained death, particularly at a young age	Discuss diagnosis, inheritance, recurrence risks, and identify syndromes, when possible

Source: From Ref. [20] with permission.

TABLE 6.5: Potential Screening Strategies for CF

Patient History	Testing Considerations
No family history	• Initial screening of one partner
Sequential	• Other partner tested if first partner is positive • Low-risk racial/ethnic groups
Concurrent	• Other partner not available • Both partners tested simultaneously • Both partners' results revealed • Assesses couple's risk • Identifies couples at risk more rapidly • More precise
Known family history	• Ideally, test for specific mutation of affected family member

Source: Adapted from Ref. [21].
Abbreviation: CF, cystic fibrosis.

Nonetheless, screening can be concurrent or sequential, and both strategies are acceptable. Details of these screening strategies are shown in Table 6.5. If a patient or the patient's partner has a family history of CF, medical record review should be performed to identify if information regarding the specific CFTR variant in the affected family member is available. Additionally, if a woman's reproductive partner has apparently isolated congenital bilateral absence of the vas deferens, the couple should be referred for a genetics consultation to discuss variant analysis for CF.

The interpretation of CF screening results and recommended clinical follow-up are detailed in Table 6.6. It is important to remember that screening panels cannot test for all of the possible pathogenic CFTR variants, and, as such, there exists potential for undiscovered pathogenic variants to exist in all patients who undergo screening. This concept is called the **residual risk**. The exact residual risk will differ depending on the patient's ethnicity, with ethnicities with lower prevalence typically having a higher residual risk, and the exact screening test utilized. A sample residual risk table for the most common 23-mutation CF panel is shown in Table 6.7. It is important, however, to note the specific residual risk listed in a patient's results report and use this for patient counseling.

Hemoglobinopathies

Hemoglobinopathies are a diverse group of inherited single-gene disorders that result from variations in the structure and/or function of hemoglobin. The most common hemoglobinopathies—sickle cell disease, beta-thalassemia, and alpha-thalassemia—are all autosomal recessive conditions. A brief discussion of each of these disorders is included next. ACOG recommends carrier screening for individuals of African, Southeast Asian, and Mediterranean ancestry. Figure 6.1 outlines a screening strategy [22]. A complete blood count (CBC) in combination with a hemoglobin electrophoresis is recommended for screening individuals of African ancestry. A CBC with red cell indices is the initial recommended screening test for individuals of Southeast Asian and Mediterranean ancestry. Individuals with a low mean corpuscular volume (MCV) and normal iron status should have a hemoglobin electrophoresis. Southeast Asians with a normal hemoglobin electrophoresis should have molecular testing to rule out alpha-globin gene deletions characteristic of alpha-thalassemia. Couples determined to be at increased risk for having a child with sickle cell disease or thalassemia should be referred to a genetic counselor [24]. For additional information regarding hemoglobinopathies, refer to Chaps. 14 and 15 in *Maternal-Fetal Medicine Evidence Based Guidelines*.

Sickle cell disease

Sickle cell disease refers to a group of autosomal recessive disorders involving hemoglobin S. Hemoglobin S differs from hemoglobin A due to a single nucleotide substitution in the beta-globin gene on chromosome 11. The most severe form of sickle cell disease, sickle cell anemia, occurs in individuals with two copies of hemoglobin S. Sickle cell disorders can also occur in individuals who have hemoglobin S and another abnormality of B-globin structure or production such as hemoglobin C or beta-thalassemia. Sickle cell disease occurs most commonly in people of African origin. One in 12 African Americans has sickle cell trait. Patients with sickle cell disease are prone to distortion, or sickling, of their red blood cells under conditions of decreased oxygen tension. These distorted cells can result in increased viscosity, hemolysis, and anemia, resulting in interrupted blood supply to vital organs. These vasoocclusive crises can cause interruption of normal perfusion and function of several organs, including the spleen, lungs, kidney, heart, and brain. See Chap. 15 in *Maternal-Fetal Medicine Evidence Based Guidelines*.

Beta-thalassemia

Beta-thalassemia is also caused by a mutation in the beta-globin gene on chromosome 11. This results in the inability to produce hemoglobin A. Individuals who are heterozygous for this mutation have beta-thalassemia minor. Depending upon the amount of normal beta-globin chain production, disease severity varies. Typically, asymptomatic mild anemia is present. Individuals who are homozygous for this mutation have beta-thalassemia major, or Cooley anemia. This disease is characterized by severe anemia with extramedullary hematopoiesis, delayed sexual development,

TABLE 6.6: Interpretation of Cystic Fibrosis Test Results and Recommended Follow-Up

Partner One Carrier Testing	Partner Two Carrier Testing	Recommended Follow-Up
Negative	Negative	Review residual risk Diagnostic testing not indicated
Negative	Screening not completed	Can utilize ethnic-specific carrier risk Diagnostic testing not indicated
Positive	Negative	Review residual risk Diagnostic testing not indicated
Positive	Screening not completed	Genetic counseling Efforts made to screen partner
Positive	Positive	Genetic counseling Offer prenatal diagnostic testing or PGT-M (if preconception)

Source: Adapted from Ref. [21].
Abbreviation: PGT-M, preimplantation genetic testing for monogenetic/single gene disorders.

TABLE 6.7: Incidence and Carrier Risk for CF Based on Race or Ethnicity

Racial or Ethnic Group	Detection Rate (%)	Estimated Carrier Risk before Test	Estimated Carrier Risk after a (–) Test
Ashkenazi Jewish	94	1/24	~1/380
Non-Hispanic white	88	1/25	~1/200
Hispanic white	72	1/58	~1/200
African American	64	1/61	~1/170
Asian American	49	1/94	~1/180

Source: From Ref. [21] with permission.

and poor growth. Although elevated levels of Hb F are produced in an attempt to compensate for the absence of Hb A, this condition is universally fatal in late childhood unless treatment with periodic blood transfusions is initiated early. See Chap. 14 in *Maternal-Fetal Medicine Evidence Based Guidelines*.

Alpha-thalassemia

Alpha-thalassemia results from a gene deletion of two or more copies of the four alpha-globin genes on chromosome 16. It is common among individuals of Southeast Asian, African, West Indian, and Mediterranean ancestry. Deletion of two genes, alpha-thalassemia trait, causes a mild hemolytic anemia. The deletions may occur on the same chromosome (cis aa/-) or on two different chromosomes (trans a-/a-). Individuals of Southeast Asian descent are more likely to carry the cis configuration compared to their African counterparts. Individuals with alpha-thalassemia trait are at increased risk for having a child with a more severe form of alpha-thalassemia. Hemoglobin H disease is caused by the deletion of three alpha-globin genes. Affected individuals have mild to moderate hemolytic anemia. Alpha-thalassemia major (Hb Bart disease) results from the absence of functional alpha-globin genes. Fetal hydrops and intrauterine fetal demise is the expected outcome in these cases due to the inability to produce functional HbF. Hemoglobin Bart disease does not usually occur in fetuses of alpha-thalassemia carriers of African origin, since individuals of African descent usually have the trans-configuration genotype. See Chap. 14 in *Maternal-Fetal Medicine Evidence Based Guidelines*.

Fragile X syndrome

Fragile X syndrome is the most common inherited cause of intellectual disability. The prevalence is 1 in 3600 males and 1 in 4000–6000 females [25].

Affected males may display a wide range of behavioral and cognitive manifestations, but they are never asymptomatic [23]. The behavioral phenotype is characterized by autism spectrum behaviors such as attention deficit/hyperactivity, expressive delay, tactile defensiveness, perseverative speech, and echolalia, as well

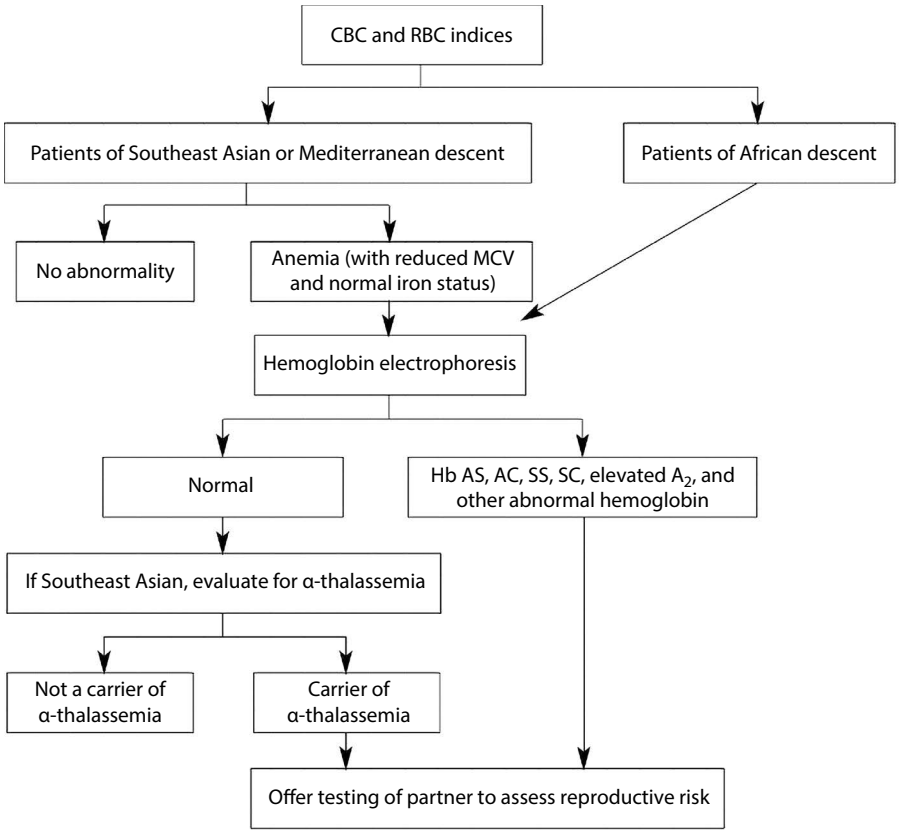


FIGURE 6.1 Screening strategy for anemia. (From Ref. [24] with permission.) *Abbreviations*: CBC, complete blood count; Hb, hemoglobin; MCV, mean corpuscular volume; RBC, red blood cells.

as social anxiety and avoidance of eye contact. The cognitive phenotype generally is moderate to severe mental impairment. Ten to twenty percent have seizures. Physical characteristics are more readily identifiable around or after puberty. These findings are similar to a connective tissue disorder, including hyperextensible joints; soft, smooth skin; flat feet; and mitral valve prolapse. The facial appearance is often described as long and narrow with prognathism and large ears. Macrocephaly may also be present. Most develop macroorchidism [25].

Affected females tend to have more normal cognitive development, with approximately 33% of affected females having mental retardation. The remaining either have mild learning disabilities or normal intelligence Their physical features are also often less pronounced than their male counterparts.

Fragile X is an X-linked dominant disorder caused by expansion of a repetition of the CGG trinucleotide segment of the fragile X mental retardation 1 (FMR-1) gene. This gene is located on the X chromosome at Xq27.3.The full mutation (>200 repeats) results in the reduction or absence of fragile X mental retardation protein (FMRP), an RNA-binding protein involved in the maturation and elimination of synapses.

The FMR-1 gene is typically composed of a limited number (<45) of CGG repeats. This region is usually stable and passes from one generation to the next. It is possible for this region to expand during meiosis in oocytes, reaching either intermediate (45–54 repeats) or premutation (55–200 repeats) lengths. As repeat size increases, stability decreases, and further increases in the number of repeats become likely. Once the premutation reaches expansion to >90 repeats, the likelihood of expansion to a full mutation is at least 80% (Table 6.8) [26].

In addition to the presence of CGG trinucleotide repeats, there may be AGG trinucleotide repeats within the FMR-1 gene. The presence of AGG repeats is associated with increased stability of the permutation allele. In contrast, few or no AGG repeats are associated with an increased risk of expansion in the next generation, as seen in Figure 6.2.

Only women with a premutation FMR-1 can pass the full mutation to their offspring. Fathers with premutations usually pass the gene in a stable fashion to all of their daughters and risk having affected grandsons. Premutation male and female carriers are at risk for FXTAS, usually after age 50 years [25]. Female carriers are also at risk of premature ovarian insufficiency.

TABLE 6.8: Fragile X: Risk of Full Mutation (and Therefore Affected Child) Based on Number of Maternal CGG Repeats

No. Maternal CGG Repeats	% Risk Expansion to Full Mutation
55–59	4
60–69	5
70–79	31
80–89	58
90–99	80
100–200	98

Source: From Ref. [26] with permission.

Prenatal testing for fragile X syndrome should be offered to known carriers of the fragile X premutation or full mutation. Women with a family history of fragile X–related disorders, FXTAS, unexplained intellectual disability or developmental delay, autism, or premature ovarian insufficiency are candidates for genetic counseling and fragile X premutation carrier screening [25]. Careful assessment of the family history for males with cognitive impairment should be performed to identify individuals at sufficient likelihood of premutation or full mutation carrier status to warrant screening.

Women who accept fragile X premutation screening should be offered FMR-1 DNA mutation analysis after genetic counseling about the risks, benefits, and limitations of screening [25]. All identified carriers should be referred for follow-up genetic counseling. Diagnostic modalities for prenatal diagnosis (including chorionic villus sampling [CVS] and amniocentesis) should be discussed.

Spinal muscular atrophy

SMA refers to a group of diseases that affect the motor neurons of the spinal cord and brainstem. These neurons are responsible for supplying electrical and chemical signals to muscle cells. Malfunction of these neurons causes improper muscle cell functioning and atrophy, resulting in muscle degeneration and weakness. The prevalence of SMA is 1/10,000 infants [27].

SMA is classified into one of four types depending on the age of onset and disease severity. See Table 6.9 for details regarding these types [27].

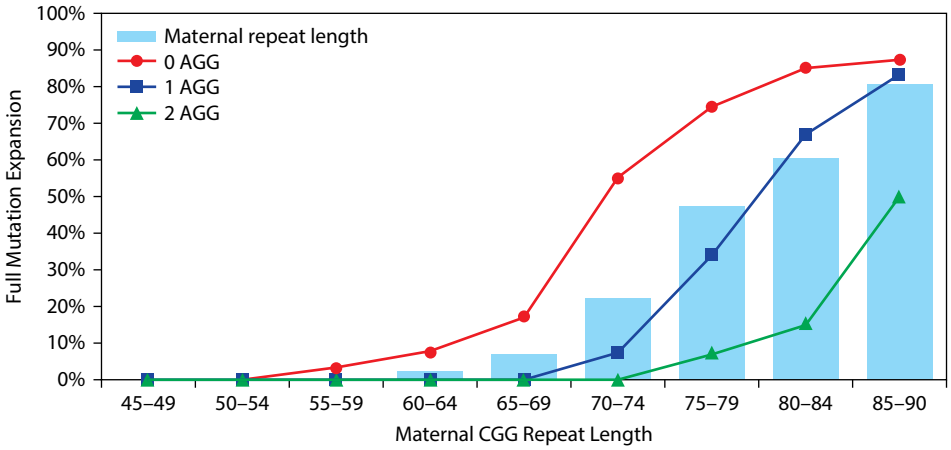


FIGURE 6.2 The likelihood for expansion to a fragile X full mutation. (From http://asuragen.com/products-and-services/clinical-lab/xpansion-interpreter/, with permission from Dr. Sally Nolin.)

TABLE 6.9: SMA Types

	Age of Onset	Clinical Findings
Type I (Werdnig-Hoffman)	Prior to 6 months of age	Never able to sit up Difficulty breathing and swallowing Respiratory failure within first 2 years of life
Type II	<18 months of age	Never able to stand Death in childhood
Type III	>18 months of age	Able to stand alone but may have frequent falls Extremity weakness in legs more than arms Death in adulthood
Type IV	>21 years of age	Able to stand alone Death in adulthood

Source: Adapted from Ref. [27].
Abbreviation: SMA, spinal muscular dystrophy.

SMA is an autosomal recessive condition caused by a deletion of a segment of DNA in exon 7 and exon 8 in the SMN1 (survival motor neuron) gene located on chromosome 5. Rarely, SMA is caused by a point mutation in the SMN1 gene. There does not appear to be a correlation between the type of SMN1 pathogenic variant and disease severity. SMN2 generates small amounts of SMN protein. The number of copies of SMN2 does correlate with SMA phenotype. Individuals with fewer copies of SMN2 typically have more severe forms of SMA (type I or II). See Table 6.10.

Pan-ethnic carrier screening for SMA is recommended by the ACMG and ACOG [10, 19, 27]. Approximately 1 in 50 individuals is a carrier for SMA.

Carrier testing for SMA measures the number of copies of the deleted segment in the SMN1 gene. A noncarrier is expected to have two copies present (no deletion), while a carrier will have only one copy present (a deletion of one copy). SMA carriers most commonly have one functional SMN1 gene on one chromosome and an SMN1 gene deletion on the other chromosome (in trans). Carriers can also have two functional SMN1 gene copies on one chromosome (in cis) and none on the other chromosome (the "2 + 0" genotype) or one chromosome with a nonfunctional SMN1 gene with a point mutation or a microdeletion. The potential outcomes of carrier testing can be seen in Figure 6.3. The 2 + 0 genotype occurs in 5%–8% of the general population, with black individuals of sub-Saharan African heritage having a higher frequency of this genotype. Polymerase chain reaction (PCR)–based carrier testing is unable to identify this genotype reliably, and, as such, the sensitivity for carrier screening in the black population is 70% compared to 87%–95% in the nonblack population [28]. More recently, two variants in intron 7 and exon 8 of the SMN1 gene have been found to be more prevalent in carriers of the 2 + 0 genotype. In the Ashkenazi Jewish population, these variants occur in approximately 20% of patients with the 2 + 0 genotype compared to <1% of noncarriers [29, 30]. Testing for these variants has been added by some laboratories for routine carrier testing.

TABLE 6.10: SMN2 Copy Number and SMA Clinical Phenotype

SMN2 Copy Number	SMA I	SMA II	SMA III/IV
1	96%	4%	0%
2	79%	16%	5%
3	15%	54%	31%
≥4	1%	11%	88%

Source: From Ref. [27] with permission.

Importantly, the presence of the variant does not confirm the 2 + 0 genotype, but rather alters the likelihood of this genotype for an individual undergoing carrier screening, thereby affecting the residual risk after screening.

Carrier testing may also report the number of SMN2 copies. While this does not determine carrier status, this number may help to predict disease severity in the event of an affected pregnancy.

Historically, treatment for SMA has been mainly supportive. More recently, however, **disease-modifying agents, including nusinersen, onasemnogene abeparvovec, and risdiplam, have**

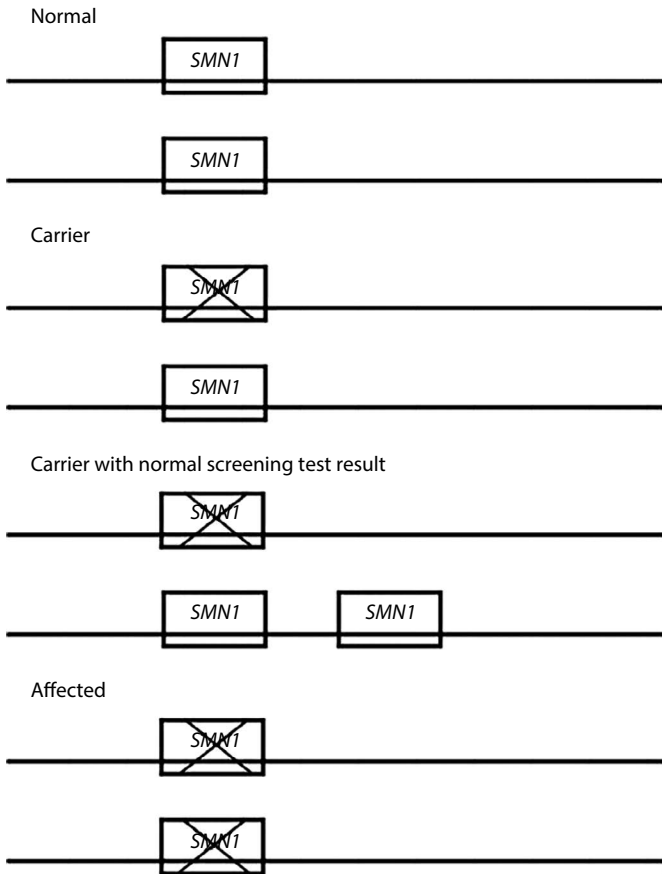


FIGURE 6.3 SMN1 gene in normal, carrier, and affected states. (From Ref. [27] with permission.)

become options for infants and children <2 years of age who are not ventilator-dependent. Older children and adults with moderate symptoms may also derive benefit from nusinersen or risdiplam.

Nusinersen is an oligonucleotide that modifies splicing of the SMN2 gene to increase production of normal, full-length SMN protein. It is administered intrathecally with four loading doses over 8 weeks followed by maintenance dosing every 4 months. In a multicenter, double-blinded trial, improvement in motor milestones as measured by the Hammersmith Infant Neurological Examination was observed in 37 of 73 (51%) infants receiving nusinersen vs. 0 of 37 (0%) infants receiving sham therapy. They were also less likely to die or receive permanent assisted ventilation (39 vs. 68%) [31].

Onasemnogene abeparvovec is a recombinant adeno-associated viral vector containing complementary DNA encoding the normal human SMN protein. This medication is administered as a one-time intravenous infusion. The ongoing STRIVE trial demonstrated that 62% of treated infants had reached the age of 14 months without the need for permanent ventilation and 48% of infants achieved the ability to sit without support [32].

Risdiplam is a small-molecule SMN2 splicing modifier that increases the level of full-length SMN protein. This medication is administered daily by mouth using a syringe. The FIREFISH and SUNFISH trials demonstrated a greater number of treated patients without permanent ventilation and an improvement in the 32-item Motor Function measure score in treated individuals, respectively [33, 34].

Additional disorders

In addition to the conditions described earlier and the conditions listed under "Ashkenazi Jewish Ancestry Genetic Screening," the ACOG includes the following three conditions in consideration for a proposed expanded carrier screening panel [35].

Phenylketonuria

Carrier frequency: Unknown in general population. The carrier frequency in Caucasians is 1 in 50.
Affected gene: PAH
Clinical features: This disorder is caused by a deficiency in PAH, which catalyzes conversion of phenylalanine to tyrosine. Insufficient enzyme activity results in an elevated blood and urine concentration of phenylalanine. Newborn infants are asymptomatic prior to the initiation of feeds containing phenylalanine. In untreated patients, hallmark of the disease is irreversible intellectual disability, seizures, behavioral abnormalities, and microcephaly.
Treatment: The mainstay of therapy is dietary restriction of phenylalanine.
Testing: Carrier testing detects 99% of carriers [36].

Smith-Lemli-Opitz syndrome

Carrier frequency: The carrier frequency in Caucasians is 1 in 70.
Affected gene: DHCR7
Clinical features: This disorder is caused by a deficiency of 7-dehydrocholesterol reductase. Smith-Lemli-Opitz syndrome has been associated with low maternal serum unconjugated estriol levels less than 0.25 MoM on second-trimester maternal serum screening. The clinical manifestations of this disorder include intellectual disability, poor growth, and characteristic phenotypic abnormalities, including microcephaly, characteristic facies, hypospadias, and polysyndactyly.
Treatment: The mainstay of treatment is supplementary dietary cholesterol. Clinical benefits from this therapy include improved growth, improved developmental progress, and a lessening of behavioral abnormalities.
Testing: Carrier testing detects 99% of carriers [36].

Medium-chain acyl-CoA dehydrogenase deficiency

Carrier frequency: The carrier frequency in Caucasians is 1 in 50.
Affected gene: ACADM
Clinical features: This disorder is caused by a deficiency of medium-chain acyl-CoA dehydrogenase. This disorder is characterized by an intolerance to prolonged fasting, recurrent episodes of hypoglycemic coma, impaired ketogenesis, and low plasma and tissue carnitine levels.
Treatment: Treatment includes L-carnitine supplementation and avoidance of prolonged fasting.
Testing: Carrier testing detects 99% of carriers [36].

Ashkenazi Jewish ancestry genetic screening

Who to screen

The family history of individuals considering pregnancy, or who are already pregnant, should **determine whether either member of the couple is of Eastern European (Ashkenazi) Jewish ancestry (one grandparent is Ashkenazi Jewish) or has a relative with one or more of the following genetic conditions**: TSD, Canavan disease, CF, familial dysautonomia, Fanconi anemia group C, Niemann-Pick disease type A, mucolipidosis IV, Bloom syndrome, and Gaucher disease [37].

What to screen for

The ACOG and ACMG guidelines differ with respect to the conditions that should be included when performing carrier screening in individuals of Ashkenazi Jewish descent. **ACOG recommends that carrier screening for TSD, Canavan disease, CF, and familial dysautonomia** should be offered to Ashkenazi Jewish individuals before conception or during early pregnancy. If the woman is already pregnant, simultaneous screening can be considered based upon gestational age, partner ethnicity, and patient/partner preference so that results are obtained in a timely fashion to ensure that prenatal diagnostic testing is an option. ACOG acknowledges that carrier screening is available also for **mucolipidosis IV, Niemann-Pick disease type A, Fanconi anemia group C, Bloom syndrome, and Gaucher disease**. The ACMG recommends screening for these five additional disorders, for a total of nine [38]. ACMG provides criteria for adding new diseases to the panel of Jewish genetic diseases based on significant burden of the disorder, carrier rate >1/100, and/or test sensitivity >90%.

In all cases, a general description of the disorders for which screening is planned should be provided to the patient and partner. Thorough counseling should also include a discussion on the variable phenotype of many of these conditions and a discussion on the concept of residual risk. Formal genetic counseling should be made available to anyone desiring it.

Currently 19 diseases are available for screening on Jewish genetic disease panels. In addition to those mentioned previously, the following diseases are included: maple syrup urine disease, glycogen storage disease type 1a, dihydrolipoamide dehydrogenase (DLD) deficiency, familial hyperinsulinism, Joubert syndrome, nemaline myopathy, SMA, Usher syndrome type 1F, Usher syndrome type III, and Walker-Warburg syndrome [37].

How to screen

All the disorders on the Ashkenazi Jewish genetic disease panel are autosomal recessive. A carrier is unaffected, but if two carriers of a mutation in the same gene have a child together, they have a 25% risk with each pregnancy of having an affected child.

When only one partner is of Ashkenazi Jewish descent, that individual should be screened first. If it is determined that this individual is a carrier, the other partner should be offered screening for that disorder. However, the couple should be informed that the carrier frequency and the detection rate in non-Jewish individuals are unknown for many of these disorders. Therefore, it is difficult to accurately predict the couple's risk of having a child with the disorder, and gene sequencing may be necessary to determine if a non-Jewish partner is a carrier. Referral to a genetic counselor is recommended in these cases.

Individuals with a positive family history of one of these disorders should be offered carrier screening for the specific disorder utilizing the family's known variant. If possible, genetic counseling should be offered in these cases.

When an individual is found to be a carrier, his or her relatives are at risk for carrying the same disease-causing variant. The patient should be encouraged **to inform his or her relatives of the risk and the availability of carrier screening**. The provider should not contact these relatives because there is no provider–patient relationship with the relatives, and confidentiality must be maintained [37].

When both partners are carriers of one of these disorders, they should be referred for genetic counseling and offered prenatal diagnosis. Carrier couples should be informed of the disease manifestations, range of severity, and available treatment options. Prenatal diagnosis by DNA-based testing can be performed on cells obtained by CVS and amniocentesis.

Brief descriptions of selected disorders with increased prevalence in the Ashkenazi Jewish population are listed next. The listed carrier frequencies apply to the Ashkenazi Jewish population.

Tay-Sachs disease

Carrier frequency: 1 in 30. The carrier frequency is also increased in individuals of French Canadian and Cajun descent.
Affected gene: HEXA
Clinical features: This is the most well-known disorder affecting the Ashkenazi Jewish population. In this lysosomal storage disease, GM2 gangliosides accumulate throughout the body due to functional deficiency in hexosaminidase A. The accumulation of these gangliosides in the central nervous system results in progressive functional decline. An apparently healthy child begins to lose skills around 4–6 months of age, and there is a progressive neurologic decline leading to blindness, seizures, and unresponsiveness. Death usually occurs by the age of 4–6.
Treatment: Supportive
Testing: Carrier testing can be performed using DNA-based testing and hexosaminidase enzymatic activity testing [37]. Labs that use a sequencing approach may detect 99% of carriers regardless of ethnicity [36]. Historically, genotyping was used to determine carrier status in individuals of Ashkenazi Jewish descent and enzyme testing was used to evaluate individuals of non- Ashkenazi Jewish descent, as the enzyme assay detects all carriers, regardless of ethnicity [30]. Enzyme testing in pregnant women and women taking oral contraceptives should be performed using leukocyte testing, as serum testing is associated with an increased false-positive rate in these populations.

Familial dysautonomia

Carrier frequency: 1/32 with disease incidence of 1/3700.
Affected gene: ELP1
Clinical features: This is a disorder of the sensory and autonomic nervous system. Malfunction of these systems affects the regulation of body temperature, blood pressure, and stress response and may also cause decreased sensitivity to pain. Frequent pneumonia and poor growth may occur. Survival into adulthood is possible with careful medical care.
Treatment: Supportive
Testing: Carrier testing for one major pathogenic variant and one additional variant accounts for 99.5% of carriers [36].

Canavan disease

Carrier frequency: 1/40 with a disease incidence of 1/3000–1/6000.
Affected gene: ASPA
Clinical features: This is a severe degenerative neurologic disease caused by a variant in the gene for aspartoacylase. The phenotype is variable, but presentation typically occurs in the first few months of life with delayed motor milestones. Thereafter, they may demonstrate macrocephaly, hypotonia, and intellectual disability. Life expectancy is variable.
Treatment: Supportive
Testing: Carrier testing detects 98% of carriers [36].

Bloom syndrome

Carrier frequency: 1/100 with a disease incidence of 1/48,000.
Affected gene: BLM
Clinical features: This disorder is caused by increased chromosomal breakage. Affected individuals may demonstrate short stature; a sun-sensitive skin rash; an increased susceptibility to infections; and higher incidence of leukemia and other cancers, infertility, and immunodeficiency. Individuals often survive into adulthood.
Treatment: Supportive
Testing: Carrier testing detects 95%–97% of carriers [36].

Fanconi anemia type C

Carrier frequency: 1/89 with disease incidence of 1/32,000.
Affected gene: FANCC
Clinical features: This disease is caused by disruption to normal DNA repair mechanisms, resulting in genomic instability, abnormal cell cycle regulation, and cell death. Clinical features include congenital anomalies such as thumb or other radial ray anomalies, microcephaly, and facial or renal abnormalities. Affected children are predisposed to short stature, bone marrow failure, and leukemia and other cancers.
Treatment: Pancytopenia can be treated with stem cell transplantation.
Testing: Carrier testing detects 99% of carriers [36].

Gaucher disease type 1 (non-neuropathic Gaucher disease)

Carrier frequency: 1/15 with disease incidence of 1/900.
Affected gene: GBA
Clinical features: This condition is a lysosomal storage disease caused by a deficiency in glucocerebrosidase. Onset of symptoms can occur at any time, with approximately 50% of patients not presenting until late adulthood. It may present with a painful hepatosplenomegaly, anemia, and leukopenia. Bone deterioration and fractures are a major cause of pain and disability.

Treatment: Treatment options include enzyme replacement therapy and substrate reduction therapy.
Carrier testing: Seven pathogenic variants account for >96% of cases [36].

Mucolipidosis type IV

Carrier frequency: 1/100 with disease incidence of 1/40,000.
Affected gene: MCOLN1
Clinical features: This disorder is caused by the accumulation of lipids and polysaccharides in cell lysosomes due to abnormal endocytosis. This results from a lack of functional mucolipin-1 protein. It is a progressive neurologic disorder characterized by physical and developmental delays, severe intellectual disability, corneal clouding, and retinal degeneration. Language and motor skill function beyond that of a 1 or 2 year old is typically not achieved.
Treatment: Supportive
Carrier testing: Carrier testing detects 99% of carriers [36].

Glycogen storage disease, type 1a

Carrier frequency: 1 in 64 with disease incidence of 1/16,000.
Affected gene: G6PC
Clinical features: This disease is caused by the accumulation of glycogen in various organs. Symptoms, including hypoglycemia and hepatomegaly, typically develop during the first year of life. Growth restriction, delayed puberty, and hepatic adenomas can be seen in later years.
Treatment: Disease management involves lifelong diet modification.
Carrier testing: Carrier testing detects 99% of carriers [36].

Maple syrup urine disease

Carrier frequency: 1 in 81 with disease incidence of 1/50,000 (type 1b).
Affected gene: BCKDHB (type 1b)
Clinical features: This disorder is caused by an inability to break down specific amino acids. The disease is associated with ketonuria within 48 hours of life that, if left undiagnosed and untreated, can progress to lethargy, dystonia, seizures, cerebral edema, and death. It is named for the characteristic maple syrup smell of urine in those with the disorder.
Treatment: Disease management involves lifelong diet modification.
Carrier testing: Carrier testing detects 99% of carriers [36].

Niemann-Pick disease type a

Carrier frequency: 1 in 90 with disease incidence of 1/32,000.
Affected gene: SMPD1
Clinical features: This disease is a lysosomal storage disorder caused by a deficiency of sphingomyelinase. Affected infants will appear normal at birth but develop hepatosplenomegaly, feeding difficulty, and motor regression within the first few months of life. Macular cherry red spots on fundoscopic exam can be seen in 50% of patients. Death typically occurs by 2–3 years of age.
Treatment: Supportive
Carrier testing: Carrier testing detects 99% of carriers [36].

Dihydrolipoamide dehydrogenase deficiency (DLD deficiency)

Carrier frequency: 1 in 107 with disease incidence of 1/35,000.
Affected gene: DLD
Clinical features: This disease is caused by an inability to break down specific amino acids and a resultant buildup of lactic acid. It presents in early infancy with hypotonia and lethargy. Affected individuals ultimately develop seizures and hepatomegaly. Many individuals succumb to this disease in early childhood. Survival into adulthood is associated with intellectual disability, spasticity, ataxia, and seizures.
Treatment: Supportive with dietary modifications.
Carrier testing: Carrier testing detects 99% of carriers [36].

Familial hyperinsulinism

Carrier frequency: 1 in 68 with disease incidence of 1/18,000.
Affected gene: ABCC8
Clinical features: This syndrome is characterized by excessive insulin secretion. One-third of infants are macrosomic at delivery due to hyperinsulinemia in fetal life. Persistent hypoglycemia is often recognized within the first few days of life.
Treatment: Treatment options include diazoxide or surgery (pancreatic resection).
Carrier testing: Carrier testing detects 90% of carriers [36].

Joubert syndrome

Carrier frequency: 1 in 92 with disease incidence of 1/34,000.
Affected gene: TMEM216 is more prevalent in the Ashkenazi Jewish population (30 additional pathogenic variants in >30 genes that affect the structure and function of primary cilia have been identified).
Clinical features: This syndrome is characterized by abnormal structure and function of cilia, resulting in abnormal development of the brainstem and cerebellar vermis. Polydactyly and prominent cerebellar peduncles, known as the "molar tooth sign," may be seen on prenatal imaging. Cystic renal dysplasia is seen in approximately 25% of cases. Affected individuals have ataxia, hypotonia, abnormal eye movements, and developmental and intellectual disability.
Treatment: Supportive
Carrier testing: Detection rate is 99% for the TMEM216 variant [36].

Nemaline myopathy

Carrier frequency: 1 in 168 with a disease incidence of 1/50,000.
Affected gene: NEB (accounts for 50% of total cases of nemaline myopathy)
Clinical features: This disease causes disorganization of the proteins found in sarcomeres in skeletal muscles and is the most common congenital myopathy. There are different types based on the degree of severity. Proximal muscle weakness is the most common and may worsen over time.
Carrier testing: Carrier testing detects 99% of carriers of NEB variants [36].

Usher syndrome type 1F

Carrier frequency: 1 in 147 with disease incidence of 1/86,000.
Affected genes: PCDH15, USH1F
Clinical features: This syndrome is characterized by profound hearing loss beginning at birth. Affected individuals achieve walking at later ages due to vestibular areflexia and develop retinitis pigmentosa in childhood, which results in progressively constricted visual fields.
Treatment: Supportive, hearing aids or cochlear implant
Carrier testing: Carrier testing detects ≥75% of carriers [36].

Usher syndrome type III

Carrier frequency: 1 in 120 with disease incidence of 1/57,000.
Affected gene: CLRN1
Clinical features: This syndrome is associated with the same features as Usher syndrome type 1F. In contrast to type 1F, however, hearing loss develops later in childhood and retinitis pigmentosa develops in the second decade.
Carrier testing: Carrier testing detects 99% of carriers [36].

Walker-Warburg syndrome

Carrier frequency: 1 in 149 with disease incidence of 1/60,000.
Affected genes: Over a dozen genes that prevent glycosylation of alpha-dystroglycan have been associated, including POMT1, POMT2, CRPPA, FKRP, and LARGE1.
Clinical features: This syndrome is caused by abnormal glycosylation of alpha-dystroglycan. This abnormal protein causes progressive weakness of skeletal muscles and abnormal migration of neurons. Affected individuals have hypotonia and can never walk. Cobblestone lissencephaly results in development and intellectual disability. Microphthalmia is also common. Most individuals do not survive past age 3.
Carrier testing: Detection rate is unknown (not enough data).

Summary

Preconception carrier screening maximizes patients' reproductive choices and planning. Current society guidelines recommend universal carrier screening for CF, SMA, and hemoglobinopathies. Although historically, additional genetic testing has been recommended based on a patient's race, ethnicity, or family history, more recent data have highlighted the limitations of this strategy and demonstrated the benefits of expanded carrier screening, particularly in individuals of uncertain ethnic backgrounds or consanguineous couples. The widespread use of expanded carrier screening will introduce several issues for future consideration, including which conditions to include on the panel and the best method for providing pretest and posttest education for patients considering expanded carrier screening. The reporting of variants of uncertain significance and the creation of a repository of these findings and their associated phenotype is also an area of future interest as expanded carrier screening increases.

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7

PREPARATION BEFORE LABOR

Daniele Di Mascio and Leen Al-Hafez

Key points

- Barometric pressure is not an effective method to predict spontaneous onset of labor in pregnancies at term. Diurnal rhythms seem to show a higher rate of starting labor, with **maximal frequency of labor starting in the evening and night hours**.
- **Transvaginal ultrasound cervical length** (TVU CL) evaluation is a good predictor of the onset of spontaneous labor in women at ≥37 weeks: a woman with a CL of 30 mm has a <50% chance of delivering within 7 days, while one with a CL of 10 mm has an over 85% chance of delivering within 7 days.
- **Antenatal classes** to prepare for labor and delivery are associated with **arriving to the labor and delivery unit more often in active labor, using less epidural analgesia, and fewer mean number of visits to the labor ward before the onset of labor**.
- **Mind–body relaxation, yoga, and music** might play a role in decreasing pain and increasing satisfaction with pain relief.
- **Mindfulness-based childbirth education** is associated with lower postcourse depression symptoms and with a trend toward a lower rate of opioid analgesia use in labor.
- **Intensive counseling in women with fear of childbirth** reduces anxiety and concerns related to pregnancy and birth and is associated with shorter labors.
- **Antenatal perineal massage** is associated with a **reduction in the incidence of trauma** requiring suturing and the rate of episiotomy, particularly in women without previous vaginal birth.
- **Pelvic floor muscle training** is associated with a **lower risk of reporting urinary incontinence** in continent women either in late pregnancy and in the mid-postnatal period from 3–6 months postpartum.
- Routine use of **sweeping of membranes from 37 to 38 weeks** of pregnancy onwards is significantly associated with **reduced duration of pregnancy** and reduced frequency of pregnancy continuing beyond 41 weeks.
- Women undergoing x-ray pelvimetry are more likely to be delivered by cesarean delivery.
- **Planned home birth is usually associated with a higher risk of perinatal and neonatal deaths**, compared to hospital or hospital-like (hospital-attached birth center).
- **The hospital is the safest setting for labor and delivery**, and women with risk factors for an abnormal outcome should deliver in a hospital setting.
- Allocation to an **alternative hospital setting (e.g. birth center alongside the hospital)** increased the likelihood of the following: no intrapartum analgesia/anesthesia, spontaneous vaginal delivery, breastfeeding at 6–8 weeks, and very positive views of care. Allocation to an alternative setting decreased the likelihood of epidural analgesia, oxytocin augmentation of labor, and episiotomy.
- Women who had **midwife-led continuity models of care were less likely to receive some medical interventions, such as amniotomy, episiotomy, and intrapartum analgesia/anesthesia; had shorter labors, less instrumental vaginal birth, preterm birth <37 weeks, less fetal loss/neonatal death before 24 weeks, less overall fetal/neonatal death**; and were **more likely to experience spontaneous vaginal birth.**
- **Continuous support during labor by a doula is associated with a higher rate of spontaneous vaginal birth, lower rates of cesarean and instrumental vaginal deliveries, less likely negative feelings about the childbirth experience, less intrapartum analgesia, shorter labors, and lower rates of low 5-minute Apgar score**.
- Training of **traditional birth assistants in middle- and low-income countries** is associated with a trend for less maternal mortality and significantly less perinatal mortality.
- There is insufficient evidence to assess the effects of training and teamwork education for labor and delivery personnel.
- **Delayed admission until active labor** is associated with less time in the labor ward, less intrapartum oxytocics, and less analgesia. Women in the labor assessment and delayed admission group report higher levels of control during labor. **Suggested criteria for admission are a cervix of at least 3–4 cm dilatation and regular painful contractions**.
- Women allocated to **admission** cardiotocography (CTG) have an **increase in the incidence of cesarean delivery** than women allocated to intermittent auscultation. Obtaining an amniotic fluid index in early labor is associated with a higher incidence of cesarean delivery and similar neonatal outcomes.
- **Enemas do not have a significant beneficial effect** on infection rates such as perineal wound infection or other neonatal infections and women's satisfaction.
- There is **no support for routine perineal shaving** for women prior to or in labor.

Introduction

This chapter will review the evidence in preparation to labor. A summary of recommendations is reported in Table 7.1.

Prediction of the onset of spontaneous labor

Weather effects

There is **no strong association** between changes in **barometric pressure and spontaneous onset of labor** in pregnancies at term [1].

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TABLE 7.1: Summary of Recommendations

Preparation before Labor Issues	Evidence
Prediction of the onset of spontaneous labor	
• Transvaginal ultrasound cervical length	Good predictor of the onset of spontaneous labor in women at ≥37 weeks
• Weather effects	No association between changes in barometric pressure and spontaneous onset of labor in pregnancies at term
Antenatal classes	Associated with arriving to labor and delivery unit more often in active labor and using less epidural analgesia
Antenatal perineal massage	Lower incidence of trauma requiring suturing and the rate of episiotomy
Pelvic floor muscle training	Lower risk of reporting urinary incontinence in continent women either in late pregnancy and in the midpostnatal period
Sweeping of membranes	Lower duration of pregnancy and lower frequency of pregnancy continuing beyond 41 weeks, when started from 37 to 38 weeks
Pelvimetry	Likely associated with higher rates of cesarean delivery
Place of birth	
• Home birth	Higher risk of perinatal and neonatal deaths
• Hospital	Safest setting for labor and delivery, particularly for women with risk factors for abnormal outcome
• Alternative hospital settings	Increased likelihood of the following: no intrapartum analgesia/anesthesia, spontaneous vaginal delivery, breastfeeding at 6–8 weeks, and very positive views of care
Attendant at birth	
• Midwife-led care	Less likely to receive amniotomy, episiotomy, and intrapartum analgesia/anesthesia; shorter labors, less instrumental vaginal birth, preterm birth <37 weeks, less fetal loss/neonatal death before 24 weeks, less overall fetal/neonatal death
• Doulas	Higher rate of spontaneous vaginal birth, lower rates of caesarean and instrumental vaginal deliveries, less likely negative feelings about the childbirth experience, less intrapartum analgesia, shorter labors and lower rates of low 5-minute Apgar score
Training of birth assistants	Trend for less maternal mortality and significantly less perinatal mortality
Teamwork training	Conflicting evidence, likely to improve team performance and medical technical skills, and therefore quality of care
Delayed admission to labor and delivery unit	Less time in the labor ward, less intrapartum oxytocic, and less analgesia
Fetal assessment tests upon admission	
• Fetal heart rate tracing	Higher incidence of cesarean delivery than women allocated to intermittent auscultation
• Amniotic fluid index evaluation	Higher incidence of cesarean delivery and similar neonatal outcomes
Enemas	No significant beneficial effect on infection rates such as perineal wound infection or other neonatal infections and women's satisfaction
Perineal shaving	No evidence to support shaving

Time of day

Diurnal rhythms seem to show a **higher rate of starting labor**, with maximal frequency in the evening and night hours [2].

Transvaginal ultrasound cervical length

The majority of women at term desire to know roughly the timing of the onset of labor, and this information might be useful also for clinicians, mostly when further care is needed at the time of delivery. **Transvaginal ultrasound cervical length (TVU CL) evaluation is a good predictor of the onset of spontaneous labor in women at term**: a woman with a **CL of 30 mm** has a **<50% chance of delivering within 7 days**, while one with a **CL of 10 mm** has an over **85% chance of delivering within 7 days** [3].

Antenatal classes and education regarding self-diagnosis of active labor

A woman's satisfaction with her birth experience is mainly related to the personal expectations, the amount of support she receives, the quality of the relationship between her and the birth attendant, and her involvement in labor management [4].

Antenatal classes include types of educational programs to help the mother get familiar with labor and delivery. Compared to no such training, **9 hours of antenatal training to prepare for labor and delivery** are associated with **arriving to the labor and delivery unit more often in active labor** (relative risk [RR] 1.45, 95% CI 1.26–1.65) and **using less epidural analgesia** (RR 0.84, 95% CI 0.73–0.97) [5].

Specific antenatal education programs are also associated with a **reduction in the mean number of visits to the labor ward before the onset of labor** (mean difference [MD] −0.29, 95% CI −0.47 to −0.11) [6].

Another typical key issue during antenatal classes is the education regarding the management of pain during labor. In this scenario, there is a lack of high-quality evidence to assess whether specific approaches are more effective than others to reduce labor pain.

Compared to no such education, **antenatal education focusing on natural childbirth preparation** with training in breathing

and relaxation techniques is **not associated with any effects on maternal or perinatal outcomes**, including similar incidences of epidural analgesia, childbirth, or parental stress, in nulliparous women and their partners [7].

However, evidence from low-quality randomized controlled trials (RCT) showed that some relaxation techniques for pain management, such as **mind–body relaxation, yoga, and music, might assume a role in decreasing pain** and **increasing satisfaction with pain relief** [8].

Moreover, **a complementary medicine technique program containing six items** (acupressure, visualization and relaxation, breathing, massage, yoga techniques, and facilitated partner support) is associated with a **significant reduction in epidural use** (RR 0.37 95% CI 0.25–0.55), **cesarean delivery** (RR 0.52 95% CI 0.31–0.87), **and perineal trauma** (RR 0.88 95% CI 0.78–0.98), compared to standard antenatal care [9].

Mindfulness-based childbirth education is associated with **lower postcourse depression symptoms** and with a trend toward a lower rate of opioid analgesia use in labor [10].

The aim of antenatal classes is also to help women cope better with the fear of labor and childbirth. Fear of childbirth is associated with a 47-minute longer duration of labor, compared to no fear of childbirth [11]. **Intensive counseling in women with fear of childbirth reduces anxiety and concerns related to pregnancy and birth** and is associated with shorter labors [11–13].

Finally, there is no conclusive evidence supporting any antenatal breastfeeding education for improving initiation and continuation of breastfeeding, at least in high-income countries [14].

Antenatal perineal massage

Perineal trauma is often related to vaginal birth, usually due to episiotomies, perineal lacerations, or both, and might be associated with both short- and long-term complications, such as perineal pain, discomfort, and dyspareunia.

Antenatal digital perineal massage with sweet almond oil for 5–10 minutes daily, starting from approximately 35 weeks of gestation, is significantly associated with a **reduction in the incidence of trauma requiring suturing** (RR 0.91 95% CI 0.86–0.96) and in the **rate of episiotomy** (RR 0.84 95% CI 0.74–0.95), particularly in women without previous vaginal birth. Conversely, women with a previous vaginal birth experience significant less pain at 3 months postpartum (RR 0.45 95% CI 0.24–0.87). No significant differences are observed in the incidence of instrumental deliveries; sexual satisfaction; or incontinence of urine, feces, or flatus for any women practicing perineal massage before childbirth [15].

Pelvic floor muscle training

Urinary incontinence and involuntary loss of flatus or feces might be debilitating problems in both the late pregnancy and the postpartum period.

Pelvic floor muscle training (PFMT) usually involves **more than one daily set of repeated voluntary contractions of the pelvic floor muscles, performed several times per day, for at least 8 weeks** [16]. A **structured PFMT antenatal program** is associated with a **lower risk of reporting urinary incontinence in continent women either in late pregnancy** (RR 0.38, 95% CI 0.20–0.72) or **in the mid-postnatal period** (RR 0.71, 95% CI 0.54–0.95) from 3 to 6 months postpartum. There is not enough evidence to ascertain whether PFMT might be effective also as an intervention in incontinent women in late pregnancy or in the mid- and late postpartum period.

Evidence is weaker when considering the effect of antenatal PFMT on the incidence of fecal incontinence. In **women with or without fecal incontinence**, antenatal PFMT is associated with **little or no difference in the prevalence of fecal incontinence in late pregnancy**. Similar results have also been found for the role of postnatal PFMT on fecal incontinence in the postnatal period and beyond 12 months postpartum [17].

Sweeping of membranes

Sweeping of membranes usually involves **inserting one finger between the cervix and the membranes and sweeping 360 degrees at least two to four times** to potentially increase the local production of prostaglandins [16].

Routine use of sweeping of membranes from 38 weeks of pregnancy onwards is significantly associated with **reduced duration of pregnancy** and **reduced frequency of pregnancy continuing beyond 41 weeks** (RR 0.59, 95% CI 0.46–0.74) **and 42 weeks** (RR 0.28, 95% CI 0.15–0.50), with no difference in cesarean delivery and maternal or fetal infection rates. Women allocated to sweeping more frequently experienced discomfort during vaginal examination and other adverse effects, such as bleeding or irregular contractions [18]. Women randomized to membrane sweeping may also be more likely to experience spontaneous onset of labor and less likely to experience induction of labor [19]. These results are concordant with those found in a subsequent RCT on 742 low-risk pregnant women assigned to serial sweeping of the membranes every 48 hours until labor at 41 weeks of gestation [20] and in a recent meta-analysis of seven trials involving 2252 women that confirmed membrane sweeping as an effective method to promote spontaneous labor and to reduce the need for induction of labor, starting from 38 weeks of gestation [21].

Pelvimetry

There is not enough evidence to support the use of x-ray pelvimetry in women whose fetuses have either a cephalic or noncephalic presentation. **Women undergoing x-ray pelvimetry are more likely to be delivered by cesarean delivery**. No significant impact is detected on perinatal outcome, but the numbers are small, insufficient for meaningful evaluation (e.g. perinatal mortality 1% vs. 2%). The results are similar for women with or without a prior cesarean delivery (CD) [22]. There are insufficient data regarding MRI or clinical pelvimetry.

Place of birth

Planned home birth

The American College of Obstetricians and Gynecologists (ACOG) recommend counseling women planning to deliver at home that hospitals and accredited birth centers (especially those alongside a hospital) are the safest settings for birth, although each woman keeps the right to make an informed decision about her place of delivery [23].

There is **limited evidence** to assess the **safety and efficacy of planned home birth for low-risk pregnant women**, as there is only one RCT with only 11 women ever published [24, 25]. In healthy low-risk women, compared to planned hospital birth, **planned home birth is associated with a higher risk of neonatal deaths (0.2% vs. 0.09%)** in a meta-analysis of nonrandomized

TABLE 7.2: Level of Maternal Care

Level of Care	Example (Not Requirement)
Accredited birth center	Women with an uncomplicated term singleton vertex fetus who are expected to have an uncomplicated birth
Level I	Low-risk women with uncomplicated pregnancies and women with higher-risk conditions such as the following: uncomplicated twin gestation, labor after cesarean, uncomplicated cesarean delivery, preeclampsia, well-controlled gestational diabetes
Level II	Any patient appropriate for level I care, plus higher-risk conditions such as the following: placenta previa with no previous uterine surgery; maternal medical conditions that require additional monitoring such as pregestational diabetes, poorly controlled asthma, or poorly controlled or complicated chronic hypertension; anticipated complicated cesarean delivery
Level III	Any patient appropriate for level II care, plus higher-risk conditions or complications such as the following: moderate maternal cardiac disease; suspected placenta accreta or placenta previa and previous uterine surgery; suspected placenta percreta; adult respiratory distress syndrome or other conditions that require ventilatory support antepartum or postpartum; acute fatty liver of pregnancy; coagulation disorders; complex hematologic or autoimmune disorders; expectant management of preeclampsia with severe features remote from term
Level IV	Any patient appropriate for level III care, plus higher-risk conditions or complications such as the following: severe maternal cardiac conditions; severe pulmonary hypertension; pregnant women who require neurosurgery or cardiac surgery; pregnant women in unstable condition and in need of an organ transplant

Source: Adapted from Ref. [31].

studies including over 500,000 births [26]. In a large (>79,000 women with singletons, term, cephalic, and nonanomalous pregnancies) retrospective cohort study, planned out-of-hospital births were associated with a higher rate of **perinatal deaths** (3.9 vs. 1.8 deaths per 1000 deliveries; Adjusted odd ratio (aOR) 1.52, 95% CI 0.51–2.54) than planned in-hospital deliveries, as well as more neonatal seizures [27].

There are diverging opinions even in Western countries, with about >15% of Dutch births occurring at home versus <1% of U.S. births. Data from U.S. births showed a significantly increased risk of neonatal deaths, low Apgar scores, and neonatal seizures associated with home births or births in free-standing birth centers compared to hospital births [28, 29]. Some of these studies included free-standing (not alongside—very nearby or inside—a hospital) birth centers with home births. This means, therefore, that the **hospital is the safest setting for labor and delivery**, and **women with risk factors for abnormal outcome should deliver in a hospital setting** [30].

Tables 7.2 and 7.3 show ACOG and Society for Maternal-Fetal Medicine (SMFM) recommendations for a standardized and integrated system of risk-appropriate maternal care and perinatal care [31, 32].

TABLE 7.3: Level of Neonatal Care

Level of Care	Capabilities
Level I well newborn nursery	Provide neonatal resuscitation at every delivery; evaluate and provide postnatal care to stable term newborn infants; stabilize and provide care for infants born at 35–37 weeks of gestation who remain physiologically stable; stabilize newborn infants who are ill and those born before 35 weeks of gestation until transfer to a higher level of care
Level II special care nursery	Level I capabilities plus: provide care for infants born at 32 weeks of gestation or later and weigh 1500 g or more who have physiologic immaturity or who are moderately ill with problems that are expected to resolve rapidly and are not anticipated to need subspecialty services on an urgent basis; provide care for infants convalescing after intensive care; provide mechanical ventilation for brief duration (less than 24 hours) or continuous positive airway pressure or both; stabilize infants born before 32 weeks of gestation and weigh less than 1500 g until transfer to a neonatal intensive care facility
Level III neonatal intensive care unit	Level II capabilities plus: provide sustained life support; provide comprehensive care for infants born before 32 weeks of gestation and weigh less than 1500 g and infants born at all gestational ages and birth weights with critical illness; provide prompt and readily available access to a full range of pediatric medical subspecialists, pediatric surgical specialists, pediatric anesthesiologists, and pediatric ophthalmologists; provide a full range of respiratory support that may include conventional ventilation and/or high-frequency ventilation and inhaled nitric oxide; perform advanced imaging, with interpretation on an urgent basis, including computed tomography, magnetic resonance imaging, and echocardiography
Level IV regional neonatal intensive care unit	Level II capabilities plus: located within an institution with the capability to provide surgical repair of complex congenital or acquired conditions; maintain a full range of pediatric medical subspecialists, pediatric surgical subspecialists, and pediatric anesthesiologists at the site; facilitate transport and provide outreach education

Source: Adapted from Ref. [32].

Freestanding birth center

There are no RCTs of freestanding (far from any hospital) birth centers, and therefore the evidence is insufficient to recommend this setting [33]. For non-RCT evidence, see "Planned Home Birth."

Planned hospital birth: alternative setting (homelike, e.g. hospital or alongside birth center) vs. conventional hospital ward setting

Several RCTs have evaluated the option of "alternative setting" versus the conventional hospital ward setting for labor and delivery. **For the alternative setting, most trials included care by midwives in a location in the hospital, close to the regular labor and delivery ward, that did not look like a usual labor and delivery setting**. There no RCTs of freestanding birth centers. Some RCTs randomized women in labor, while others at the beginning of pregnancy. So continuity of care was usually higher in the alternative setting group. **Usually about 40%–50% of patients randomized to alternative setting** (often about 60% for nulliparous women, 20%–30% for multiparous women) **need to be moved in labor to the conventional labor and delivery ward**.

Compared to the conventional hospital ward, allocation to an alternative hospital setting **increased the likelihood of the following: no intrapartum analgesia/anesthesia** (RR 1.18, 95% CI 1.05–1.33), **spontaneous vaginal delivery (SVD)** (RR 1.03, 95% CI 1.01–1.05), **breastfeeding at 6–8 weeks** (RR 1.04, 95% CI 1.02–1.06), and **very positive views of care** (RR 1.96, 95% CI 1.78–2.15). Allocation to an alternative setting **decreased the likelihood of epidural analgesia** (RR 0.80, 95% CI 0.74–0.87), **oxytocin augmentation** of labor (RR 0.77, 95% CI 0.67–0.88), and **episiotomy** (RR 0.83, 95% CI 0.77–0.90) [26]. There was no apparent effect on maternal morbidity and mortality, serious perinatal morbidity/mortality (RR 1.17, 95% CI 0.51–2.67), perinatal mortality (RR 1.67, 95% CI 0.93–3.00), other adverse neonatal outcomes, or postpartum hemorrhage. The 4% increase in SVD may be secondary to less epidural anesthesia, which may in turn be secondary to less availability in homelike settings and/or to less intrapartum monitoring. **The trend for a 67% higher perinatal mortality should be weighed against the significant 4% increase in SVD and 96% higher satisfaction during counseling**. No firm conclusions can be drawn regarding the effects of variations in staffing, organizational models, or architectural characteristics of the alternative settings [33]. **A birth center in the hospital is a safe location for birth** [30].

Attendant at birth

Midwife-led care

In many parts of the world, **midwives are the primary providers of care for childbearing women**. Elsewhere it may be medical doctors or family physicians who have the main responsibility for care, or the responsibility may be shared. The underpinning philosophy of midwife-led care is normality, continuity of care, and being cared for by a known and trusted midwife during labor. There is an emphasis on the natural ability of women to experience birth with minimum intervention [34].

The effect of midwife-led care compared to physician-led care or to other provider-led care has been evaluated mostly for the whole pregnancy, including both antepartum care and care during labor and delivery. Therefore it is difficult to assess the effect of midwife-led care just on labor and delivery.

Women who have midwife-led continuity models of pregnancy care are **less likely to experience regional analgesia** (RR 0.85, 95% CI 0.78–0.92), **instrumental vaginal birth** (RR 0.90, 95% CI 0.83–0.97), **preterm birth less than 37 weeks** (RR 0.76, 95% CI 0.64–0.91), and **less overall fetal/neonatal death** (RR 0.84, 95% CI 0.71–0.99) [34]. Women who have midwife-led continuity models of care are **more likely to experience spontaneous vaginal birth** (RR 1.05, 95% CI 1.03–1.07). There are no differences between groups for cesarean births or intact perineum. In addition, women assisted by midwives are **less likely to receive** some medical interventions, such as **amniotomy** (RR 0.80, 95% CI 0.66–0.98), **episiotomy** (RR 0.84, 95% CI 0.77–0.92), and **intrapartum analgesia/anesthesia** (RR 1.21, 95% CI 1.06–1.37). Women who have midwife-led continuity models of care are **less likely to experience longer mean length of labor** (hours) (MD 0.50, 95% CI 0.27–0.74), to be **attended at birth by a known midwife** (RR 7.04, 95% CI 4.48–11.08), and have **less fetal loss/neonatal death before 24 weeks** (RR 0.81, 95% CI 0.67–0.98). There were no differences between groups for fetal loss or neonatal death more than or equal to 24 weeks, induction of labor, antenatal hospitalization, antepartum hemorrhage, augmentation/artificial oxytocin during labor, opiate analgesia, perineal laceration requiring suturing, postpartum hemorrhage, breastfeeding initiation, low-birth-weight infant, 5-minute Apgar score less than or equal to 7, neonatal convulsions, admission of infant to special care or neonatal intensive care unit(s), or mean length of neonatal hospital stay (days). The majority of included studies report a **higher rate of maternal satisfaction** in midwife-led continuity models of care [34].

Doulas

A doula is a continuous support person that a woman may choose for emotional support and advice about coping techniques and comfort measures (comforting touch, massage, warm baths/showers) [16].

Compared to usual care without continuous support, **continuous support during labor** (mostly performed **by a doula**, but also by midwives or nurses) is associated with a **higher rate of spontaneous vaginal birth** (RR 1.08, 95% CI 1.04–1.12), **lower rates of cesarean delivery** (RR 0.75, 95% CI 0.64–0.88) and **instrumental vaginal deliveries** (RR 0.90, 95% CI 0.85–0.96), **less likely negative feelings about the childbirth experience** (RR 0.69, 95% CI 0.59–0.79), **less intrapartum analgesia** (RR 0.90, 95% CI 0.84–0.96), **shorter labors** (MD −0.69 hours, 95% CI −1.04 to −0.34), and **lower rates of low 5-minute Apgar score** (RR 0.62, 95% CI 0.46–0.85) [35].

Training of birth assistants

Training of traditional birth assistants **in middle- and low-income countries is associated with a trend for less maternal mortality and significantly less perinatal mortality** [36]. There are no trials in high-income countries.

Teamwork training

Evidence is conflicting when focusing on the effects of training and teamwork education for labor and delivery personnel. In a 2007 RCT, a standardized teamwork training curriculum based on crew resource management that emphasized communication and team structure was not associated with a significant effect on adverse maternal and perinatal outcomes compared to no such training [37]. Conversely, two subsequent RCTs showed that team performance and medical technical skills may significantly improve after multiprofessional obstetric team training in a simulation center and that a simulation-based training program

may improve the use of evidence-based practices at birth, thus improving the quality of care [38, 39].

Admission to a labor and delivery unit

Delayed vs. early hospital admission

Labor assessment programs, which aim to **delay hospital admission until active labor**, may benefit women with term pregnancies. Active labor was defined as regular painful contractions and cervical dilatation >3 cm in these studies. In one RCT, compared to direct admission to hospital, delayed admission until active labor was associated with **less time in the labor ward, less intrapartum oxytocics**, and **less analgesia** [40]. Women in the labor assessment and delayed admission group report **higher levels of control during labor. CD rates are similar, with a nonsignificant 30% decrease**. A 30%–40% decrease in CD has been reported in retrospective studies with delayed versus direct admission. There is insufficient evidence (a larger trial is needed) to assess the true effects on the rate of CD and other important measures of maternal and neonatal outcome. Potential risks of delayed admission include unplanned out-of-hospital births and the potentially harmful effects of withholding caregiver support and attention to women in early or latent-phase labor.

In another RCT, compared to no use of algorithm, use of an algorithm by midwives to assist in their diagnosis of active labor (painful regular contractions with at least one of the following: 3 cm dilated, rupture of membranes [ROM], or "show") was associated with more women being discharged after their first labor ward assessment and no effect of oxytocin augmentation and other medical interventions in labor [41].

Suggested criteria for admission based on these studies are a cervix of at least 3–4 cm dilatation and regular painful contractions. Pregnant women should be informed of these data during prenatal care.

Fetal assessment tests upon admission

Fetal heart rate tracing for 20 minutes

Women allocated to **admission CTG** have an **increase in the incidence of cesarean delivery compared with women allocated to intermittent auscultation** (RR 1.20, 95% CI 1.00–1.44). There is no significant difference in instrumental vaginal birth (RR 1.10, 95% CI 0.95–1.27) and fetal and neonatal deaths (RR 1.01, 95% CI 0.30–3.47) [42].

Amniotic fluid volume index

Obtaining an amniotic fluid index (AFI) in early labor is associated with a higher incidence of CD and similar neonatal outcomes compared to no AFI [43].

Neither a 2-cm pocket (abnormal in 8%) nor an AFI (abnormal in 25%) upon admission for labor identifies a pregnancy at risk for adverse outcome such as nonreassuring fetal heart rate tracing (NRFHT) or CD for NRFHT [44].

Other tests

There is insufficient evidence to support the use of vibroacoustic stimulation or Doppler ultrasound as fetal admission tests, as there are no RCTs on these interventions.

Enemas

Enemas do not have a significant beneficial effect on infection rates such as perineal wound infection or other neonatal infections and women's satisfaction. Compared to no enema, enema in labor is associated with no significant differences for infection rates in puerperal women (RR 0.66, 95% CI 0.42–1.04) and no significant differences in neonatal umbilical infection rates (RR 3.16, 95% CI 0.50–19.82). No significant differences are found in the incidence of neonatal lower or upper respiratory tract infections [45].

One RCT described labor to be significantly shorter (50 minutes) with enema versus no enema. A second RCT found labor to be significantly longer (112 minutes) with an enema compared to no enema. No significant differences in the duration of labor were found in the third RCT that scored as having a low risk of bias and were adjusted for parity. One RCT that researched women's views found no significant differences in satisfaction between groups. **The routine use of enemas during labor should be discouraged** [45]. This intervention (enema) generates discomfort in women and increases the costs of delivery.

Perineal shaving

There is **no supportive level 1 evidence for routine perineal shaving** (shaving with a razor) for women prior to or in labor. In a very old trial, 389 women were alternately allocated to receive either skin preparation and perineal shaving or clipping of vulvar hair only. In the second old trial, which included 150 participants, perineal shaving was compared with the cutting of long hairs for procedures only. In the third trial, 500 women were randomly allocated to shaving of perineal area or cutting of perineal hair. Compared to no shaving, shaving was associated with a similar incidence of maternal febrile morbidity (RR 1.14, 95% CI 0.73–1.76), perineal wound infection (RR 1.47, 95% CI 0.80–2.70), and perineal wound dehiscence (RR 0.33, 95% CI 0.01–8.00). In the smaller trial, fewer women who had not been shaved had gram-negative bacterial colonization compared with women who had been shaved (OR 0.43, 95% CI 0.20–0.92). There were no differences in maternal satisfaction immediately after birth [46]. The potential for complications (redness, multiple superficial scratches, burning and itching of the vulva, and embarrassment and discomfort afterward when the hair grows back), which often occur later, suggests that **shaving should not be part of routine clinical practice**. The first two trials are old (1922 and 1965) and included the clipping of long hairs in their control groups to aid in operative procedures, which is itself usually unnecessary and can lead to complications.

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8

FIRST STAGE OF LABOR

Leen Al-Hafez

Key points

- Vaginal chlorhexidine irrigation is not recommended.
- **Universal prenatal maternal screening with anovaginal specimen at 36–37 weeks and intrapartum antibiotic treatment** are the most efficacious of the current strategies for prevention of neonatal early-onset group B streptococcus (GBS) disease.
- Prophylactic antibiotics in term prerupture of membranes (PROM) with latency longer than 12 hours can be considered.
- Aromatherapy with essential oils through inhalation or back massage in labor can be considered.
- **Water immersion** during the *first stage* of labor **slightly reduces the use of analgesia**, without adverse maternal or neonatal outcomes.
- **There is little justification for the restriction of fluids and food in labor for women at low risk of complications.**
- **In the setting of oral restriction, intravenous (IV) fluids at 250 mL/hour containing dextrose are associated with shorter duration of labor and fewer cesarean deliveries compared to 125 mL/hour**.
- **Upright positions** (either standing, sitting, kneeling, or walking around) for women without regional anesthesia in the first stage of labor **reduces the length of labor** by approximately **over 1 hour** and are associated with **less epidural analgesia**. Women with regional anesthesia can take up whatever position or ambulate as they please.
- **Ambulating should be recommended in the first stage of labor in women without regional anesthesia**. **Women with regional anesthesia can ambulate or not ambulate in the first stage**.
- Continuous bladder catheterization cannot be recommended in labor.
- **There is insufficient evidence to recommend any particular frequency of vaginal cervical exams in labor**. Most studies, including those with active management, perform cervical exams every 2 hours in active labor, but the risk of chorioamnionitis increases with increasing number of exams.
- **Routine sweeping of membranes in labor cannot be recommended**.
- The routine use of the partogram is not recommended in labor.
- The routine use of a peanut ball cannot be recommended in labor.
- The use of a birthing ball during the first stage of labor can be considered.
- Antispasmodics are not recommended for routine use in the first stage of labor.
- **Routine amniotomy in normally progressing spontaneous labor cannot be recommended as part of standard labor management and care, but early amniotomy (e.g. after Foley balloon is ejected and so about 3–4 cm of cervical dilation) in labor induction is recommended**.
- **For women making slow progress in the first stage of spontaneous labor**, the use of **oxytocin augmentation** is associated with a **reduction in the time to delivery of approximately 2 hours**.
- **Early intervention with oxytocin and amniotomy for the prevention and treatment for dysfunctional or slow labor is recommended**.
- The routine use of intrauterine pressure catheter (IUPC) in the first stage of labor is not recommended.
- The routine use of ultrasound during a normally evolving first stage of labor is not recommended.
- **Dystocia cannot be diagnosed unless rupture of membranes (ROM) has occurred and adequate oxytocin** to achieve at least three to five adequate contractions per hour has been instituted. Dystocia also **cannot be diagnosed reliably before the first stage of labor has entered the active phase, which has been defined, especially in nulliparous patients with epidurals in place, as at least 6 cm of cervical dilatation. Before performing a cesarean delivery (CD) for active-phase labor arrest, labor should be arrested for a minimum of 4 hours (if uterine activity is greater than 200 Montevideo units as documented with IUPC) or 6 hours (if greater than 200 Montevideo units could not be sustained).**

Please also see Chaps. 7 and 9 for other guidance during labor.

Introduction

For management of induction, meconium, oligo/polyhydramnios, intrapartum monitoring (including amnioinfusion for variables), operative vaginal delivery, shoulder dystocia, trial of labor after cesarean (TOLAC), fetal growth restriction (FGR), macrosomia, abnormal third stage, etc., **see appropriate distinct guidelines** in this book and its companion, *Maternal-Fetal Evidence Based Guidelines.* This chapter discusses interventions in the first stage of labor that can influence labor and delivery outcomes (Table 8.1) [1].

Vaginal chlorhexidine

There is **no evidence to support the use of vaginal chlorhexidine by either irrigation or vaginal wipes during labor** in order to prevent maternal and neonatal infections. The effect on the incidence of postpartum endometritis is not statistically significant (relative risk [RR] 0.83; 95% confidence interval [CI] 0.61–1.13) [2]. Chlorhexidine solution is safe and inexpensive, and vaginal irrigation is easy to perform, but not beneficial. In summary, **vaginal chlorhexidine by either irrigation or vaginal wipes during labor is not recommended**.

GBS prophylaxis

Maternal colonization with group B streptococcus (GBS) increases the neonatal risk of developing early-onset group B

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TABLE 8.1: Summary of Interventions in the First Stage of Labor[a]

Intervention	Recommendation
Vaginal disinfection	Not recommended
GBS prophylaxis if GBS positive	**Recommended**
Antibiotics in PROM	Consider[b]
Aromatherapy	Consider
Water immersion	Consider
Oral restriction of fluid or solid foods as tolerated	Not recommended
IV fluids with dextrose at 250 mL/hr in the setting of oral restriction	**Recommended**
Upright position in women without regional anesthesia	**Recommended**
Position in women with regional anesthesia	As desired by woman
Ambulation in women without regional anesthesia	**Recommended**
Ambulation in women with regional anesthesia	As desired by woman
Continuous bladder catheterization	Not recommended
Cervical exam/membrane sweeping	Insufficient evidence
Routine partogram	Not recommended
Routine peanut ball	Consider
Routine birthing ball	Consider
Antispasmodics	Not recommended
Routine use of amniotomy alone	Not recommended
Use of oxytocin in slow labor progression	**Recommended**
Early amniotomy and oxytocin in slow labor progression	**Recommended**
Routine use of IUPC	Not recommended
Routine ultrasound use	Insufficient evidence
Labor dystocia in the first stage should be defined as labor that has been arrested for a minimum of 4 hours with adequate uterine activity, or 6 hours with inadequate uterine activity in a woman with ROM, adequate oxytocin, and ≥6 cm dilated cervix	**Recommended**

[a] Refers mostly to singleton gestations at term, vertex.
[b] Consider when PROM expected to be >12 hours.

streptococcal disease (EOGBSD), which is defined as vertical transmission resulting in sepsis, pneumonia, and, less commonly, meningitis within 7 days of birth [3, 4].

Universal prenatal maternal GBS screening with **anovaginal specimen collected at 36–37 weeks and antibiotic (penicillin as first line) treatment** to GBS-colonized women is recommended [3]. **Women with GBS bacteriuria** in the current pregnancy or who had a **prior infant with GBS sepsis** are candidates for intrapartum antibiotic prophylaxis (IAP) and **should be the only two groups not screened**. **Intrapartum treatment for chorioamnionitis is recommended regardless of GBS maternal status** (see Chaps. 24 and 39 in *Maternal-Fetal Evidence Based Guidelines*). For those with an unknown GBS culture result in labor, antibiotics should be given to all women with recognized risk factors: Previous infant affected by GBS sepsis, GBS bacteriuria during the current pregnancy, preterm labor <37 weeks, prelabor rupture of membranes ≥18 hours and/or fever in labor ≥38°C, or women known to be colonized with GBS in a prior pregnancy [3, 4]. There is no intervention shown to be efficacious for prevention of late-onset GBS sepsis.

In summary, women with GBS bacteriuria in the current pregnancy or who had a prior infant with GBS sepsis are candidates for IAP and do not require screening. Universal GBS culture screening is recommended at $36^{0/7}$ and $37^{6/7}$ weeks of gestation. IAP in labor for GBS-positive women is recommended to reduce neonatal EOGBSD. Penicillin should be used as the first-line agent: 5 million units loading dose followed by 2.5 million units every 4 hours, ideally for ≥4 hours before delivery. For women with a penicillin allergy that are at low risk for anaphylaxis, cefazolin is the recommended antibiotic. For women with a penicillin allergy that are at high risk for anaphylaxis, clindamycin is the recommended antibiotic if the GBS isolate is susceptible. If susceptibilities are not available or the GBS isolate is resistant to clindamycin, vancomycin is the recommended antibiotic for women with a penicillin allergy at high risk of anaphylaxis.

Antibiotic prophylaxis for term prelabor rupture of membranes

The administration of routine antibiotic prophylaxis for term prelabor rupture of membranes (PROM) is not associated with either maternal or neonatal beneficial outcomes compared to no antibiotic prophylaxis. However, in women with PROM and latency longer than 12 hours, prophylactic antibiotics are associated with significantly lower rates of intraamniotic infection by 51% and endometritis by 88%, and a trend toward a decrease in neonatal sepsis, RR 0.34 (0.11–1.04). The most commonly used antibiotics were ampicillin and gentamicin. For women with a penicillin allergy, clindamycin or erythromycin was used [5].

In summary, **antibiotic prophylaxis can be considered in women with term PROM in which >12 hours of latency are expected between PROM and delivery**.

Aromatherapy

Compared to no such intervention, administration of selected essential oils (such as lavender, jasmine, rose, almond, or a combination) through inhalation or back massage during labor is not associated with significant effects on cesarean delivery (CD),

instrumental delivery, or use of oxytocin. In a recent meta-analysis of 17 randomized trials, it was shown to have a **reduction in labor pain and duration** compared to no aromatherapy. However, the heterogeneity of the trials included calls for a larger trial with a more stringent study design in order to provide recommendations for or against aromatherapy [6].

In summary, **aromatherapy with essential oils through inhalation or back massage can be considered in labor**.

Immersion in water

Compared to controls (labor not in water), water immersion **during the first stage of labor reduces the use of epidural/spinal analgesia by 9%** (RR 0.91, 95% CI 0.83–0.99). There is **no difference in other outcomes**: Duration of labor (mean difference [MD] –11.53 minutes, 95% CI –45.42 to –22.36), mode of delivery (RR 1.01, 95% CI 0.97–10.4), augmentation of labor by artificial rupture of membranes or use of oxytocin infusion (RR 1.02, 95% CI 0.90–1.16), perineal trauma or maternal infection, Apgar score <7 at 5 minutes (RR 1.58, 95% CI 0.63–3.93), or other neonatal outcomes [7]. There is no evidence of increased adverse effects to the fetus/neonate or woman from laboring in water. Laboring in water is usually linked to midwifery care, which is associated with its own benefits (see Chap. 7). There are no trials evaluating different baths/pools, immersion in water during pregnancy, or during the third stage of labor.

In summary, **if there is reassuring fetal and maternal status and it is desired by the patient, immersion in water in the first stage of labor can be considered. For water birth and immersion in water in the second stage, see Chap. 9**.

Nutrition in labor

Since the evidence shows a shorter duration of labor without an in increase in harm, **there is little to no justification for the restriction of fluids and food in labor for women at low risk of complications**.

A meta-analysis of 10 randomized trials assessing various diets versus ice chips, water, or only water, included 3982 low-risk laboring women. All studies looked at women in active labor and at low risk of potentially requiring a general anesthetic. Three studies allowed women to select from a low-residue diet, one study allowed honeydate syrup, and five allowed carbohydrate drinks. All the included studies allowed patients to have the assigned diet throughout the entire course of labor until delivery. Compared to only ice, water, or sips of water, **a policy of unrestricted food intake was associated with a significantly shorter duration of labor** (MD –16 minutes, 95% CI –25 to –7). There were **no significantly different rates of CD. No events of aspiration occurred in either group** [8].

Given that no studies found an increased risk of complication, as well as the general rarity of its occurrence (about 15/10,000 CDs) [9], there is no evidence to support food restrictions in women in labor.

In summary, **oral restriction of fluid or solid food in the first stage of labor is not recommended**.

Acid prophylaxis drugs

There is **no good evidence to support** the routine administration of acid prophylaxis drugs in normal labor to prevent gastric aspiration and its consequences [10]. Giving such drugs to women once a decision to give general anesthesia is made is discussed in Chap. 12.

Intravenous fluids

There have been many studies assessing type and rate of intravenous (IV) fluids in labor. A meta-analysis of seven randomized trials including 1215 women showed that fluids at a rate of 250 mL/hour are associated with a 1-hour reduction in labor compared to fluids at a rate of 125 mL/hour where oral intake is restricted. This review also found a 30% reduction in CDs compared to fluids at a rate of 125 mL/hour. These differences were not significant in the trials where oral intake was not restricted [11].

The benefits are substantiated by the fact that several trials in nonpregnant adults demonstrate that increased fluid intake improves exercise performance.

Compared to normal saline without dextrose, those containing dextrose are associated with a 75-minute shorter duration of the first stage of labor where oral intake is restricted [12]. Similarly to the results discussed earlier, this meta-analysis did not find a significantly shorter duration of labor when the trials had a policy of unrestricted oral intake. Five percent dextrose has also been associated with less umbilical cord acidemia compared to lactated Ringer's solution [13].

In summary, in the setting of oral restriction, **IV fluids containing dextrose at 250 mL/hour are associated with shorter duration of labor and fewer cesarean deliveries compared to 125 mL/hour without dextrose and should be preferred. In the setting of liberal oral intake, no specific rate or type of IV fluid is recommended**.

Maternal position

Upright and mobile positions (either standing, sitting, kneeling, or walking around) **in the first stage of labor reduce the length of labor** and do not seem to be associated with increased intervention or negative effects on mothers' and babies' well-being. Compared to recumbent positions, the first stage of labor in women without regional anesthesia is approximately **1 hour and 22 minutes shorter** when randomized to upright and mobile positions. Women randomized to upright positions are **less likely to have epidural analgesia** (RR 0.81, 95% CI 0.66–0.99) **and CD** (RR 0.71, 95% CI 0.54–0.94) [14]. There are no differences between groups for other outcomes, including length of the second stage of labor, or other outcomes related to the well-being of mothers and babies, except for a **lower incidence of neonatal intensive care unit admission** in the upright group. For women who had epidural analgesia, there were no differences between those randomized to upright versus recumbent positions for any of the outcomes examined in the review [15]. A woman semireclining or lying down on the side or back during the first stage of labor may be more convenient for staff and can make it easier to monitor progression and check the baby. Fetal monitoring, epidurals for pain relief, and use of IV infusions also limit movement.

In summary, upright positions in the first stage of labor should be recommended in women without regional anesthesia. Women with regional anesthesia in the first stage can adopt whatever position they find most comfortable.

Ambulation

Compared to remaining in bed, women without regional anesthesia who walk during labor have a 3-hour and 57-minute shorter duration during the first stage, are more likely to have a spontaneous vaginal delivery, are less likely to have operative vaginal delivery, and have a lower risk of requiring a CD [14]. For those with regional anesthesia who ambulate, it is associated with a similar length of first stage of labor, use of oxytocin, use of analgesia, need for forceps vaginal delivery, or CD [15].

In summary, ambulating should be recommended in the first stage of labor in women without regional anesthesia. Women with regional anesthesia can ambulate or not ambulate in the

first stage. See also "Maternal Position," as upright position *and* mobility have been associated with shorter labors.

Bladder catheterization

Compared to intermittent bladder catheterization, continuous bladder catheterization during the first stage of labor in patients with an epidural is associated with no differences in the length of labor or incidence of urinary tract infections (UTIs), but significantly higher likelihood of CD. However, this finding is based on one small trial that was unable to reach the original sample size from the power analysis. Thus, more research is needed on bladder catheterization in labor [16].

In summary, **routine continuous bladder catheterization cannot be recommended in labor**.

Frequency of cervical exams

Only one randomized controlled trial (RCT) assessed different frequencies of cervical assessment in labor. Comparing two-hourly with four-hourly vaginal examinations in labor, there was no difference in length of labor (MD in minutes −6.00, 95% CI −88.70 to 76.70; 1 RCT, $n = 109$). There were no data on maternal or neonatal infections requiring antibiotics and women's overall views of labor. There were no differences in augmentation, epidural for pain relief, CD, spontaneous vaginal birth, and operative vaginal birth [17].

The only other RCT on cervical assessment in labor compared routine vaginal examinations with routine rectal examinations to assess the progress of labor. There was no difference in neonatal infections requiring antibiotics (RR 0.33, 95% CI 0.01–8.07; 1 RCT, $n = 307$). There were no data on length of labor, maternal infections requiring antibiotics, and women's overall views of labor. The study did show that significantly fewer women reported that vaginal examination was very uncomfortable compared with rectal examinations (RR 0.42, 95% CI 0.25–0.70). There were no differences in augmentation, CD, spontaneous vaginal birth, operative vaginal birth, perinatal mortality, and admission to neonatal intensive care.

In summary, cervical assessment should be done by cervical and not rectal examination, as per patient's safety and comfort. **There is insufficient evidence to recommend any particular frequency of vaginal cervical exams in labor**. Most studies, including those regarding active management, perform cervical exams every 2 hours in labor. However, the risk of chorioamnionitis increases with increasing number of exams [18].

Membrane sweeping in labor

There has only been one RCT on membrane sweeping in labor with 400 participants. For the intervention group, membrane sweeping was performed twice with every vaginal exam during the first stage of labor. Sweeping was defined as digital separation 2–3 cm from the internal cervical os and rotating the finger 360 degrees between the lower uterine segment and the fetal head. Women in the control group only received cervical examinations. The duration of labor and mode of delivery did not differ between the two groups [19].

In summary, **routine membrane sweeping during the first stage of labor is not recommended**.

Use of partogram

A partogram is a preprinted form, the aim of which is to provide a pictorial overview of labor to plot progress and to alert health professionals of any problems with the mother or baby. The general intervention with the partogram is early use of oxytocin as soon as the cervical dilatation falls to the right of the partogram, usually on the 2-hour cervical exams.

The use of the partogram cannot be recommended as a routine intervention in labor. Compared to no partogram, the use of the partogram is **not associated with significant effects** on cesarean delivery (RR 0.77, 95% CI 0.40–1.46), oxytocin augmentation (RR 1.02, 95% CI 0.95–1.10), duration of the first stage of labor (RR 0.80 hours, 95% CI −0.06 to 1.66), or Apgar score <7 at 5 minutes (RR 0.77, 95% CI 0.29–2.06), in two RCTs including 1590 women [20].

When compared to a 4-hour action line, women in the 2-hour action line group were more likely to receive oxytocin augmentation (RR 2.44, 95% CI 1.36–4.35), with no differences in caesarean delivery rates (RR 1.06, 95% CI 0.88–1.28), duration of first stage of labor (RR 0.81 hours, 95% CI 0.32–2.04), or Apgar score <7 at 5 minutes (RR 0.93, 95% CI 0.61–1.42) [20].

In summary, **the use of a partogram cannot be recommended as a routine intervention in labor**.

Peanut ball

A peanut ball, which is an enlarged and elongated exercise ball that is placed between the women's legs, has long been used with the aim to decrease the amount of time in labor. The routine use of a peanut ball during the first stage of labor is associated with a nonsignificant 79-minute shorter duration and no decrease in the total length of time to delivery compared to no peanut ball. However, there were also trends toward an increased incidence in spontaneous vaginal deliveries and lower incidence of CD [21].

In summary, **the use of the peanut ball can be considered in labor**.

Birthing ball

Birthing balls (also known as Swiss balls) are round exercise balls that women in labor can sit on and perform different movements such as pelvic rotation and rocking back and forth. They are thought to widen the maternal pelvic outlet to assist in progression of labor, while also decreasing pain. A recent systematic review and meta-analysis of seven RCTs that included 533 women demonstrated that the use of a birthing ball versus no birthing ball resulted in no significant difference in the incidence of spontaneous vaginal delivery, cesarean delivery, operative vaginal delivery, or duration of labor. However, it did significantly reduce pain in the active phase of the first stage of labor [22].

In summary, **the use of a birthing ball during the first stage of labor can be considered**.

Antispasmodics

Antispasmodics (e.g. valethamate bromide, hyoscine butyl-bromide, drotaverine hydrochloride, rociverine, and camylofin dihydrochloride) have been used with the thought that they could lead to faster and more effective dilation of the cervix. In a meta-analysis of 17 randomized trials, they were shown to be associated with a 74-minute shorter duration of the first stage of labor and an increased rate of cervical dilatation by an average of 0.61 cm/hour. Antispasmodics are not associated with a significant effect on the duration of the second and third stage of labor. However, the quality of the evidence is low to very low [23].

In summary, **antispasmodics cannot be routinely recommended in labor**.

Early artificial rupture of membranes (aka Amniotomy)

Compared to no amniotomy, routine amniotomy in normally progressing spontaneous labor is not associated with significant differences in length of the first stage of labor (MD –20.43 minutes, 95% CI –95.93 to 55.06), CD (RR 1.27, 95% CI 0.99–1.63), maternal satisfaction with childbirth experience, or low Apgar score <7 at 5 minutes (RR 0.53, 95% CI 0.28–1.00). Other maternal and perinatal outcomes are also not different. There is no consistency between RCTs regarding the timing of amniotomy during labor in terms of cervical dilatation [24].

However, in the setting of labor induction, early amniotomy (which is defined most consistently as amniotomy prior to the active phase of labor) has been shown to decrease the duration in the first stage of labor by approximately 5 hours (MD –4.95 hours; 95% CI –8.12 to –1.78) without an increase in CD rates [25] **(see Chap. 23)**.

In summary, routine **amniotomy in normally progressing spontaneous labor cannot be recommended as part of standard labor management and care, but early amniotomy in labor induction after cervical ripening and expulsion of the balloon is recommended**.

Oxytocin augmentation

There are **no trials to evaluate the timing and dosing of oxytocin in labor in women making normal progress in labor**.

For women making slow progress in the first stage of spontaneous labor, treatment with oxytocin as compared with no treatment or delayed oxytocin treatment does not result in any discernable difference in the number of cesarean deliveries performed in one meta-analysis. In addition, there are no detectable adverse effects for mother or baby [26]. The meta-analysis included eight appropriate studies, for a total of 1338 women with low-risk singleton pregnancies at term in the active stage of labor. **IV oxytocin versus placebo or no treatment** (three trials; 138 women) showed **no difference** as for CD rates; only three small trials were considered, so the comparison was clearly underpowered to make any firm conclusions. **Early use of IV oxytocin versus delayed use** (five trials; 1200 women), however, was much larger and also showed **no effect on CD rates**. The early use of oxytocin did significantly increase uterine tachysystole with fetal heart rate changes; however, this did not translate into serious neonatal morbidity or perinatal death. The early use of oxytocin, as opposed to its delayed use, did significantly **shorten the time to delivery by approximately 2 hours**, which might be important to some women.

In a different meta-analysis, early oxytocin was associated with a 9% significant increase in the probability of spontaneous vaginal delivery (SVD), but also a tripling of the rate of tachysystole, without apparent perinatal consequences [27].

There is insufficient evidence to assess how to best use (i.e. dosing issues) oxytocin for augmentation of labor. There are four variables to assess: (1) type of dilution, (2) initial dose, (3) incremental increase, and (4) maximum dose [28]. In a meta-analysis, a higher initial dose (e.g., 2 mU/minute) of oxytocin and incremental dose (e.g., 4 mU/minute or more) was associated with a significant reduction in the length of labor reported from one trial (MD –3.50 hours, 95% CI –6.38 to –0.62, 1 RCT, $n = 40$). There was a decrease in the rate of CD (RR 0.62; 95% CI 0.44–0.86) and an increase in the rate of spontaneous vaginal birth (RR 1.35; 95% CI 1.13–1.62). There were no significant differences for neonatal mortality, tachysystole, chorioamnionitis, or epidural analgesia or neonatal outcomes of Apgar scores, umbilical cord pH, or admission to special care baby unit. Many outcomes were not evaluated, such as perinatal mortality, women's satisfaction, instrumental vaginal birth, uterine rupture, postpartum hemorrhage, abnormal cardiotocography, women's pyrexia, dystocia, and neonatal neurological morbidity [29]. Based mostly on physiologic studies, an oxytocin dilution of 10 mU/mL and initial dose of 2 mU/minute (12 mL/hour), incremental increase of 2 mU (12 mL) every 30–45 minutes until adequate labor, and maximum dose of 16 mU/minute (up to 24 mU) have been proposed [28, 29].

Stopping oxytocin instead of continuing it once the active phase of labor is reached in women in spontaneous labor is **not associated with maternal or perinatal benefits**. Stopping oxytocin is associated with a **longer (by about 30 minutes) time to delivery** [30].

In summary**, oxytocin augmentation in women making slow progress in the first stage is associated with a 2-hour shortening of labor, without apparent effect on mode of delivery or other maternal and perinatal outcomes. Higher doses of oxytocin can be considered**.

For use of oxytocin in induction, see Chap. 23.

Active management of labor

Active management of labor was originally devised to shorten labor and therefore prevent prolonged labor. Its components have varied somewhat in the literature but generally include antenatal classes, admission not before premature rupture of membranes (PROM) or 2 cm dilatation and full effacement (active labor), early amniotomy, support by doula, use of partogram, and vaginal exams every 2 hours, with oxytocin started for rate of progress off the partogram or <1 cm/hour. Oxytocin rate is started at 4–6 mU/minute, increased by 4–6 mU every 15 minutes to reach contractions every 2–3 minutes (but not more than 7/15 minutes), or 40 mU/minute. Early amniotomy and early use of high-dose oxytocin are the two most characteristic interventions of active management of labor.

Compared to "routine" care (no active management), active management of labor with early oxytocin and amniotomy for the *prevention* of dysfunctional or slow labor is associated with a shorter duration of the first stage (MD –1.28 hours; 95% CI –1.97 to –0.59) and lower rates of CD (RR 0.87; 95% CI 0.77–0.99). For *treatment* of dysfunctional labor, active management is also associated with a shorter duration in the first stage; however, no differences in CD rates were found, although it is important to note that the number of trials reporting on *treatment* intervention and outcome were only 3, compared to 11 in the *prevention* group, thus limiting the sample size [31].

In summary, early intervention with oxytocin and amniotomy for the prevention and treatment for dysfunctional or slow labor is recommended.

Use of continuous vs. intermittent monitoring, amnioinfusion for variables, scalp sampling, etc.

See Chap. 10.

Epidural or other anesthesia

See Chap. 11.

Use of intrauterine pressure catheter

The intrauterine pressure catheter (IUPC) can measure more objectively than external tocomonitor the intensity of uterine contractions. It necessitates rupture of membranes (ROM).

Intensity is usually calculated by Montevideo units, that is, the sum of peak pressures above baseline of all contractions in 10 minutes.

Several RCTs have assessed the effect of IUPC on labor outcomes. In the largest RCT, compared to no IUPC, IUPC use is associated with **no effect** in the rate of operative deliveries, maternal or fetal infection, or other maternal or perinatal recorded outcome [32]. In the meta-analysis, the neonatal outcome was not statistically different between groups: Apgar score <7 at 5 minutes (RR 1.78, 95% CI 0.83–3.83), umbilical artery pH <7.15 (RR 1.31, 95% CI 0.95–1.79), admission to the neonatal intensive care unit (RR 0.34, 95% CI 0.07–1.67), and more than 48 hours hospitalization (RR 0.92, 95% CI 0.71–1.20). The pooled risk for instrumental delivery (including CD, vacuum, and forceps extraction) was not statistically significantly different (RR 1.05, 95% CI 0.91–1.21). Tachysystole was similar between groups (RR 1.21, 95% CI 0.78–1.88). **No serious complications** were reported in the trials, and **no neonatal or maternal deaths occurred** [33].

In summary, the routine use of the IUPC cannot be recommended in labor, unless clinically indicated. See also "Criteria for Diagnosis of Failure to Progress in First Stage."

Use of ultrasound during labor

There is growing evidence, including RCTs, to assess the effect of using ultrasound during labor and delivery. There are several potential uses, including as an aid to the diagnosis of malposition, dystocia, etc. [34]. Performing routine ultrasound to assess fetal head position in singleton pregnancies in labor ≥8 cm, compared to digital vaginal assessment alone, is associated with an increase in operative vaginal delivery, with no other effects on maternal or perinatal outcomes [35].

In summary, the routine use of ultrasound during a normally evolving first stage of labor cannot be recommended.

Criteria for diagnosis of failure to progress in first stage

According to studies now >60 years old in women without regional anesthesia by Friedman, the active phase began at 2.5 cm and ended at complete dilatation, with an average duration of 4.6–4.9 hours, a mean rate of cervical dilation of 3 cm/hour, and the slowest acceptable rate (95th percentile) of 1.2 cm/hour [36, 37]. More recently, investigators found that the active phase of labor in nulliparous women lasts longer than previously thought. According to a systematic review, which included 18 studies (for a total of 7009 women), the active phase of labor among healthy, low-risk, nulliparous women at term with a spontaneous labor onset lasts 6 hours, on average, and the average cervical dilation rate is 1.2 cm/hour. This means that rates of cervical dilatation during active labor from 4 cm forward are much slower than those reported by Friedman. According to recent evidence, it seems that the slowest acceptable rate of cervical dilation is 0.6 cm/hour. In term women in labor necessitating oxytocin and with epidural, the fifth percentile rate for dilatation is about 0.5 cm/hour for both nulliparous and parous women [38]. In term women with epidural, **labor may take more than 6 hours to progress from 4 to 5 cm and more than 3 hours to progress from 5 to 6 cm of dilation** [39]. Moreover, cervical dilation during the active phase of labor is often conceptualized linearly; however, recent evidence suggests that cervical dilation rates accelerate throughout the majority of labor. So, in common practice, the likelihood of accelerative intervention is much greater in earlier active labor. It must be kept in mind that progression in the earlier part of "active labor" will typically be slower than 0.6 cm/hour, while progression in more advanced active labor will typically be more rapid [40].

Abnormal progression of labor, including terms such as dystocia, dysfunctional labor, failure to progress, cephalopelvic disproportion, and others, is the most common problem in labor and the **reason for the majority of CDs** [41]. Risk factors for dystocia are, among others, as follows: Obesity, induction, Bishop <5 at start of labor, station higher than –2, persistent occiput posterior, macrosomia, epidural anesthesia, etc. There are no RCTs on interventions for asynclitism [42]. (See also Chap. 24.; for malposition, see Chap. 24). **Dystocia cannot be diagnosed unless ROM has occurred and adequate oxytocin** to achieve at least 3–5 adequate contractions per hour has been instituted. Dystocia also **cannot be diagnosed reliably before the first stage of labor has entered the active phase, which has been defined, especially in nulliparous with epidurals in place, as at least 6 cm of cervical dilatation** [38, 39]. The majority (>60%) of women who experience 2 hours of labor arrest despite a sustained uterine contraction pattern of at least 200 Montevideo units in the first stage of labor will achieve a vaginal delivery if oxytocin is continued [43]. **Before performing a CD for active-phase labor arrest, labor should be arrested for a minimum of 4 hours (if uterine activity is greater than 200 Montevideo units as documented with IUPC) or 6 hours (if greater than 200 Montevideo units could not be sustained)** [43, 44]. These data are not from an RCT, and there was a significant higher risk of shoulder dystocia among parturients who had arrest for 4 hours or more. Vaginal birth after cesarean (VBAC) and women with diabetes were not included in this study. Please see Chap. 8 for additional evidence on dystocia.

In women at term with singleton gestations and requiring oxytocin by obstetrician because of "dystocia" at 4–6 cm, **meperidine 100 mg IV does not affect operative delivery rates and worsens neonatal outcomes compared to placebo** [45] (see also Chap. 8).

In summary, CD for arrest in the first stage of labor should not be performed unless labor has arrested for a minimum of 4 hours with adequate uterine activity, or 6 hours with inadequate uterine activity in a woman with ROM, adequate oxytocin, and ≥6 cm cervical dilation.

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9

SECOND STAGE OF LABOR

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Key points

- **Prophylactic intrapartum maternal oxygen should not be used** in the second stage of normal labor, since it is associated with more frequent low cord blood pH values (<7.20) than the control group.
- **Prophylactic intrapartum betamimetics should not be used** in the second stage of normal labor, since their usage is associated with an increase in forceps deliveries.
- **Women without epidural anesthesia should be encouraged to give birth in the position they find most comfortable, which is usually upright**. Use of any **upright or lateral position**, compared with supine or lithotomy positions, is associated, **in women without epidural analgesia,** with **reduction in duration of second stage of labor, reduction in assisted deliveries, reduction in episiotomies, increase in second-degree perineal tears, increase in estimated blood loss >500 mL, reduction in reporting of severe pain during second stage of labor**, and **reduction in abnormal fetal heart rate patterns**.
- **There is insufficient evidence** to support **the best position for giving birth in women with epidural anesthesia**.
- **There is insufficient evidence to recommend for or against maternal stirrup use in the second stage of labor**.
- **Water immersion in the second stage of labor should be avoided, as the risks have not been adequately assessed**.
- In **nulliparous women at term with epidural analgesia and a singleton, cephalic fetus, delayed pushing (waiting 1 hour or until "urge to push") is associated with similar rate of spontaneous vaginal delivery (SVD) and operative vaginal delivery (OVD)** compared with early (immediately upon entering second stage) pushing. Additionally, with delayed pushing, the duration of the second stage is **increased by about 30 minutes, the incidence of chorioamnionitis and postpartum hemorrhage is increased, and neonatal cord pH is decreased**. **Careful monitoring of mother and fetus is necessary** to allow labor to continue safely, and risks and benefits of delayed pushing should be discussed with the patient prior to decision-making.
- In women without epidural anesthesia, compared with encouraging a woman's own urge to push (open glottis), **pushing using the Valsalva maneuver (closed glottis)** is **associated with shorter (by 19 minutes) duration of labor, similar incidences of OVDs, need for perineal repair, postpartum hemorrhage, and similar neonatal outcomes**. Labor attendants should counsel women in labor regarding these data and **support the parturient in her own choice of pushing technique**.
- **Women with levator ani coactivation, as demonstrated by transperineal ultrasound, have a longer active second-stage duration** (by about 32 minutes).
- **Traditional coaching during pushing** in the second stage of labor **may shorten the second stage, but lack of available coaching support does not adversely affect labor outcomes**. **Ultrasound-assisted coaching is associated with a shorter second stage of labor** (by about 15 minutes).
- **Use of a dental support device/mouthguard has been associated with a shorter second stage of labor and reduction in failure to descend requiring operative intervention**.
- **Manual fundal pressure, gentle assisted pushing, and belt fundal pressure have not been associated with an effect on spontaneous vaginal delivery rate. Fundal pressure is associated with increased levator ani injury and cervical tears. Gentle assisted pushing is associated with greater discomfort. Belt fundal pressure is associated with a shorter second stage in nulliparas, but overall less satisfaction with delivery**.
- **Perineal massage and stretching of the perineum with a water-soluble lubricant** in the second stage of labor are associated with **similar rates of intact perineum** compared with the control group. The incidence of **third-degree lacerations is decreased**.
- **There is insufficient evidence for or against the use of perineal hyaluronidase (HAase) injection as a method to reduce perineal trauma**.
- The use of **perineal gel** in the second stage of labor **does not appear to have an effect on shortening the duration or decreasing the risk of perineal lacerations**, but there do not appear to be any adverse effects.
- Use of **perineal warm packs** in the second stage of labor **is associated with a reduction in third- and fourth-degree tears, as well as a reduction in pain on postpartum days 1 and 2**.
- **Heating pad use on the perineum may decrease the need for episiotomy**.
- A **perineal protection device has been shown to decrease the risk of first- and second-degree lacerations**.
- In fetuses with persistent occiput posterior, there is **insufficient evidence to recommend manual rotation** in labor to improve SVD success.
- **Routine use of the Ritgen maneuver does not appear to be associated with any benefits** and may increase postpartum pain.
- **"Hands-poised" is preferred to the "hands-on" method**, since they are associated with similar incidences of perineal and vaginal tears, but the hands-on method is associated with a higher incidence of episiotomies.
- **Routine episiotomy should not be performed during the second stage of labor**, as restricting episiotomy use is associated with less posterior perineal trauma.
- **Use of ultrasound in the second stage of labor can be valuable in predicting SVD**.

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TABLE 9.1: Summary of Interventions in the Second Stage of Labor

Intervention	Recommendation
Prophylactic oxygen	Not recommended
Prophylactic tocolytic administration	Not recommended
Upright position without epidural	**Recommended**
Upright position with epidural	Insufficient evidence
Maternal stirrup use	Insufficient evidence
Water immersion in the second stage	Insufficient evidence
Water birth	Not recommended
Immediate Pushing	**Recommended**
Open versus closed glottis pushing	Insufficient evidence
Ultrasound-assisted coaching	Insufficient evidence
Dental support device	Insufficient evidence
Fundal pressure	Not recommended
Perineal Massage	**Recommended**
Perineal hyaluronidase injection	Insufficient evidence
Perineal gel	Not recommended
Perineal Warm Packs/Heating Pad	**Recommended**
Perineal protection device	Insufficient evidence
Manual rotation	Insufficient evidence
Routine Ritgen maneuver	Not recommended
"Hands-Poised" Position	**Recommended**
Routine episiotomy	Not recommended
Ultrasound use in the second stage	Not recommended
Allow a 4-hour second stage in nulliparas, epidural[a]	**Recommended**

[a] See Table 9.2.

- **Nulliparous women with epidurals should be allowed to labor for at least 1 additional hour after prolonged (3-hour) second stage of labor**, since this results in a 55% lower chance of cesarean delivery (CD) without a large absolute increase in perinatal morbidities. There is insufficient evidence to determine exactly when the second stage is considered to be prolonged and associated with enough complications as to justify either OVD or CD.

See Table 9.1 for a summary of suggested interventions.

Prophylactic interventions

Maternal oxygen

Prophylactic intrapartum maternal oxygen in the second stage of normal labor is **associated with more frequent low (<7.20) cord blood pH** values than the control group in a Cochrane review [1]. There were no other statistically significant differences between the groups. There is a tendency toward reduced cord arterial blood oxygen content and oxygen saturation in mothers treated with oxygen compared with controls. In a large recent randomized controlled trial (RCT), there was no difference in cord pH with the administration of oxygen during the second stage of labor in uncomplicated pregnancies [2]. **In summary, routine maternal oxygenation throughout the second stage should not be performed**.

Prophylactic tocolysis

There is no evidence to support the prophylactic use of betamimetics to prevent nonreassuring fetal heart rate tracing (NRFHT) during the second stage of labor. Compared with placebo, prophylactic betamimetic therapy is **associated with an increase in forceps deliveries**. The trial protocol required forceps to be used if the second stage of labor exceeded 30 minutes in both groups. There are no clear effects of prophylactic tocolysis on postpartum hemorrhage, neonatal irritability, feeding slowness, umbilical arterial pH values, or Apgar scores at 2 minutes [3]. **In summary, routine prophylactic tocolysis should not be performed in the second stage of labor**.

Prophylactic positioning to prevent shoulder dystocia

See Chap. 25.

Management

Maternal position

There are several benefits for upright posture in women without epidural anesthesia during the second stage of labor: Sitting (obstetric chair/stool), semi-recumbent (trunk tilted backward 30 degrees to the vertical), kneeling, squatting unaided or using squatting bars, and squatting aided with birth cushion are all considered upright positions for women in labor.

Use of any **upright or lateral position**, compared with supine or lithotomy positions, is associated, **in women without epidural analgesia**, with a **small** (4 minutes) **reduction in duration of second stage of labor**, a 20% **reduction in assisted deliveries**, a 17% **reduction in episiotomies**, a 23% **increase in second-degree perineal tears**, a 63% **increase in estimated blood loss >500 mL**, a 23% **reduction in reporting of severe pain during second stage of labor**, and a 69% **reduction in abnormal fetal heart rate patterns** [4]. Use of the birth stool showed no effect, and results with the birth chair were variable. Estimation of blood loss in the upright group may be influenced by the fact that blood loss in the birth chair is assisted by gravity and collected in a receptacle. Physiologic advantages for upright labor may include lessened risk of aortocaval compression, improved acid–base outcomes in the neonates, stronger and more efficient uterine contractions, improved alignment of the fetus for passage through the pelvis ("drive angle"), and larger anteroposterior and transverse pelvic outlet diameters, resulting in an increase in the total outlet area in the squatting and kneeling positions [4].

In women with epidural anesthesia, the evidence is mixed; however, a large RCT supports the lying-down position in nulliparas with epidural anesthesia. In the largest trial on position in the second stage for nulliparous women with epidural anesthesia, there were 14% **fewer spontaneous vaginal births** in the upright group in comparison to the lying-down group [5]. In a smaller RCT, compared with a supported sitting position, lateral position was associated with a lower chance of an operative vaginal delivery (OVD) [6]. Kneeling and sitting upright are associated with a similar duration of second stage and other outcomes, except for a more favorable maternal experience and less pain associated with kneeling [7]. **In a Cochrane review of eight RCTs, there was no significant difference in OVD, cesarean delivery (CD), postpartum hemorrhage, or duration of second stage based on position during labor** [8]. **Maternal satisfaction** with the overall childbirth experience **was slightly lower in the upright group; however, 57% less babies were born with low cord pH in the upright group** [8].

In summary, women without epidural anesthesia should be encouraged to give birth in the upright position, which is also the position they usually find most comfortable [4]. **There**

is insufficient evidence supporting the best position for giving birth in women with epidural anesthesia. The American College of Obstetricians and Gynecologists (ACOG) therefore supports position changes as desired to sustain maternal comfort and to maintain appropriate monitoring during labor of women with epidural anesthesia [9].

Maternal stirrup use

Routine use of stirrups during labor has had limited **study insufficient to make a recommendation**. In one small RCT, women who delivered in bed with stirrups vs. those who delivered without stirrups had similar perineal lacerations, incidence of prolonged second stage, OVD, and CD incidence [10]. **In summary, there is insufficient evidence to make a recommendation regarding use of stirrups in labor**.

Epidural or other anesthesia

See Chap. 11.

Water immersion

Although there is some evidence that water immersion in the first stage of labor may reduce the need for epidural/spinal anesthesia and decrease the length of the first stage of labor (see Chap. 8), **immersion during the second stage has been insufficiently studied** and may be best avoided, given the lack of sufficient safety data. Of the three trials that compared water immersion during the second stage with no immersion, only one trial showed a significantly higher level of satisfaction with the birth experience (relative risk [RR] 0.24, 95% confidence interval [CI] 0.07–0.70). There are reports of neonatal water aspirations from birth (at the end of the second stage) in water [11, 12]. Both ACOG and National Institute for Health and Care Excellence (NICE) conclude that as the safety has not been well established, water immersion in the second stage of labor should be avoided. **In summary, water immersion in the second stage of labor should be avoided, as the risks have not been adequately assessed** [13, 14].

Pushing

Delayed vs. early pushing

In nulliparous women at term with **epidural** analgesia and a singleton, cephalic fetus, **delayed pushing** (waiting an hour or until the urge to push) is associated with **a similar rate of spontaneous vaginal delivery (SVD)** compared with early (immediately upon entering second stage) pushing (RR 0.99, 95% CI 0.96–1.03) [15]. **Women who delay pushing have a longer second stage** (about 32 minutes) and **a shorter duration of pushing** (about 10 minutes). **Women who push immediately have a 30% lower risk of chorioamnionitis and a 40% lower risk of postpartum hemorrhage, but a 10% higher risk of third-degree lacerations** [15]. **Umbilical cord pH < 7.1 and suspected sepsis were more common in the delayed pushing group**. In a meta-analysis of 12 RCTs, similar results were noted [16]. Due to the adverse outcomes associated with delayed pushing and potentially prolonged second stage, **careful monitoring of both mother and fetus is necessary to allow labor to continue safely if desired by the patient and provider**. (see also "Criteria for Diagnosis of Prolonged Second Stage"). ACOG is therefore in support of immediate pushing for nulliparas with epidural anesthesia [9]. **In summary, immediate pushing is recommended upon entering the second stage**.

Pushing method: Valsalva vs. spontaneous

Most women spontaneously choose to Valsalva during the second stage of labor. In women without epidural anesthesia, compared with encouraging a woman's own urge to push (open glottis), **pushing using the Valsalva maneuver (closed glottis**: Taking a deep breath, holding it, and pushing for as long and hard as possible two to three times during each contraction) is **associated with shorter (by 19 minutes) duration of labor, similar incidences of OVDs, need for perineal repair, postpartum hemorrhage, and neonatal outcomes** [17]. Urodynamic studies done 3 months after delivery are worse in the closed glottis group, but long-term outcome has not been studied [17]. Labor attendants should counsel women in labor regarding these data and **support the parturient in her own choice of pushing technique**. ACOG supports an individualized pushing technique as preferred by the patient [9]. **In summary, there is insufficient evidence to make a recommendation regarding pushing method**.

Coactivation during Valsalva

The Valsalva maneuver is ordinarily associated with relaxation of the levator ani muscle, which expands around the presenting fetus; but in some women Valsalva produces levator ani muscle contraction, which is referred to as levator ani muscle coactivation. This has been demonstrated by transperineal ultrasound. In one prospective study, transperineal ultrasound in the second stage of labor was used to measure levator ani muscle coactivation in a group of nulliparous women undergoing labor induction to assess labor outcomes and duration. **Women with levator ani muscle coactivation had significantly longer active second-stage duration** (about 32 minutes). There was no significant difference between women who underwent operative delivery when compared with the SVD group in the prevalence of levator ani muscle coactivation [18]. **In summary, women with levator ani coactivation have a longer second stage but no difference in SVD rate**.

Coached pushing

Although **traditional coached pushing confers the benefit of a slightly shorter second stage** (about 13 minutes), coached maternal pushing confers no other advantages, and withholding such coaching is not detrimental to maternal or fetal outcomes [19]. Sonographically coached pushing, i.e. using visual demonstration by transperineal ultrasound of the progression of fetal head descent, is associated with a **shorter active phase of the second stage of labor** (about 15 minutes) [20]. **In summary, coached pushing is not harmful to women in labor, and ultrasound-assisted pushing seems helpful but has been insufficiently studied**.

Use of a dental support device

In one RCT, wearing a dental support device (mouthguard) is associated with a shorter second stage (19 minutes). In addition, less operative intervention was used in the dental support group. Further research into optimizing maternal expulsive efforts is needed to evaluate the overall benefit of dental devices [21]. **In summary, use of a dental support device during the second stage of labor is recommended**.

Fundal pressure

In the second stage of labor, fundal pressure has been evaluated by manual pressure, by gentle assisted pressure, or by use of an obstetric belt wrapped around the woman's abdomen above the level of the uterine fundus.

Compared with no manual fundal pressure, **manual fundal pressure (Kristeller maneuver) concomitant with each contraction while the patient has the urge to push during the second stage is not associated with any significant changes in**

duration of labor or with other maternal and perinatal outcomes in one RCT [22]. Additionally, manual fundal pressure is associated with a **higher rate of levator ani muscle injury** in comparison to control [23]. A Cochrane review of manual fundal pressure of nine trials showed that manual fundal pressure was not associated with changes in SVD, OVD, CD, duration of second stage, or low arterial cord pH. **More women who received manual fundal pressure had cervical tears** than in the control group (RR 4.90, 95% CI 1.09–21.98 [24].

"Gentle assisted pushing (GAP)" is a method of applying gentle, steady pressure to a woman's fundus during the second stage of labor. In the GAP method, the woman is assisted to assume an upright kneeling or squatting position on the bed. The provider kneels on the bed or stands behind the woman, wraps the arms around her, and places both open palms, overlapping, on the uterine fundus. Steady pressure is applied in the long axis of the uterus during contractions for a maximum of 30 seconds, with at least 30 seconds of rest before the next application. One trial of nulliparous women showed that the duration of the second stage of labor was not different in the GAP group versus control. There were no differences in secondary outcomes, except that at two sites **maternal discomfort was greater for the GAP group compared** with control [25].

The **fundal pressure belt** inflates with each contraction to a maximum of 200 mmHg for 30 seconds. Compared with no belt, the **inflatable obstetric belt is associated with similar incidence of SVD** in nulliparous women with singleton term pregnancies and an epidural. All other maternal and neonatal outcomes are similar, but **women with no belt have greater satisfaction** [26]. In a Cochrane review, fundal pressure by inflatable belt did not reduce OVD or CD. **Duration of second stage was shortened** in nulliparous women (mean difference −50.80 minutes, 95% CI −94.85 to −6.74 minutes). The inflatable belt **did not affect the incidence of low arterial cord pH babies, but third-degree perineal tears were increased in the inflatable belt group** (RR 15.69, 95% CI 2.10–117.02) [24].

In summary, **manual fundal pressure, GAP, and belt fundal pressure** have not been associated with an effect on method of delivery, but they are associated with **decreased maternal satisfaction, increase in cervical and third-degree tears, and shorter second stage in nulliparas; therefore, all types of fundal pressure should be avoided**.

Perineal massage

Perineal massage has been evaluated for a decrease in perineal lacerations. Perineal massage has not been associated with complications. For perineal massage during pregnancy and before labor, see Chap. 2. Perineal massage and stretching of the perineum with a water-soluble lubricant in the second stage of labor are associated with **a 40% increased rate of intact perineum, a 51% decreased rate of severe perineal trauma, and a 44% decreased rate of episiotomy compared with controls** [27]. A Cochrane review also favored perineal massage versus hands off for a 51% **reduction in third- or fourth-degree tears** [28]. **In summary, perineal massage is recommended in the second stage of labor to decrease perineal trauma**.

Perineal hyaluronidase injections

Perineal hyaluronidase (perineal HAase) injections have also been used to reduce perineal trauma. In a Cochrane review of this strategy, hyaluronidase injection during the second stage of labor had a lower incidence of perineal trauma compared with no intervention. Data from additional trials that contained a placebo injection show no clear evidence of a reduction in the incidence of perineal trauma, episiotomy, and third- and fourth-degree perineal lacerations. **In summary, the potential use of perineal HAase injection as a method to reduce perineal trauma has yet to be determined** [29].

Perineal gel

The use of a sterile obstetrical gel (lubricant) without perineal massage has been assessed in women in the second stage of labor. The rates of **OVD and CD were comparable** between the gel group and control. There was **no reduction in perinatal lacerations or in the length of the second stage**. No adverse perinatal outcomes were noted [30]. A meta-analysis of the use of gel to shorten the second stage of labor supported these findings [31]. **In summary, use of a perineal gel as a lubricant without perineal massage is not recommended**.

Perineal warm packs

Application of perineal warm packs during the second stage of labor was associated with less severe (third- or fourth-degree) tears than was standard management. In addition, **pain scores were less** on postpartum days 1 and 2 in the intervention group. After 3 months, a trend toward decreased symptoms of urinary incontinence was seen in the intervention group [32]. An RCT evaluating the effect of warm compresses on episiotomy showed a **decrease in episiotomy** use in primiparous women in the second stage of labor without analgesia (90% vs. 45%, $p < 0.001$) [33]. A Cochrane review also supports a **decrease in third- or fourth-degree lacerations**, and a meta-analysis of seven trials showed that warm compresses were associated with a **higher rate of intact perineum, a lower rate of third- and fourth-degree tears, and episiotomy** in comparison to controls [28, 34].

Use of a **heating pad** at the start of the second stage has been evaluated in primiparous women delivered by Ritgen maneuver in one RCT and showed that **episiotomy risk was lower** in the heating pad group [35]. **In summary, warm packs should be recommended in the second stage**.

Perineal protection device

A **perineal protection device**, a plastic device inserted into the perineum when the fetal head is visible at the introitus during crowning, **has been shown to decrease the risk of first- and second-degree tears** in the vaginal and perineum during vaginal birth in comparison to no device in one trial (34.9% vs. 26.6%, $p = 0.03$). The number needed to treat to prevent one laceration was 12 [36]. **In summary, the use of a perineal protection device has insufficient evidence to make a recommendation**.

Manual rotation

Persistent fetal occiput posterior position is a risk factor for prolonged labor and higher rate of CD. **Malposition includes occiput transverse or posterior positions**. These are often associated with asynclitism, defined often as the "oblique malpresentation of the fetal head in labor" [37]. In a pilot RCT of 30 women with occiput posterior fetuses who were randomized to manual rotation or sham procedure, operative delivery (CD plus OVD) were similar in both groups [38]. In an RCT of 65 nulliparas where manual rotation was attempted at the beginning of the second stage, the manual rotation group had a shorter second stage (about 13 minutes) and a higher rate of SVD [39]. When assisted by ultrasound, manual rotation and SVD success rate

were improved (see also Chap. 26) [40]. Therefore, **there is insufficient evidence to evaluate the efficacy of manual rotation in labor, but limited data are encouraging**.

Ritgen maneuver

The Ritgen maneuver (originally described by Ritgen in 1855) involves reaching for the fetal chin when it reaches the plane between the maternal anus and the coccyx and pulling it anteriorly while using the fingers of the other hand on the fetal occiput to control the speed of delivery and keep flexion of the fetal neck. Its aim is to protect the perineum from lacerations. In a meta-analysis, compared with no Ritgen maneuver, Ritgen maneuver performed for delivery of the fetal head during uterine contractions is **not associated with any benefit** on the incidence of perineal tears, but may be associated with a higher risk of postpartum pain [41]. **In summary, Ritgen maneuver does not appear to be associated with any benefits and is not recommended**.

"Hands-on" vs. "hands-poised"

The hands-on method (also described by Ritgen) involves employing pressure on the infant's head upon crowning and supporting the perineum with the other hand. The aim is to protect against lacerations. In the hands-poised method, the fetal head and perineum are not touched or supported by the delivering personnel. These two methods are associated with **similar incidences of perineal and vaginal tears, but the hands-on method is associated with a 42% higher incidence of episiotomies** [28]. A policy of hands-poised has also been supported by a meta-analysis of five RCTs. The hands-on method **does not protect against** severe perineal trauma and was associated with increased risk of third-degree lacerations (RR 3.41, 95% CI 1.39–8.37) [42]. **In summary, the hands-on method should be avoided in labor**.

Episiotomy

Routine episiotomy should not be performed, as restrictive episiotomy policies have a number of benefits compared with routine episiotomy policies. In a recent large trial there was **no difference in severe perineal laceration** between a policy of restrictive episiotomy and no such policy [43]. Restrictive episiotomy resulted in **more intact perineums** in multiparous women, but **increased the risk of vaginal laceration** in primiparous and multiparous women. Restrictive episiotomy did not lead to more suturing [43]. In the most recent Cochrane review, 83% of women had episiotomies in the routine episiotomy group, while the rate in the restrictive episiotomy group was 32% (median). Compared with routine use, **restrictive episiotomy is associated with less severe perineal trauma** (RR 0.70, 95% CI 0.52–0.94). **Compared to routine episiotomy, restrictive use of episiotomy had a similar rate of blood loss (average of 27 mL less; 95% CI 75 mL less to 20 mL increase), similar Apgar score of <7 at 5 minutes, and perineal infection** (RR 0.90, 95% CI 0.45–1.8). There was a similar rate of moderate to severe perineal pain at 3 days postpartum (RR 0.71, 95% CI 0.48–1.05), dyspareunia (RR1.14, 95% CI 0.84–1.53), and long-term (6 months or more) urinary incontinence (RR 0.98, 95% CI 0.67–1.44) [44]. There is insufficient evidence to evaluate if there are indications for any use of episiotomy, such as in OVD, preterm delivery, breech delivery, predicted macrosomia, or presumed imminent tears. **Episiotomy should be avoided if at all possible**, but if used, it is unknown which episiotomy technique (mediolateral or midline) provides the best outcome. The restrictive use of episiotomy is supported by practice guidelines endorsed by both ACOG and NICE [14, 45]. **In summary, routine episiotomy should not be performed, as restrictive episiotomy policies have many benefits compared with routine episiotomy policies**.

Ultrasound

Transabdominal and transperineal ultrasound have been used as adjuncts in the second stage of labor to predict SVD. In one prospective cohort study of nulliparas and second stage >2 hours, SVD was associated with a higher rate of occiput anterior position, lower head–perineum distance and head–symphysis distance, narrower midline angle, and wider angle of progression. At logistic regression analysis, **the midline angle and the head–symphysis distance proved to be independent predictors of SVD** [46]. **In summary, there is insufficient evidence to support the routine use of ultrasound in the second stage of labor for prediction of SVD or management of labor, as outcomes are unchanged by the use of ultrasound as studied so far**.

Criteria for diagnosis of prolonged second stage

There is insufficient evidence to determine when the second stage is prolonged and associated with enough complications with continuing labor so as to justify either OVD or CD. Some have proposed the criteria in Table 9.2 for the diagnosis of prolonged second stage (or criteria for dystocia or failure to progress), but these are not based on level 1 evidence [47–49]. Clinically, the start of the second stage is imprecise and begins when the subjectively timed cervical exam reveals complete (10 cm) cervical dilation. It is also important to realize that, historically, women often do not begin to push until 1 hour or more of delayed pushing and complete dilation has been ascertained.

The second stage can be further divided into passive and active second stage. According to the Agency for Healthcare Research and Quality (AHRQ), passive second stage is defined as full dilation of the cervix without voluntary or involuntary pushing [14]. Active second stage is defined as when the fetus is visible or once pushing has started with or without contractions [14]. These guidelines suggest that the passive phase in a nulliparous woman can be allowed for up to 2 hours regardless of anesthesia. In a multiparous woman, passive phase is suggested to be allowed for 1 hour without an epidural and 2 hours with an epidural. The active phase of the second stage of labor is suggested in nulliparous women to have a time limit of 1 hour without an epidural and 2 hours with an epidural. In a multiparous woman, active phase is suggested as 1 hour regardless of anesthesia [14]. Epidural anesthesia is shown to increase the length of the second stage by 13.66 minutes regardless of parity in a large meta-analysis [50, 51]. The suggestions regarding length of the active second stage are not supported by level 1 data, and longer second stages are allowed if maternal and fetal conditions permit (see Table 9.2).

TABLE 9.2: Proposed Criteria for Prolonged Second Stage

Maternal Characteristics	Suggested Upper Limit of Length of Second Stage (hour)
Nulliparous, epidural	4
Nulliparous, no epidural	3
Multiparous, epidural	3
Multiparous, no epidural	2

Source: Modified from Ref. [55].

Several non–level 1 studies have compared maternal and perinatal outcomes between women with shorter versus "prolonged" second stage. In a review of all studies up to 2004, a strong **association between prolonged second stage and OVD** was noted [52], although the definition of prolonged second stage was inconsistent across studies. In addition, significant associations with maternal outcomes such as **postpartum hemorrhage, infection, and severe obstetric lacerations** were reported, but again, methods varied widely. Urinary incontinence may also be increased with prolonged second stage [48]. Anal incontinence does not seem to be affected [53]. In general, SVD without morbidity decreases with increasing duration of the second stage [54, 55]. However, these risks may not be entirely related to the duration of the second stage and may also be related to management of the second stage by the health care provider [55]. Additionally, the negative consequences of a prolonged second stage seem to have a low absolute risk difference [55]. **No clear associations between prolonged second stage and adverse neonatal outcomes have been reported** [52, 56]. The length of the second stage is not associated with poor neonatal outcome as long as reassuring fetal testing is present. A recent large retrospective study suggested that neonatal sepsis (odds ratio [OR] 2.08, 95% CI 1.60–2.70), asphyxia (OR 2.39, 95% CI 1.28–4.27), and mortality (OR 5.92, 95% CI 1.43–24.51) were increased in nulliparous women with prolonged second stage of labor [57]. Nevertheless, these data are limited by their retrospective nature.

In a large observational study of 53,285 women, time spent during active pushing was found to be associated with increases in postpartum hemorrhage, third- and fourth-degree lacerations, and composite neonatal adverse outcome. The composite neonatal outcome in nulliparous women with active pushing ≥240 minutes was increased (OR 2.2; 95% CI 1.2–4.2) in comparison to the reference group of <60 minutes and was also increased for parous women with active pushing ≥120 minutes (OR 2.7; 95% CI 1.5–4.8) in comparison to the referent group of <60 minutes [58].

Long-term outcome data are also lacking in the area of pelvic floor dysfunction (PFD). In one survey of women immediately and 3 months postpartum, all women had a large difference in PFD symptoms during pregnancy and 3-month postpartum ($p < 0.001$). A larger recovery of colorectal and anal dysfunction symptoms was associated with a shorter duration of the second stage of labor [59].

The challenge with the evidence presented here is that these maternal detriments of prolonged second stage occur when these women are compared with women without prolonged second stage. It is evident that a planned CD before labor might decrease some of these complications (e.g. bleeding, infection, lacerations, and incontinence). **The clinical issue is different, however. Once a woman is having a prolonged second stage, should she be delivered operatively or should she continue labor?** CD performed after prolonged second stage has been associated with longer surgery time, increased postoperative fevers, maternal intraoperative trauma including higher risk of extensions of the uterine incision, and higher composite maternal morbidity, but similar perinatal outcomes compared with CD performed before prolonged second stage [60].

In a small RCT, extending the second stage of labor beyond 3 hours by at least 1 additional hour in nulliparous women with epidural anesthesia decreased the CD incidence by 55% without incurring any additional increase in neonatal or perinatal morbidity (RR 0.45, 95% CI 0.22–0.93) [61]. Operative intervention is also not warranted based solely on the time elapsed in the second stage. This trial is supported by a large retrospective study comparing outcomes of women in two different periods. Period 1 consisted of a definition of prolonged second stage in nulliparous women after 3 hours with regional anesthesia or 2 hours if no such anesthesia was provided. Period 2 allowed nulliparous and multiparous women to continue the second stage of labor an additional 1 hour. The primary CD rate in period 2 was decreased in nulliparous women (RR 0.67; 95% CI 0.61–0.74) and in multiparous women (RR, 0.75; 95% CI 0.67–0.84). The rate of OVD in nulliparous women was higher in period 2 than in period 1 (19.2% vs. 17.7%, p <0.0001). Rates of third- and fourth-degree lacerations and of shoulder dystocia were also higher in period 2. The rate of arterial cord pH <7.0 and the rate of admission to the neonatal intensive care unit were higher in period 2, but the early neurologic outcome was not different [62].

If there are no signs of infection (maternal or fetal), no maternal exhaustion, and reassuring fetal testing, labor can be allowed to continue beyond current limits (Table 9.2) **as long as some progress has been made**. This is supported by the AHRQ recommendations [63]. Nevertheless, even if contractions are adequate, the chance of vaginal delivery decreases progressively after 3–5 hours of pushing in the second stage [64].

A mandatory second opinion is associated with 22 fewer intrapartum CDs per 1000 deliveries without affecting maternal or perinatal outcomes (see Chap. 13) [65].

In summary, prolongation of the second stage by at least 1 hour (over the 3 hours that define prolonged second stage) in nulliparous women with epidural anesthesia is recommended; a mandatory second opinion is beneficial to reduce the CD rate.

Second-stage duration during a trial of labor after cesarean delivery

Most women with a previous CD who reach the second stage of labor deliver vaginally (90.6%). As in women without a prior CD, as the length of the second stage increases, the chance of a successful vaginal birth decreases. The risk of uterine rupture or dehiscence increases with second-stage length from less than 1 hour (0.7%), 1 to less than 2 hours (1.4%), 2 to less than 3 hours (1.5%), to 3 hours or greater (3.1%). Risk of neonatal outcomes did not differ significantly by second-stage length [66]. **In summary, the risk of uterine rupture increases with the length of the second stage in women with prior CD**.

Possible effects of cesarean delivery in the second stage of labor

In a large retrospective study of second-stage CD, the risk of preterm birth <37 weeks in the subsequent pregnancy was increased (RR 1.57; 95% CI 1.43–1.73) [67]. Length of time spent in the second stage with resultant CD and risk of preterm birth is a controversial risk factor, as there are studies both refuting and supporting this as a potential confounder [68, 69]. **In summary, women with a prior CD during the second stage may have an increased risk in a future pregnancy for preterm birth**.

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10

THIRD STAGE OF LABOR

Alyssa R. Hersh and Jorge E. Tolosa

Part 1: Normal third stage of labor

Key points

- **Oxytocin** has historically been the uterotonic of choice for postpartum hemorrhage prophylaxis, as it reduces blood loss and has fewer side effects compared with other agents such as ergot alkaloids and misoprostol. However, recent data suggest that **oxytocin combined with misoprostol or ergot alkaloids (e.g. methergine), or carbetocin alone, are more effective in reducing blood loss greater than 500 mL than oxytocin alone**. Oxytocin can be given in several ways, for example, as 20 IU (10–40 IU) IV in 500 cc normal saline (NS) or lactated Ringer's (LR) infused over 1 hour following vaginal delivery, either after delivery of the anterior shoulder or immediately after delivery of the neonate and before delivery of the placenta.
- **Tranexamic acid** in addition to oxytocin before skin incision at cesarean section or within 10 minutes of vaginal delivery is effective in reducing blood loss and improving obstetric outcomes, compared to oxytocin alone.
- **Delayed cord clamping in preterm neonates** by 30–60 (maximum 180) seconds is associated with lower risk of death before discharge, necrotizing enterocolitis, and intraventricular hemorrhage (IVH). Delayed cord clamping in term neonates is associated with higher hematocrit and lower risk of iron deficiency at less than a year of age, but with an increased risk of hyperbilirubinemia requiring phototherapy.
- **Milking of the umbilical cord** is associated with severe intraventricular hemorrhage in very preterm infants and associated with inconsistent evidence of benefit and therefore is **not recommended** for infants of any gestational age.
- **Controlled cord traction** reduces the need for manual extraction of the placenta. Uterine massage has not been associated with benefits as studied so far during vaginal delivery.
- Vaginal and perineal **lacerations should be repaired with one continuous absorbable synthetic suture**, including continuous subcuticular skin repair.
- Oral medications such as **nonsteroidal antiinflammatory agents (e.g. ibuprofen) and acetaminophen, and topical anesthetics** can decrease perineal pain and need for additional pain therapy.

Definitions

The third stage of labor is defined as the **interval between delivery of the neonate and expulsion of the placenta**. The mean length of time of the third stage of labor is about 6 minutes. An interval of **greater than 30 minutes** is the 97th percentile, which is considered a **prolonged third stage of labor**.

Pathophysiology

The third stage of labor involves separation of the placenta with capillary hemorrhage and shearing of the placental surface when the uterus contracts after delivery of the infant. Signs of separation include a gush of blood, cord lengthening, and the uterine fundus becoming more globular and firmer.

Complications (see Chap. 28)

- Postpartum hemorrhage—classically defined as an estimated blood loss (EBL) >500 mL after vaginal delivery or >1000 mL after cesarean delivery. Most recently, it has been defined as >1000 mL for both vaginal and cesarean delivery; see Chap. 28.
- Retained placenta—placenta not expelled within 30 minutes of infant delivery.
- Uterine inversion—collapse of uterine fundus into the uterine cavity.

Management

Uterotonics and tranexamic acid

An algorithm including management of the third stage of labor is shown in Figure 10.1.

Oxytocin (Syntocinon®)

Oxytocin binds to specific uterine receptors with immediate action, causing increasing strength and frequency of contractions. The mean **half-life is 3 minutes** with the plateau reached after 30 minutes. It can either be given as intravenous (IV) or intramuscular (IM), though IM injection has a time of onset of 3–7 minutes and the clinical effect is longer, lasting 30–60 minutes. It is metabolized by the liver and kidneys with a known 5% antidiuretic effect of vasopressin. If given in large volumes, greater than 40–50 mL per minute, and high concentration, or when given without dilution, it may result in hyponatremia and syndrome of inappropriate antidiuretic hormone hypersecretion (SIADH) with symptoms of headache, vomiting, drowsiness, and convulsions.

There have been different ways of administering oxytocin for prophylaxis following vaginal delivery, including IM, IV (either undiluted or as a diluted infusion), and intraumbilical. The **IM dose is 5–10 IU**, administered at the delivery of the anterior shoulder or soon after, before delivery of the placenta (Table 10.1). Oxytocin can also be given as an undiluted IV bolus (10 IU in 1 mL over 1 minute) or as a **diluted IV infusion consisting of 10–40 IU diluted in 500–1000 mL of normal saline or lactated Ringer's**. A randomized controlled trial (RCT) compared various

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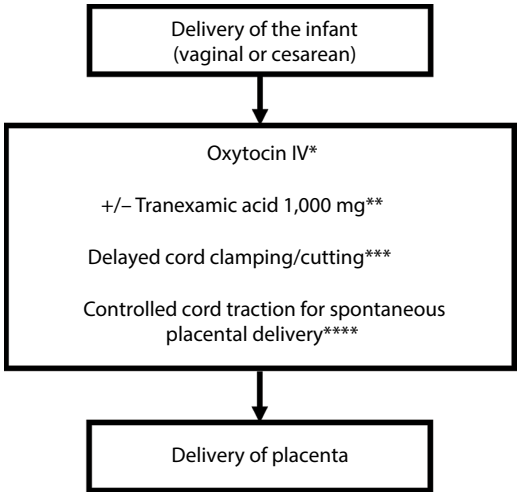


FIGURE 10.1 Suggested algorithm for management of the third stage of labor. *See dosing and timing options in text. **Consider also, in addition to oxytocin, misoprostol, or methergine, in particular in women at high risk for postpartum hemorrhage. *** If no neonatal asphyxia. **** If a skilled birth attendant is present.

oxytocin doses (10 IU, 40 IU, and 80 IU IV in 500 mL) given over 1 hour after placental delivery for primary postpartum hemorrhage (PPH) prophylaxis at vaginal delivery and showed no differences overall in incidence of PPH. However, the dose of 80 IU was associated with a lower risk of needing additional uterotonics and lower risk of ≥6% decline in hematocrit [1].

The comparative effectiveness and safety of administration by the IM or IV route have recently been assessed in multiple RCTs. The IM route is favored in some institutions, particularly in resource-poor settings, as it can be administered rapidly by providers with minimal training [2]. **Two recent RCTs have demonstrated lower rates of PPH with the IV route (10 IU in 1 mL over 1-minute bolus or 10 IU in 500 mL infusion saline) compared with the IM route (10 IU in 1 mL bolus) and no increase in adverse effects** [3, 4]. A smaller trial found no significant difference in PPH but reduced need for additional uterotonics [5]. Therefore, an IV administration of oxytocin (10 IU in 1 mL over 1 minute or 10 U in 500 mL at rate of 12 mL per minute) is safe and effective and is the preferred route for oxytocin administration.

Injection of oxytocin into the umbilical cord is not recommended. Compared to IV/IM oxytocin or to injection of saline alone, the umbilical vein injection of oxytocin does not have a significant effect on postpartum blood loss, need for transfusion, length of the third stage of labor, or need for manual placental removal [6].

Oxytocin is an effective prophylactic uterotonic in the third stage of labor. Compared with no uterotonics, prophylactic oxytocin may reduce blood loss of greater than 500 mL after vaginal delivery and the need for therapeutic uterotonics [7]. There are similar incidences of manual removal of the placenta and rates of blood transfusion with the use of oxytocin compared to no uterotonic.

Oxytocin is routinely administered after delivery of the anterior shoulder or immediately after delivery of the neonate and before delivery of the placenta. Timing of oxytocin administration before or after placental delivery did not show differences in rates of blood loss, length of third stage of labor, and rates of retained placenta [8, 9]. Nonsignificant trends for less PPH but more retained placenta are associated with oxytocin given before compared with after placental separation [8].

TABLE 10.1: Commonly Used Uterotonic Agents

	Route/Dose	Maximum Dose	Side Effects	Contraindications
Oxytocin	10–80 IU IV infusion in 500–1000 mL NS/LR (or 5–10 IM *if IV not available*)	80–100 IU	Hypotension Hyponatremia Fluid overload Flushing Nausea/emesis	None
Misoprostol	200–1000 mcg PO, PR, or PV	Unknown	Pyrexia Shivering Nausea/emesis Diarrhea	None
Ergometrine/methergine	0.2 mg IM *or* 0.2 mg PO Every 15 minutes × 2 doses then every 2–4 hours	1 mg (5 doses)	Nausea/emesis Vasoconstriction Hypertension	Hypertension Cardiac disease[a] Peripheral vascular disease[a]
Prostaglandin F2α/ Hemabate	0.25 mg IM Every 15–90 minutes	2 mg (8 doses)	Bronchoconstriction Hypertension Nausea/emesis Diarrhea	Asthma Active cardiac, pulmonary, renal, or hepatic disease[a]
Carbetocin	100 mcg IV (single dose)	100 mcg	Hypotension Flushing Pruritus Headache Nausea/emesis	None

[a] Relative contraindication.

Abbreviations: LR, lactated Ringer's solution; NS, normal saline; IU, international units; IM, intramuscular; IV, intravenous; PR, per rectum; PV, per vagina.

Oxytocin agonists

Carbetocin is a synthetic analogue of oxytocin; 100 µg IV has been shown to **reduce the need for therapeutic uterotonics compared to oxytocin for those women who underwent cesarean section** [10]. Compared with Syntometrine (oxytocin plus ergometrine), carbetocin is associated with less blood loss and fewer side effects when used prophylactically following vaginal delivery; however, the risk of PPH is not decreased [10, 11]. An international randomized, controlled noninferiority trial, which enrolled over 29,000 women expected to give birth vaginally, found that heat-stable carbetocin was noninferior to oxytocin for the use of additional uterotonics or blood loss of greater than 500 mL; however, noninferiority was not demonstrated with blood loss greater than 1000 mL [12]. There was no difference in adverse events. As carbetocin is similar to oxytocin in outcomes but not widely available, the decision to use it compared to oxytocin should be based on local circumstances.

Ergot alkaloids (Methergine® or ergometrine)

Ergot alkaloids cause sustained tonic contraction of uterine smooth muscle by stimulation of alpha-adrenergic myometrial receptors. The dose is **0.2 mg IM injection or PO** (orally), with a mean elimination half-life of 3.4 hours (range 1.5–12.7 hours). IV administration is not recommended, as it is associated with more severe side effects. Nausea and vomiting are common side effects, although the most concerning side effect is vasoconstriction of the vascular smooth muscle. This results in elevation of central venous pressure and systemic blood pressure, increasing the risk of pulmonary edema, stroke, or myocardial infarction. Contraindications include cardiac disease, autoimmune diseases associated with Raynaud phenomena, peripheral vascular disease, arteriovenous shunts, hypertension, preeclampsia, and eclampsia.

Compared with oxytocin, ergot alkaloids used alone as prophylactic uterotonics have similar benefits, such as reducing blood loss, reducing the need for additional uterotonics, and increasing maternal hemoglobin levels. However, they are associated with **worse side effects**, suggesting other agents such as oxytocin may be preferable as the first-line prophylactic agent [13].

Compared with oxytocin alone, ergot alkaloids in addition to oxytocin are associated with a statistically significant reduction in the risk of PPH when compared to oxytocin alone for blood loss of 500 mL or more. A network meta-analysis found a significant difference in blood loss 1000 mL or more [14]. There were no differences in blood transfusion, retained placenta, or other neonatal outcomes. Unfortunately, the adverse side effects when ergometrine is added to oxytocin are important to consider, including nausea, vomiting, and hypertension [15].

Syntometrine is a combination drug containing oxytocin 5 IU and ergometrine 0.5 mg and is administered intramuscularly. As with ergot alkaloids alone, side effects are significant, including nausea, vomiting, and hypertension [7, 15].

Prostaglandins

Misoprostol is a synthetic analog of prostaglandin E1 and is metabolized in the liver. The tablet can be given by the **oral or sublingual route at 400–600 µg, or by the vaginal or rectal route at 400–1000 µg**. It does not require sterile needles and syringes for administration. It is inexpensive, heat and light stable, and has a long shelf-life, making it more accessible and beneficial in low-resource settings. Side effects include shivering, elevated body temperature >38°C, and gastrointestinal (GI) upset with nausea, vomiting, and diarrhea. Studies suggest that these side effects are dose dependent, particularly with doses exceeding 600 µg [16].

Compared with placebo, prophylactic oral or sublingual misoprostol reduces the risk of severe PPH and need for blood transfusion [17]. When compared to conventional injectable uterotonics (oxytocin, Syntometrine, or ergometrine), the risk of PPH is no better [17–19]. Recent RCTs have found conflicting evidence for the benefit of misoprostol over oxytocin at vaginal delivery [20, 21]. For cesarean delivery, misoprostol combined with oxytocin may be more effective than oxytocin alone in reducing intraoperative and postoperative hemorrhage [22]. Furthermore, a recent network meta-analysis found that oxytocin with misoprostol was more effective in reducing blood loss greater than 500 mL [14]. However, due to the conflicting evidence of its benefit, misoprostol may be a more appropriate first-line agent in the setting of no IV access, patients with contraindications to other uterotonics, **or in resource-poor settings** (see Chap. 28).

Prostaglandin F2α (Hemabate/carboprost) causes contraction of uterine smooth muscle cells. Administration is either 0.25 mg IM or as a direct injection into the myometrium, which may be repeated every 15–20 minutes for a maximum of eight doses or 2 mg. Side effects are secondary to smooth muscle constriction and include bronchoconstriction, venoconstriction, and constriction of GI smooth muscle. Common side effects are nausea, vomiting, diarrhea, pyrexia, bronchospasm, and case reports of hypotension and intrapulmonary shunting with arterial oxygen desaturation. It is contraindicated in patients with cardiac and pulmonary disease. There is **no high-quality evidence to support the use of carboprost for PPH prophylaxis**.

Tranexamic acid

Tranexamic acid (TXA) is a synthetic derivative of the amino acid lysine that is metabolized in the kidney and functions as an antifibrinolytic that has been studied for use as treatment for PPH, as well as for prophylaxis. Side effects include nausea, vomiting, and dizziness [23]. A large multicountry RCT called "The Woman Trial" tested the use of 1 g of TXA initially (100 mg/mL at a rate of 1 mL/minute), followed by 1 g if bleeding continued, in women diagnosed with PPH compared to placebo; TXA reduced the rate of maternal death due to bleeding in women with PPH (see Chap. 14) [24].

When used for prophylaxis for women undergoing cesarean delivery, TXA given **in combination with routine traditional prophylactic uterotonics** (e.g. oxytocin) appears to decrease the risk of postpartum blood loss and need for blood transfusion in women at low risk for PPH, with data from clinical trials of mixed quality and meta-analysis from such data [23, 25]. For prophylaxis, it is administered intravenously at a dose of 10 mg/kg (usually a maximum of 1 g), 10–20 minutes before skin incision, with rapid onset of action and a mean elimination half-life of 2–10 hours. We **recommend TXA be considered for routine prophylactic use at cesarean section in addition to prophylactic oxytocin**.

For women planning to have a vaginal delivery, there is variability among published studies. For prophylaxis, it is administered intravenously at a dose of 1 g (in 10 mL over 2–3 minutes) within 10 minutes of vaginal delivery. In a recent large multicenter RCT, prophylactic TXA in addition to prophylactic oxytocin did not result in a significantly lower rate of PPH >500 mL, although women required fewer additional uterotonic agents [26]. A review combining this RCT with previously published studies found that prophylactic TXA reduced PPH >500 mL in combination with

prophylactic oxytocin, cord traction, and uterine massage [27]. Therefore, **we recommend TXA be considered for routine prophylactic use at vaginal delivery in addition to prophylactic oxytocin**.

Summary

Recent evidence suggests that numerous regimens of uterotonic agents, including oxytocin with ergot alkaloids, carbetocin alone, or oxytocin with misoprostol, are more effective at reducing blood loss at delivery than oxytocin alone. Furthermore, there is high-quality evidence that oxytocin with TXA is more effective in reducing PPH and improves outcomes compared with oxytocin alone. If just one agent is to be used for routine prophylaxis during the third stage of labor, oxytocin is recommended. Based on safety and side effect profiles, **TXA with oxytocin** is the recommended regimen to be considered to be used routinely during the third stage of labor whenever possible.

Umbilical cord

Cord gases

Cord gases are stable in a clamped segment of cord for up to 60 minutes and in a heparinized syringe for up to 60 minutes. Umbilical artery pH, pCO_2, and base deficit may be helpful in indicating timing of insult and can be collected in cases of nonreassuring fetal heart rate tracings (NRFHTs), meconium, low Apgar scores (defined as below 7 at 5 minutes), growth restriction, preterm birth, or any sentinel event, including cord prolapse, uterine rupture, or placental abruption. Umbilical vein pH may be helpful in cases of uteroplacental problems like growth restriction, placental abruption, asthma, and hypertension. A recent large prospective trial found that umbilical cord arterial lactate may be more useful than arterial pH in predicting neonatal morbidity at term [28]. While there are **no RCTs on the routine sending of umbilical cord gases**, this practice is usually not necessary or recommended for normal labor, delivery, and Apgar scores, without risk factors. A recent systematic review found that delayed cord clamping (<120 seconds) has little to no clinically significant effect on blood acid–base status among healthy, term singletons [29], but this has not been thoroughly assessed in preterm infants.

Cord blood collection

Cord blood is routinely sent for Rh status of the infant, especially in Rh-negative women. Cord blood collection for stem cells has increased in popularity in recent years. Obstetricians should support public banking of cord blood [30]. **Public banking is recommended over private banks** secondary to more stringent Food and Drug Administration (FDA) guidelines, given its increased legal responsibilities, cost-effectiveness, and greater access to cord blood by the general population. The chance of a child requiring an autologous transplant from privately banked cord blood is about 1/2700. Directed donation of cord blood when there is a disease in the family amenable to stem cell transplantation can be arranged through many public banks.

For adequate cord blood collection, at least 40 mL must be collected. A recent cohort study found that delayed umbilical cord clamping up to 60 seconds did not have a negative impact on adequate collection of total nucleated cell count [31]. It is recommended to counsel women that cord blood collection should not compromise maternal and neonatal care and therefore may not be possible in cases where maternal or neonatal health status is a concern.

Timing of cord clamping

In preterm neonates less than 37 weeks' gestation, **delayed cord clamping (DCC) by about 30–60 seconds** (180 seconds maximum) **is associated with a lower risk of death before discharge, necrotizing enterocolitis, and intraventricular hemorrhage (IVH)** than early cord clamping (ECC) [32, 33]. This intervention also benefits very preterm neonates less than 32 weeks' gestation, with decreased mortality, risk of blood transfusion, and IVH [34]. In addition, DCC has been shown to be safe and does not compromise the preterm infant; there may be small increases in polycythemia and hyperbilirubinemia, but without increased need for exchange transfusion [35, 36]. There are no clear differences in other outcomes, including respiratory distress, death, initial adaptation phase, or long-term outcomes. There is **no current recommendation on positioning of the preterm infant during DCC secondary to insufficient data**. One RCT showed no differences in neonatal outcomes during DCC by 120 seconds after vaginal delivery with the neonate held either at the level of the vagina or the level of the abdomen or chest, concluding that mothers can safely be allowed to hold their baby on their abdomen or chest for skin-to-skin and breastfeeding [37].

In **term neonates**, DCC has also been shown to have some benefits, but also some risks. Compared with early clamping, DCC is associated with higher birth weight, higher hematocrit, and a lower risk of iron deficiency at less than a year of age [38]. However, there was an increased risk of the neonate needing phototherapy for hyperbilirubinemia. The possible **increased risk of neonatal jaundice requiring phototherapy must be weighed against the physiologic benefit of greater hemoglobin and iron levels** conferred by DCC in term infants, which may be of clinical value particularly in infants where access to good nutrition is poor [38]. For women, there are likely no differences in PPH or change in hemoglobin levels, but the data are limited [38, 39]. Therefore, DCC is recommended instead of ECC (Figure 10.1).

Cord milking

Milking of the cord refers to the action of an obstetric provider during which the cord blood is manually pushed toward the infant following delivery and prior to cutting and clamping the cord. Numerous studies have assessed the safety and outcomes associated with cord milking, which have found varying evidence but together demonstrated potential benefit [32]. However, a recent large RCT was terminated prematurely for safety concerns; there was an increase in severe IVH among very preterm infants (23–27 weeks of gestation), likely related to the sudden hemodynamic changes in a fragile circulatory system [40]. Therefore, **there is evidence of harm with inconsistent evidence of benefit, and this practice is no longer recommended**.

Placenta

Controlled cord traction

Controlled cord traction (CCT) refers to the act of pulling the umbilical cord while applying counter-pressure with the goal of delivering the placenta [41]. **Cord traction alone** has been associated with **lower mean blood loss and decreased risk of PPH, shorter third stage of labor, and lower risk of needing manual placental removal** compared to no cord traction after delayed cord clamping (1–3 minutes) and vaginal delivery [41]. However, this is a skill that requires training, as there can be complications such as uterine inversion if applied incorrectly. If a skilled birth attendant is present, it is recommended to use CCT for these benefits (Figure 10.1).

After cesarean delivery, cord traction is preferred over manual removal of the placenta, as cord traction is associated with less endometritis, less blood loss, less drop in postoperative hematocrit, and shorter hospital stay [42]. CCT has not been assessed specifically in the setting of DCC after cesarean delivery. Therefore, in settings where DCC is the standard of care, the decision to use CCT can be shared between the patient and provider.

Cord drainage

In the third stage of labor, **umbilical cord drainage** refers to the unclamping of the previously clamped cord with drainage of the blood into an appropriate container [43]. **Immediate cord drainage and traction** together are associated with a slightly **shorter duration of the third stage of labor and a slightly smaller decrease in hemoglobin** compared to no drainage or traction after vaginal delivery and ECC [43, 44]. Cord drainage without traction but with administration of 5 IU oxytocin is associated with lower mean blood loss, shorter duration of the third stage, higher postdelivery hemoglobin, and less need for a blood transfusion [45]. In settings where DCC is the standard of care, the decision to use cord drainage can be shared between the patient and provider.

Massage of the uterus

There is limited evidence to evaluate the effect of massage of the uterus alone. Three studies have been conducted comparing uterine massage to no uterine massage in addition to oxytocin and CCT; uterine massage is not associated with a reduction in PPH, use of additional uterotonics, or retained placenta [46]. Therefore, **uterine massage after delivery of the placenta cannot be recommended as studied so far** [46, 47].

Placentophagy

Placentophagy or placentophagia is the consumption of the placenta postpartum. There is no evidence for maternal benefit, but there is evidence for risk of harm, such as increased risk of infection [48]. Therefore, providers should counsel patients against placentophagy based on currently available data.

Active management of the third stage of labor

Active management of the third stage of labor (AMTSL) usually consists of:

- Prophylactic oxytocin at delivery of the anterior shoulder or immediately after delivery of the baby
- ECC and cutting
- CCT

Expectant management usually consists of:

- No uterotonics
- No ECC, cutting, or traction
- Use of gravity and maternal expulsive efforts for placenta delivery

There is heterogeneity in the literature regarding the definition of AMTSL. Presented earlier is the one utilized for evaluation of the existing RCTs of AMTSL by the Cochrane collaboration [49]. Some definitions also consider uterine massage to be a component of AMTSL. AMTSL has been used mostly among women after term, vaginal births, so recommendations are limited to this population. Historically, AMTSL was thought to reduce the risk of PPH and was therefore recommended to all women, including women following preterm birth. Compared with expectant management, active management may reduce severe blood loss and anemia [49]. However, numerous adverse effects were identified, including increases in vomiting after birth, increased maternal diastolic blood pressure, increased use of analgesia and pain, more women returning to the hospital with bleeding, and decrease in infant birth weight, possibly reflecting some degree of lower blood volume from placental transfusion if ECC is performed. There is probably no difference in risk of infant admission to the neonatal unit or incidence of jaundice requiring treatment. While AMTSL is composed of multiple interventions, **each element of AMTSL should be assessed separately**, as we have done in the preceding sections (“Umbilical Cord” and “Placenta”).

Obstetric lacerations

Closure and repair

Classifications of laceration types are displayed in Table 10.2. Compared with nonclosure, closure of first- and second-degree perineal lacerations after vaginal delivery has not been shown to be associated with improved wound healing or pain. There is insufficient evidence to recommend surgical closure compared to nonclosure for first- and second-degree lacerations [50]. The **continuous suturing** techniques, compared with the interrupted, are associated with less short-term pain in second-degree and episiotomy repairs [51]. Furthermore, approximation (end-to-end) and overlap technique for third- and fourth-degree laceration repair are associated with similar outcomes in two RCTs [52, 53], while in the most recent RCT, **end-to-end repair** was associated with significantly lower rates of anal incontinence, with no difference in long-term outcomes [54]. One small, randomized trial showed that use of **antibiotics** at the time of third- and fourth-degree repairs decreased perineal wound complications (wound disruption and purulent discharge) [55]. See also Chap. 31.

Suture

Absorbable synthetic materials should be used for all layers of the repair. Compared with catgut (plain or chromic), **absorbable synthetic sutures (e.g. Vicryl)** used for perineal repair decreased women’s experience of short-term (3-day) pain, less need for analgesia, reduced rate of suture dehiscence up to day 10, and less need for repeat suturing at <3 months. There is no significant difference in long-term pain or dyspareunia experienced by women [56]. More women with catgut sutures required repeat suturing compared with synthetic sutures, while more women in the standard synthetic suture group required suture removal compared with the rapidly absorbed group. Clinical experience has shown **suture removal is necessary <5% of the time when using 3-0 or finer sutures and performing subcuticular skin closures** [56]. Polyglactin (Vicryl) and polydioxanone (PDS) have similar outcomes [57].

TABLE 10.2: Perineal Laceration Classification

	Definition
First degree	Injury limited to the skin of the perineum
Second degree	Injury to the perineum; perineal muscles involved
Third degree	3(a) <50% tear of external anal sphincter 3(b) >50% tear of external anal sphincter 3(c) Tear in both external and internal sphincter
Fourth degree	Injury to perineum, internal and external sphincter, and anal epithelium

Source: Modified from ACOG Practice Bulletin No. 198: Prevention and management of obstetric lacerations at vaginal delivery.

Anal ultrasound

Endoanal ultrasonography with clinical examination of the perineum immediately after delivery in nulliparous women with second-degree lacerations detected more sphincter tears than clinical examination alone. **Endoanal ultrasonography with immediate repair of these tears is associated with less severe fecal incontinence at 1 year compared with clinical examination only** [58, 59].

Perineal pain control

Oral medications

One dose of **oral nonsteroidal antiinflammatory agents (NSAIDS)** (any dose) is effective in achieving adequate pain relief and reducing the need for additional analgesics compared to placebo in the postpartum period without serious adverse effects [60]. Rectally administered NSAIDs appear to provide effective pain relief in postpartum women. Rectal indomethacin or diclofenac are associated with less pain up to 24 hours after birth and less requirement for additional analgesia in the first 24 hours and 48 hours postpartum [61]. Limited information is available on pain experienced >72 hours after birth or other outcomes of importance, such as the impact on daily activities, resumption of sexual intercourse, and impact on the mother–baby relationship. More studies are needed to assess the acceptability of the rectal route of administration and its direct comparison to oral NSAIDs. A single dose of aspirin (300–1200 mg) may reduce pain after an episiotomy, but the evidence is low quality, and studies did not assess for adverse effects [62].

Topical anesthetics

Compared with placebo, topical anesthetics applied to the perineum are associated with similar pain relief up to 24 hours to 72 hours postpartum, but women are more satisfied after administration of an anesthetic [63]. **Epifoam** (1% hydrocortisone acetate and 1% pramoxine hydrochloride in the mucoadhesive foam base) use is associated with less additional analgesia, while lignocaine/lidocaine showed no difference with regard to additional analgesia use compared with placebo [63]. A **lidocaine/prilocaine cream** appears to be as effective as local mepivacaine injection for pain relief during repair, with improved patient satisfaction [64]. Compared with indomethacin vaginal suppositories, **topical anesthetics** have similar mean pain scores.

Therapeutic ultrasound for perineal pain

There is insufficient evidence to evaluate the use of ultrasound in treating perineal pain and/or dyspareunia following vaginal delivery. Women treated with active ultrasound for acute perineal pain are more likely to report improvement in pain and less pain at 10 days and 3 months, but more likely to have bruising at 10 days compared with placebo [65]. Additionally, women with persistent perineal pain or dyspareunia treated with ultrasound are less likely to report pain with sexual intercourse.

Local cooling

Local cooling techniques, including ice packs, cold gel packs, or ice/cool water baths, may be associated with reduced perineal pain following childbirth [66]. However, the data regarding safety and effectiveness are limited.

Anesthesia in labor/Postpartum

An epidural is commonly used during labor for pain control. Spinal, epidural, paracervical block, nitrous oxide, or general anesthesia may be used if complications arise in the management of retained placenta, intractable PPH, uterine inversion, or assisted vaginal deliveries (see Chap. 12).

Breastfeeding

Hypertension and headache are associated with misoprostol and ergotamine use. There are no other known complications with breastfeeding after use of other uterotonics. There are limited data regarding breastfeeding outcomes with TXA, but one small study found no increase in adverse long-term outcomes [67].

Delivery note

If a complicated delivery occurs with possible fetal compromise, a detailed note should address the pertinent and immediate neonatal status, including Apgar scores, umbilical cord pH, and base deficit (if obtained), and assessment of fetal heart testing prior to delivery.

Part 2: Care of the pregnant woman who declines blood products

Key points

- A common reason for declining blood products during pregnancy and childbirth is the identification as a member of the Jehovah's Witness faith.
- Members of the Jehovah's Witness faith may decline blood transfusions due to their belief that accepting them violates God's law and would lead to excommunication and eternal damnation.
- Refusal of blood can lead to an increased risk of maternal death.
- All obstetric providers are responsible for asking *each* woman at the preconception visit or first prenatal visit if she has any objection to receiving any blood product.
- The woman's wishes should be respected, following the principle of autonomy, and documented well so that every provider understands each patient's specific beliefs and goals.
- After counseling, it is recommended that the patient sign the consent for refusal of blood products, as well as the health care power of attorney.
- It is recommended that the third stage of labor be managed in accordance with the general recommendations stated earlier in this chapter, as there are no studies specifically assessing these interventions among patients who decline blood products.

Historic context of objection to blood products by Jehovah's Witnesses

"That is why I have said to the sons of Israel: 'No soul of you must eat blood and no alien resident who is residing as an alien in your midst should eat blood'" (Holy Bible: Leviticus 17:12). Charles Russell started the Jehovah's Witness Christian sect in Pennsylvania in 1872. Nearly all members of the Jehovah's Witness faith decline blood transfusions due to their belief that accepting blood products violates God's law, which would lead to excommunication and eternal damnation, as is taken literally from the statement reported in the Bible.

Complications

One study reported the risk of obstetric hemorrhage as approximately 6% in women who are members of the Jehovah's Witness faith [68]. The risk of maternal death was estimated to be about 0.5%, a forty-fourfold increase compared with non–Jehovah's Witness controls [68].

Management

There are **no trials to assess the efficacy of interventions specifically in women who are Jehovah's Witnesses**. Therefore, obstetrics providers should refer to the guidelines for third stage and abnormal third stage for general recommendations.

Preconception counseling

Counsel regarding complications and management in pregnancy.

Prenatal care

All obstetric providers are responsible for asking *each* woman at the preconception visit or first prenatal care visit if she has any objection to receiving any blood product in case of necessity. Providers should not assume that all patients who identify as a Jehovah's Witness fully endorse refusal of blood products; therefore, each patient's individual beliefs and goals should be ascertained [69]. The woman who states she would decline blood transfusion even if medically necessary should be managed as follows:

- Counsel the woman and any family member present regarding the reasons and the risks of blood product refusal, including the possibility of maternal and fetal death. **The counseling should be documented in the medical record**. The patient might want to consult with members of her family and/or community before **signing informed refusal**. Her wishes should be respected, following the principle of autonomy. A physician has the right of refusing to provide care for a patient who refuses blood products only if an alternative caregiver agrees to accept and care for the patient [70].
- Documentation of each conversation in the medical record will help each provider on the care team understand each individual patient's specific beliefs and goals [69].
- After counseling, it is recommended that the patient sign the **consent for blood products** (Figure 10.2), as well as the **health care power of attorney** [70]. These two consents should be kept in the medical record and be available at labor and delivery. Approximately 39% of Jehovah's Witness pregnant women accept a variety of donated blood products, and 55% accept either intraoperative normovolemic hemodilution or transfusion of their own blood obtained by a cell saver [71].
- Consider including a copy of this guideline in the medical record for reference.
- Selected high-risk patients, for example, those with hemoglobin <9 mg/dL, may be considered for appropriate replacement of iron, folic acid, and erythropoietin, which can be coordinated by a maternal-fetal medicine and/or a hematologist.
- Women thought to be at high risk for PPH can be referred to an interventional radiologist for prophylactic placement of a percutaneous balloon catheter [72].

I hereby consent to the blood products marked below:
- ___Whole Blood
- ___Fresh Frozen Plasma
- ___Cryoprecipitate
- ___Albumin
- ___Erythropoietin
- ___Immune globulins (blood fraction, Rh immunoglobulin)
- ___Clotting factors
- ___PolyHeme (human hemoglobin), Hemopure products (bovine
- ___hemoglobin).
- ___Recombinant Factors
- ___Platelet cell fractions (Platelet Gel)
- ___Other surgical procedures, medical tests, or current therapy
- ___Using my own blood, i.e. tagged red cells, white cells, blood patching
- ___Hemodialysis equipment (nonblood primed)
- ___Intraoperative blood salvage ("cell saver")
- ___Intraoperative hemodilution
- ___None of the above

Patient's name _____
Patient's Signature _____
Date _____

FIGURE 10.2 Blood product consent for Jehovah's Witness patients.

- A consult with the maternal-fetal medicine service can be considered and, if available, with a bloodless surgery and medicine program.
- An ethics consult is not indicated but can be considered in specific cases.

Antepartum testing

No specific antepartum testing is indicated.

Delivery

- Consents: Upon admission and prior to the surgery or delivery, it is recommended that obstetric providers confirm all patients who refuse blood products have signed a consent form, as shown in Figure 10.2, and the previously mentioned health care power of attorney. If consents have not been previously signed or are not available, the patient should be counseled again and consents signed.
- As there are no specific studies among women who refuse blood products, providers should refer to the guidance for managing the third stage of labor presented earlier in this chapter.
- If an operative delivery or bleeding disorder is anticipated, if the patient has a history of a low-lying placenta or a placenta previa, or if an operative delivery is to occur, a **cell saver** can be on standby throughout the patient's labor and delivery. Use of the cell saver is safe in obstetrics [73].

Anesthesia

An anesthesiology consult should be obtained. The anesthesiologist will review the patient's medical record and consents, including consent or refusal for blood products.

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11

INTRAPARTUM FETAL MONITORING

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Key points

- Compared to intermittent auscultation (IA), the **use of continuous electronic fetal heart rate monitoring (EFM) decreases the likelihood of neonatal seizures and perinatal mortality and significantly increases the rate of operative interventions** (vacuum, forceps, and cesarean delivery [CD]).
- Category II EFM is indeterminate for the prediction of acidemia. However, certain high-risk category II features such as **prolonged decelerations, recurrent late decelerations, and recurrent variable decelerations**, may be associated with neonatal acidemia.
- Limited evidence (one randomized controlled trial [RCT]) demonstrates an increase in fetal oxygen saturation with maternal repositioning, intravenous fluid administration, or maternal oxygen supplementation among patients with reassuring EFM. However, none of these interventions have been shown to reduce the risk of acidemia, and **multiple RCTs have shown no benefit to fetal acid–base status with maternal oxygen administration**. Therefore, **maternal oxygen administration for fetal benefit in labor cannot be recommended**.
- **Continuous EFM should be used to monitor** the labor of **women at risk** for poor peripartum outcomes.
- Reinterpretation of EFM, especially knowing the neonatal outcome, should be avoided.
- There is **insufficient evidence** to recommend universal **computerized EFM analysis**.
- For singletons at 36 weeks or more, **fetal electrocardiogram (ECG) ST segment analysis (STAN)** used as an adjunct to conventional intrapartum electronic fetal heart rate monitoring **does not improve perinatal outcomes**.
- **Fetal pulse oximetry (FPO) is not associated with significant maternal or neonatal benefits** compared to continuous EFM alone.

Background

Electronic fetal heart rate monitoring (EFM) during labor is the most common obstetric procedure in the United States [1]. Between 1997 and 2003 in the United States, monitoring was utilized in 84% (23,273,458) of the over 27 million births [1]. For admission tests at the beginning of labor, see Chap. 8. For meconium, see Chap. 25.

EFM definitions

Intrapartum fetal monitoring usually refers to monitoring of the fetal heart rate (FHR). Outside the United States, this monitoring is often referred to as **cardiotocography (CTG)**, while the terms **intrapartum electronic fetal heart rate monitoring or EFM** are more commonly used in the United States. Adapted from the 2008 National Institute of Child Health and Human Development (NICHD) Workshop [2], the definitions of EFM patterns and features are described in Table 11.1 and depicted in Figures 11.1–11.3. The definitions were developed for the specific purpose of intrapartum monitoring. No distinction is made between short- and long-term variability [2]. Accelerations, decelerations, bradycardia, and tachycardia can be quantified by describing the nadir and the duration in minutes and seconds of the FHR change. A **recurrent deceleration** occurs with >50% of uterine contractions in any 20-minute period.

A **three-tier system for categorization of EFM patterns** has been recommended [2]. According to this classification, **category I** tracings are predictive of normal fetal acid–base status at the time of observation and may be followed in a routine manner. **Category II** tracings are indeterminate and not predictive of abnormal fetal acid–base status but require evaluation and continued surveillance and reevaluation. **Category III** tracings are abnormal and predictive of abnormal fetal acid–base status (Table 11.2, Figures 11.4–11.6). These tracings require prompt evaluation and should include efforts to expeditiously resolve the abnormal pattern. It is noteworthy that a full description of an FHR tracing requires a qualitative and quantitative description of the following: (1) uterine contractions, (2) baseline FHR, (3) baseline FHR variability, (4) presence of accelerations, (5) intermittent or recurrent decelerations, and (6) changes or trends of FHR patterns over time [2]. Of the categories and features defined by the NICHD, the presence of **recurrent late decelerations, recurrent variable decelerations, more than one prolonged deceleration, or tachycardia** in the 30 minutes before delivery are associated with acidemia [3].

In relation to uterine activity, **tachysystole** is defined as >5 contractions in 10 minutes averaged over 30 minutes, whether the contractions are spontaneous or stimulated. The terms hyperstimulation and hypercontractility should be abandoned. Terms such as "asphyxia," "hypoxia," and "fetal distress" should not be used in the interpretation of EFM.

pH definitions

Acidemia: Increased concentration of hydrogen ions in blood

Acidosis: A pathologic condition marked by increased concentration of hydrogen ions in tissue

Hypoxemia: Decreased oxygen content in blood

Hypoxia: A pathologic condition marked by decreased level of oxygen in tissue

Asphyxia: Acidemia, hypoxia, and metabolic acidosis; must have all of the following: (1) umbilical arterial pH <7.00; (2) Apgar ≤3 at >5 minutes; and (3) neonatal neurologic sequelae (e.g. seizures, coma, and hypotonia) [4]. This term should be used with caution and never before birth (see also Chap. 32).

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TABLE 11.1: Definitions of Fetal Heart Rate Patterns

	Definitions
Baseline FHR	The mean FHR rounded to increments of 5 bpm during a 10-minute period (excluding accelerations, decelerations, and periods of marked variability) The baseline must be for a minimum of 2 minutes. May need to compare the previous 10-minute segment to determine the baseline Bradycardia—baseline FHR <110 bpm Tachycardia—baseline FHR >160 bpm Sinusoidal pattern—visually apparent, smooth, sine wave–like undulating FHR baseline pattern with cycle frequency 3–5/minutes, persisting ≥20 minutes
Baseline FHR variability	Fluctuations in the baseline FHR that are irregular in amplitude and frequency (excluding accelerations and decelerations) Variability is quantitated as the amplitude of peak-to-trough in bpm Absent—amplitude range undetectable Minimal—amplitude range ≤5 bpm Moderate (normal)—amplitude range 6–25 bpm Marked—amplitude range >25 bpm
Acceleration	An abrupt (peak within 30 seconds) increase in the FHR from baseline Acme is ≥15 bpm above baseline, lasting for 15 seconds or more and <2 minutes from the onset to return to baseline Before 32 weeks, acceleration is acme ≥10 bpm over the baseline and lasting at least 10 seconds but <2 minutes Prolonged acceleration if it lasts >2 minutes but <10 minutes If the acceleration is >10 minutes, then it is a baseline change
Deceleration	An abrupt or gradual decrease in FHR as characterized: Recurrent—occur with ≥50% contractions in 20 minutes Intermittent—occur with <50% contractions in 20 minutes Prolonged—visually apparent decrease in FHR ≥15 bpm, lasting ≥2 minutes but <10 minutes
Early deceleration (Figure 11.1)	In association with a uterine contraction, a visually apparent, usually symmetrical, and gradual (onset to nadir ≥30 seconds) decrease in FHR with return to baseline Onset, nadir, and recovery of deceleration occur at same time as beginning, peak, and ending of contraction, respectively
Late deceleration (Figure 11.2)	In association with a uterine contraction, a visually apparent, gradual (onset to nadir ≥30 seconds) decrease in FHR Onset, nadir, and recovery of deceleration occur after the beginning, peak, and end of the contraction, respectively
Variable deceleration (Figure 11.3)	An abrupt (onset to nadir <30 seconds) decrease in FHR The decrease in FHR is at least 15 bpm, lasting ≥15 seconds but <2 minutes Onset, depth, and duration vary with contractions

Source: Adapted from Ref. [2].
Abbreviations: bpm, beats per minute; FHR, fetal heart rate.

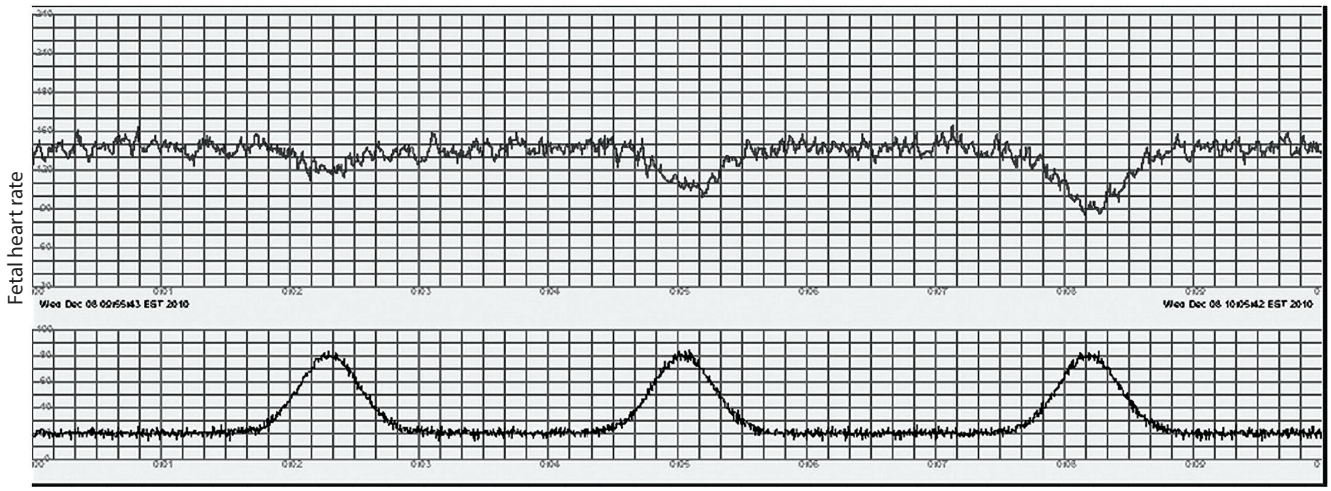


FIGURE 11.1 Early decelerations of 15, 30, and 45 bpm, respectively. *Abbreviation*: bpm, beats per minute.

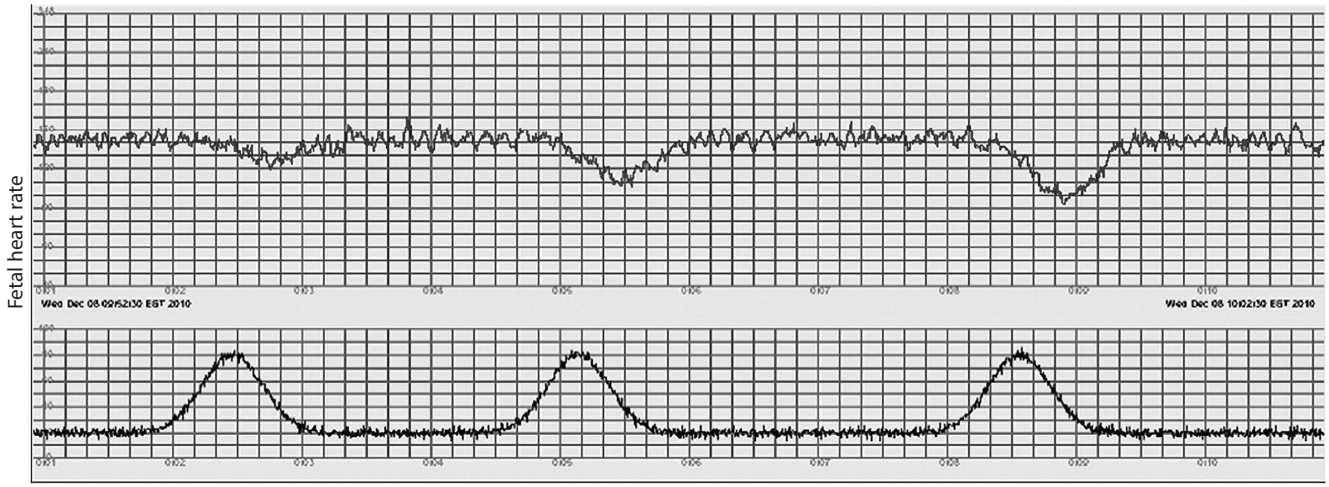


FIGURE 11.2 Late decelerations of 15, 30, and 45 bpm, respectively. *Abbreviation*: bpm, beats per minute.

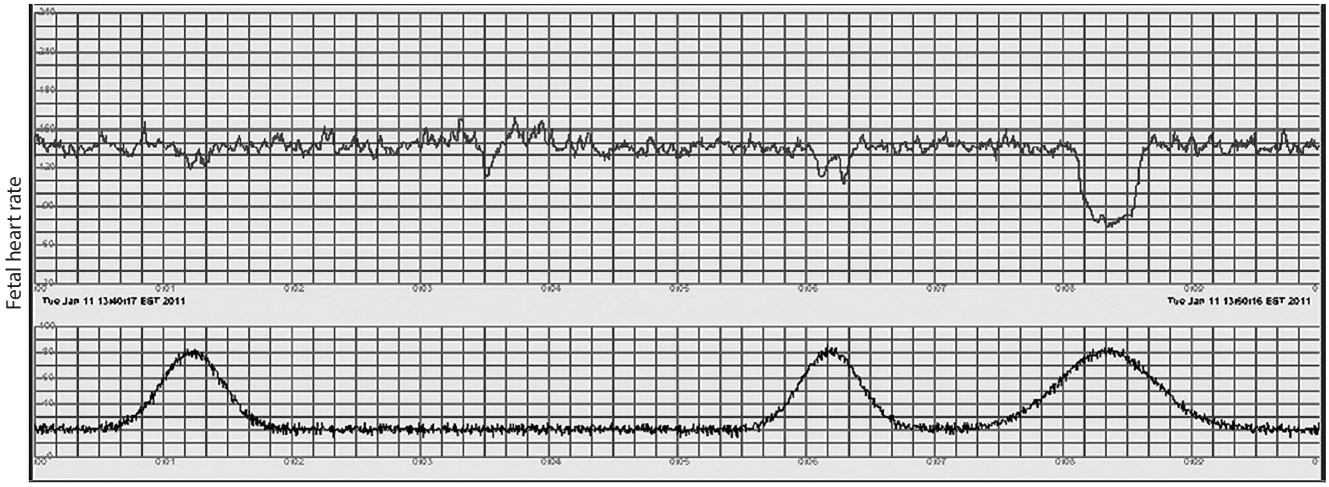


FIGURE 11.3 Variable decelerations of 15, 40, 30, and 60 bpm, respectively. *Abbreviation:* bpm, beats per minute.

TABLE 11.2: Three-Tier FHR Interpretation System

	Baseline	Variability	Acceleration	Deceleration
Category I (Figure 11.4a–c)	110–160 bpm	Moderate	Possible, not necessary	Possible early; no variable or late
Category II (includes those not in category I or III; Figure 11.5a–i)	1. Bradycardia without absent variability 2. Tachycardia	1. Minimal 2. Absent without recurrent decelerations 3. Marked	After fetal stimulation	1. Recurrent variable with minimal to moderate variability 2. Prolonged 3. Recurrent late with moderate variability 4. Variable with other characteristics (i.e. slow return to baseline, overshoots, or shoulders)
Category III (Figure 11.6a–c)	1. Bradycardia 2. Sinusoidal	Absent		1. Recurrent late 2. Recurrent variable

Source: Adapted from Ref. [2].
Abbreviations: FHR, fetal heart rate; bpm, beats per minute.

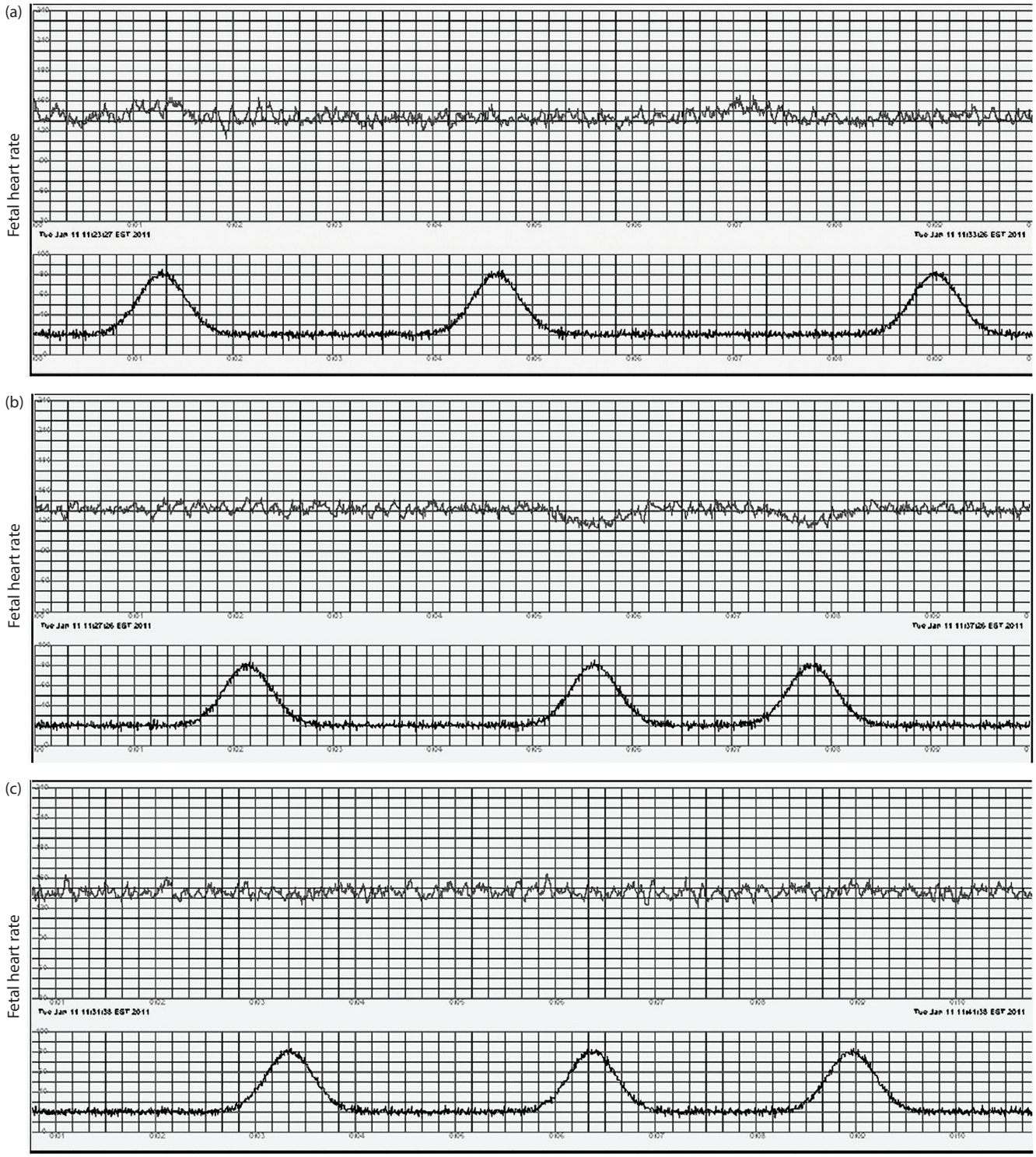


FIGURE 11.4 Category I. (a) Normal baseline, moderate variability, absence of late and variable decelerations, accelerations present. (b) Normal baseline, moderate variability, absence of late and variable decelerations, early decelerations present. (c) Normal baseline, moderate variability, absence of late and variable decelerations.

Incidence

The prevalence of cesarean delivery (CD) for nonreassuring FHR tracing (NRFHT) is approximately 3% or more, and it is increasing [5]. NRFHT is the second most common reason for CD, after arrest of labor, accounting for 23% of all primary CDs [6, 7].

Risk factors and predictors of abnormal FHR

The risk of CD for NRFHT is >20% in patients with **moderate/severe asthma, severe hypothyroidism, severe preeclampsia, postterm pregnancy, or fetal growth restriction (FGR) with abnormal Doppler studies** [5].

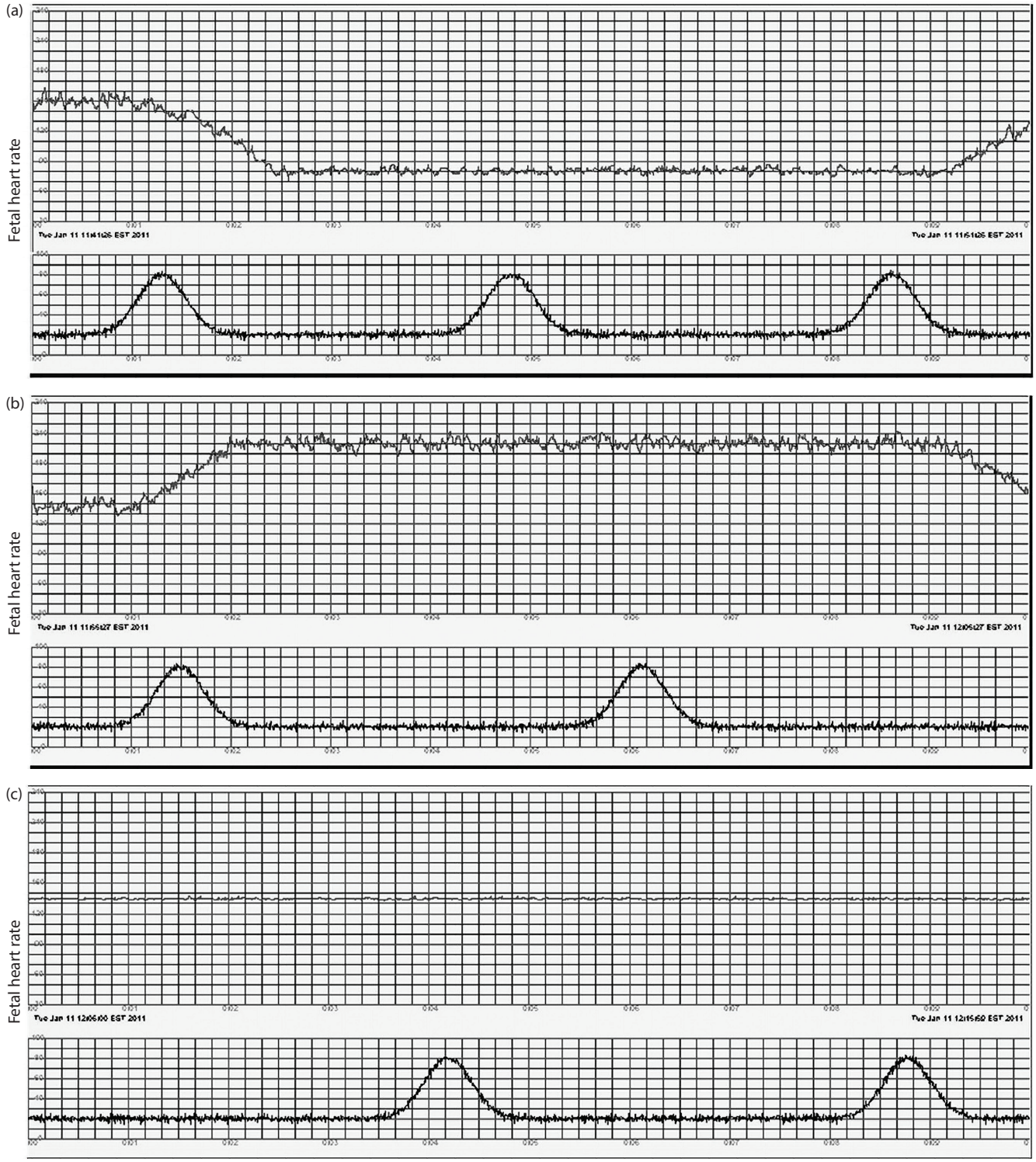


FIGURE 11.5 Category II. (a) Bradycardia with moderate variability. (b) Tachycardia. (c) Minimal variability.



FIGURE 11.5 (Continued) Category II. (d) Absent variability. (e) Marked variability. (f) Recurrent variable decelerations, minimal variability.

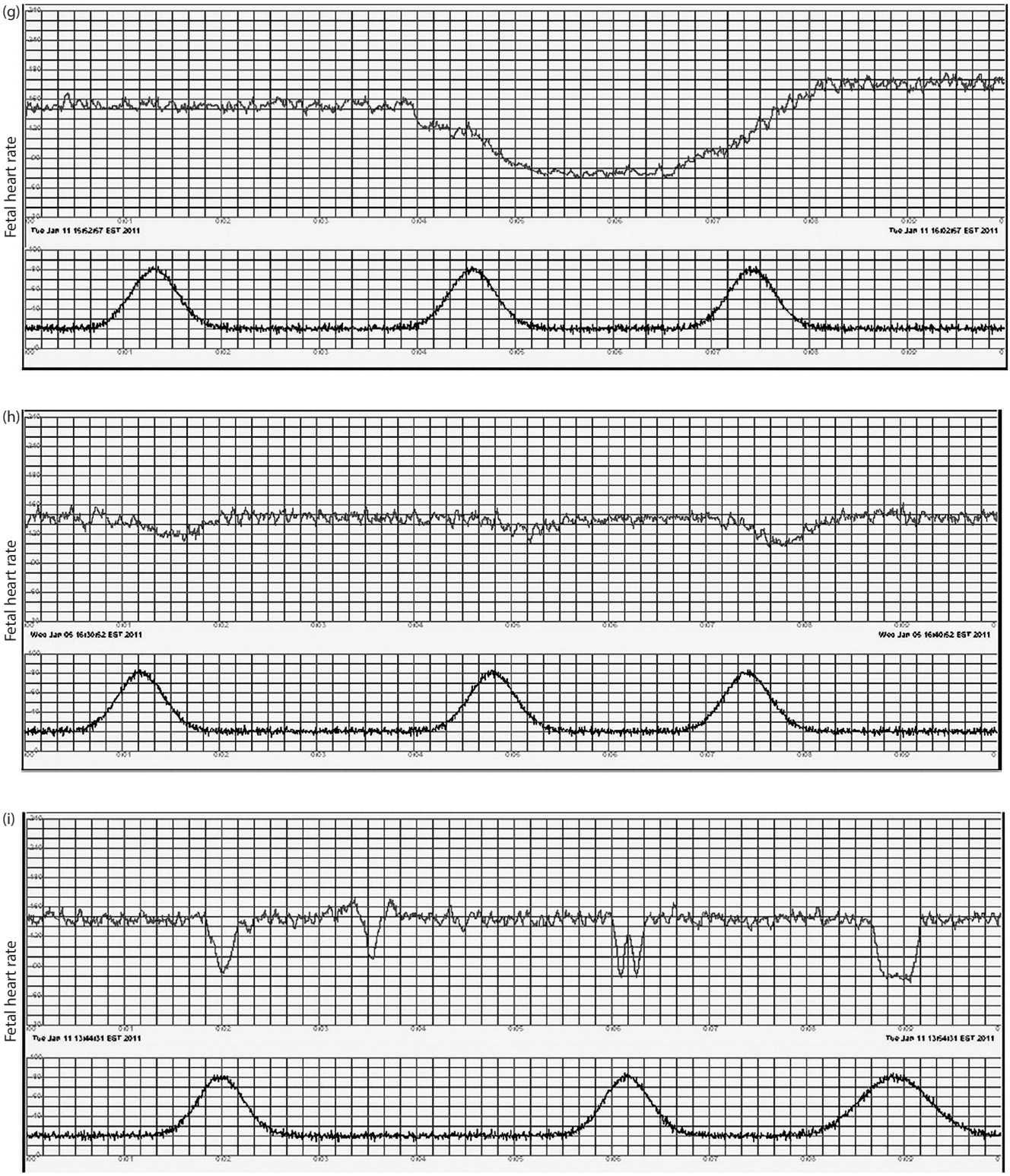


FIGURE 11.5 (Continued) Category II. (g) Prolonged deceleration. (h) Recurrent late decelerations, moderate variability. (i) Variable decelerations.

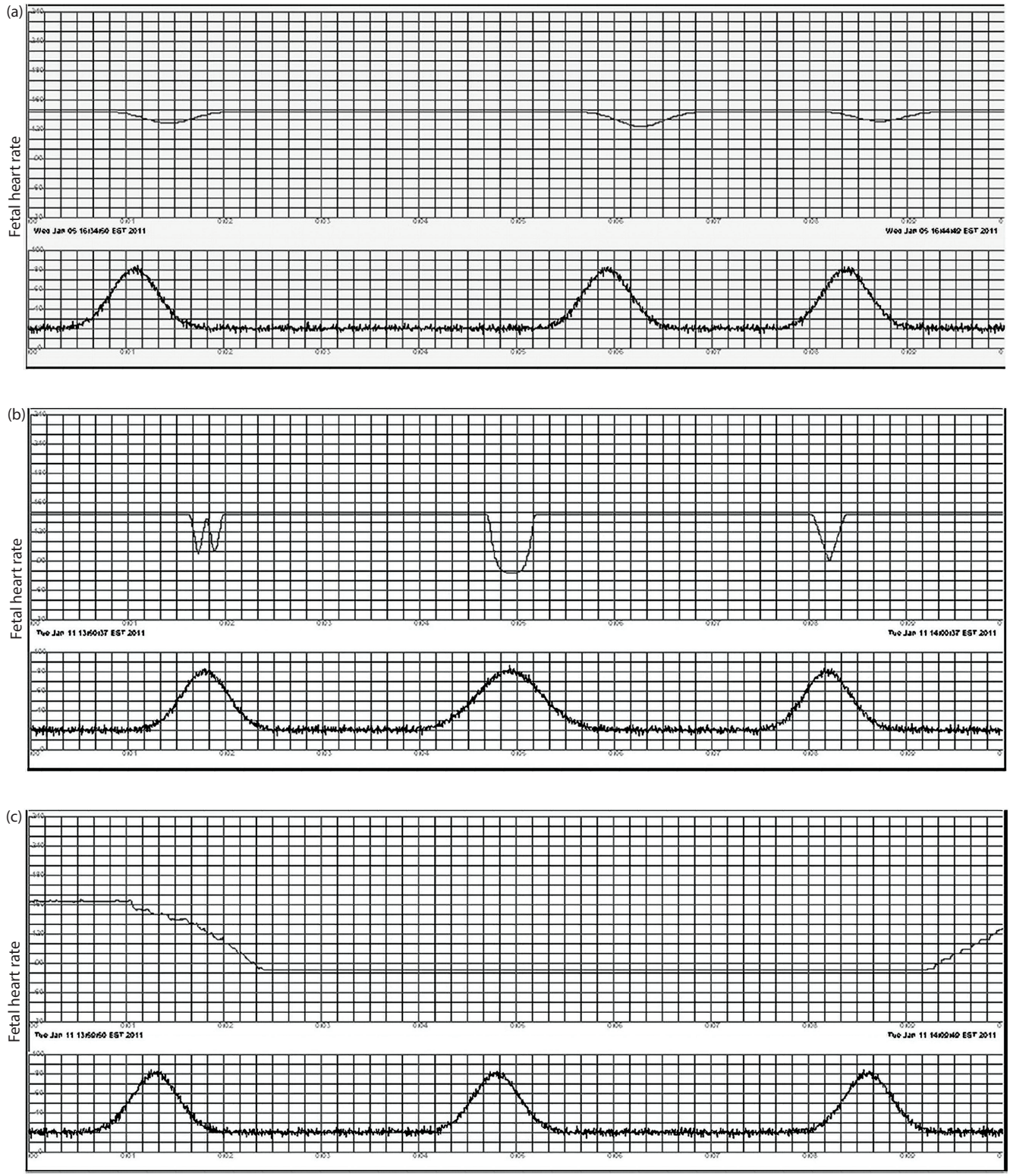


FIGURE 11.6 Category III. (a) Recurrent late decelerations, absent fetal heart rate variability. (b) Recurrent variable decelerations, absent fetal heart rate variability. (c) Bradycardia, absent fetal heart rate variability.

Although there is no formal definition of NRFHT, the diagnosis is associated with an increased risk of acidemia. The ability to predict CD for NRFHT remains limited [8]. The available evidence suggests that fetal movement count, abnormal EFM on admission, vibroacoustic stimulation, amniotic fluid index, contraction stress test, and modified biophysical profile are limited diagnostic tests to identify patients at risk of emergent CD for NRFHT [5].

Fetal heart rate monitoring

Continuous electronic FHR monitoring vs. intermittent auscultation

Despite the ubiquitous use, there is mixed evidence for the utility of EFM. As noted by the American College of Obstetricians and Gynecologists (ACOG) practice bulletin [9], the efficacy of monitoring is adjudicated by comparing the neonatal and infant morbidity, including seizure and cerebral palsy, or mortality averted versus the unnecessary interventions (operative vaginal delivery or CD) undertaken. Since all the randomized clinical trials (RCTs) with EFM compare it to intermittent auscultation (IA), the efficacy is determined by calculating the relative risks (RRs) of interventions, neonatal seizures, cerebral palsy, or death.

Compared with IA, continuous EFM shows **no significant improvement in overall perinatal death rate** (RR 0.86, 95% confidence interval [CI] 0.59–1.23), but was associated with a **halving of neonatal seizures** (RR 0.50, 95% CI 0.31–0.80). There was no significant difference in cerebral palsy rates (RR 1.75, 95% CI 0.84–3.63). The positive predictive value of NRFHT for cerebral palsy is approximately 0.1% [10]. The **false-positive rate of NRFHT is extremely high** (99%) for abnormal neonatal outcomes, especially cerebral palsy [11].

There was a **significant increase in CD** associated with the use of continuous CTG (RR 1.63, 95% CI 1.29–2.07). Women were also **more likely to have an operative vaginal birth** (RR 1.15, 95% CI 1.01–1.33). Data for subgroups of low-risk, high-risk, and preterm pregnancies, as well as from high-quality trials, were consistent with overall results [9, 12]. EFM is associated with one additional CD for every 58 women monitored continuously; 661 women need to have continuous EFM during labor to prevent one neonatal seizure [12].

While the efficacy of EFM is debated, it is noteworthy that there are concerns regarding the 13 RCTs, which enrolled over 37,000 women, on continuous FHR monitoring versus IA [12]. Only two of these trials were rated to be of high quality [10, 13], and only three trials reported data in low-risk women [10, 13, 14]. The authors of the meta-analysis on this subject [12] noted that to test the hypothesis that continuous monitoring can prevent 1 death in 1000 births, more than 50,000 women would have to be randomized. Inadequate study size may not reflect the outcomes in contemporary obstetrical practice [15]. However, additional observational data have demonstrated that the rising rate of continuous EFM use is associated with a **decrease in neonatal mortality and reduction in Apgar score <4 at 5 minutes** [1, 16].

If IA is available on the labor and delivery unit, shared decision-making should be used to discuss the risks and benefits of IA versus continuous EFM in low-risk patients [17]. Admittedly, both patients and clinicians prefer continuous EFM to evaluate the fetus during labor [18]. The explanations for the preference include the ease of use, the reassurance women derive from hearing the heartbeat during labor, and the different value patients and clinicians place on the route of delivery and neonatal outcomes. Compared with pregnant patients and mothers, obstetricians overestimate the burden posed by CD, and contrary to obstetricians, women value a newborn with permanent neurologic handicap over neonatal death [18].

Clinicians choosing to utilize IA should be aware of some of the problems associated with its use. **Continuous EFM has a significantly better ability to detect acidemia** (umbilical arterial pH <7.15 in this study) than IA: A sensitivity of 97% versus 34% and a higher positive predictive value of 37% versus 22%, respectively [19]. Continuous EFM was superior to IA for the detection of respiratory, metabolic, and mixed acidosis. It is possible that ominous EFM patterns are poorly assessed by IA. Logistically, **it may not be feasible to adhere to guidelines of how frequently the heart rate should be auscultated with IA**. One prospective study noted that the protocol for IA was successfully completed among only 3% of the cases [20].

Not all pregnancies should be monitored with IA because **those at risk for adverse outcomes like cerebral palsy, neonatal encephalopathy, and perinatal death should be monitored with EFM during labor** [21]. Thus, high-risk pregnancies that undergo antepartum surveillance should not be evaluated with IA, nor should those who are likely to have CD for NRFHT [5]. These include but are not limited to FGR, oligohydramnios, polyhydramnios, placenta previa, postterm pregnancy (≥42 weeks), multiple gestation, isoimmunized pregnancy, prior intrauterine fetal demise (IUFD), maternal renal disease, diabetes, preeclampsia, collagen disorders, hemoglobinopathies, and cardiovascular disease. Additionally, parturients should be monitored with continuous EFM if they are being induced, are augmented, or have dysfunctional labor. Patients with suspected FHR abnormalities with auscultation, abnormal fetal presentation, regional anesthesia, abruption, infection, preterm labor, prior CD (vaginal birth after cesarean [VBAC] attempt), hypertonic uterus, and meconium staining of the amniotic fluid should also be monitored with continuous EFM [22]. In these cases, EFM should be continued until delivery.

Reviewing electronic FHR monitoring

When EFM is utilized during labor, the nurses or physicians should review it frequently. If the patient is low risk, the FHR tracing should be reviewed at least every 30 minutes in the first stage of labor and at least every 15 minutes during the second stage. The corresponding frequency for high-risk parturients is 15 and 5 minutes, respectively. The maternal pulse should be taken to make sure the FHR is indeed fetal and not maternal. **Health care providers should document** that they have reviewed the tracing by a narrative note, use of comprehensive flow sheets, or by placing one's initials on the monitor strip [22]. NICHD terminology should be utilized in any assessment of intrapartum EFM [2]. Among low-risk patients, it is more feasible to confirm that the strips are reviewed according to the guidelines, whereas among high-risk patients, compliance during the active phase, and especially during the second stage of labor, is more demanding and difficult. The FHR tracing, as a part of the medical chart, should be labeled and available for review if the need arises. Alternatives like computer or server storage of the FHR tracing that do not permit overwriting or revisions are reasonable [22].

Due to the **interobserver and intraobserver variability**, FHR tracing should be interpreted cautiously and preferably without knowing the neonatal outcome [23–25]. When four obstetricians, for example, examined 50 CTGs, they agreed in only 22%

of the cases. Two months later, during the second review of the same 50 tracings, the clinicians interpreted 21% of the tracings differently than they did during the first evaluation [24]. Factors that influence the interpretation of CTGs include the clinician's experience, whether the tracing is normal versus equivocal or ominous with greater agreement if the tracing is reassuring, and the time of the day, with possibly greater error at night. With retrospective reviews, the foreknowledge of neonatal outcome alters the impressions of the tracing. Given the same intrapartum tracing but opposite neonatal outcomes, the reviewer is more likely to find evidence of fetal hypoxia and criticize the obstetrician's management if the outcome was supposedly poor versus good [25].

The positive predictive value of NRFHT for cerebral palsy is approximately 0.1% [8]. The **false-positive rate for prediction of abnormal neonatal outcomes is high** (99%) [11].

External vs. internal FHR monitoring

External FHR monitoring is accomplished via a Doppler ultrasound device applied to the maternal abdomen. An internal scalp electrode ("scalp lead") for FHR monitoring measures the R-R interval between consecutive beats. This provides an accurate representation of FHR variability. There are **no RCTs comparing these two monitoring techniques**. Internal monitoring is used, in general, for an FHR that is discontinuous or unreliable transabdominally due to factors such as maternal body habitus or multiple gestations. Placement of a fetal scalp electrode for internal monitoring requires rupture of membranes (ROM) and sufficient cervical dilation to access the fetal scalp. Contraindications to internal monitoring include maternal infections such as HIV, active hepatitis B or C, and fetal thrombocytopenia. The use of a fetal scalp electrode may be associated with a decrease in the risk of CD with no associated increase in infectious morbidity [26]. The risks of internal fetal monitoring are rare but include scalp injury, infection, and cephalohematoma [27].

Given the potential safety risks, routine or universal use of internal fetal monitoring should be avoided. If CD is performed, internal scalp monitoring can be continued until delivery, while external monitoring can be discontinued when the abdominal preparation begins.

Computerized EFM analysis

Due to limited interobserver agreement, computerized evaluation of intrapartum FHT, also called expert systems (ES), has been evaluated as a tool to improve the sensitivity of FHT for perinatal morbidity and mortality and decrease false positives associated with FHT.

Two RCTs evaluating the use of CTG with ES in labor have been published, but only one trial (n = 220) provides data for quantitative analysis. There is **no strong evidence that CTG with an ES has an effect on the incidence of CD** (RR 0.61; 95% CI 0.35–1.04) when compared with CTG with fetal scalp blood sampling (FSBS). There is **no strong evidence supporting a reduction in the incidence of neonatal seizures** (RR 0.33; 95% CI 0.01–8.09) **or fetal acidemia** (RR 0.50; 95% CI 0.09–2.67) in women monitored using a CTG with an ES versus a CTG without an ES. Perinatal mortality was not reported. No fetal deaths occurred. There was no strong evidence supporting a reduction in the incidence of forceps-assisted vaginal birth (RR 0.50; 95% CI 0.05–5.43), hypoxic ischemic encephalopathy (RR 0.33; 95% CI 0.01–8.09), admission to the neonatal intensive care unit (NICU) (RR 0.40; 95% CI 0.08–2.02), or an Apgar less than 7 at 5 minutes (RR 0.50; 95% CI 0.13–1.95).

Another RCT compared computer analysis of CTG using the Omniview-SisPorto 3.5 to standard clinician analysis of **pre-recorded cases**. Prediction of abnormal umbilical artery pH was more reproducible and accurate when clinicians had access to the computerized analysis of CTGs [28]. The most recent multicenter RCT investigating computerized interpretation of FHR through the INFANT decision support software found no difference in neonatal outcomes or developmental assessment at 2 years of age with the use of this software [29].

Therefore, **there is insufficient evidence to support routine use of computerized evaluation of EFM**.

Other fetal monitoring tests

Digital scalp or vibroacoustic stimulation

Persistent minimal variability may be associated with fetal acidemia. In the setting of minimal variability, **digital scalp or vibroacoustic stimulation** can be performed to elicit an acceleration (see the definition in Table 11.1). If there is an acceleration in response to scalp stimulation, labor should continue, as this indicates that the likelihood of fetal scalp pH <7.19 is 2% [30]. In the absence of an acceleration, the likelihood is 38%.

Allis clamp and scalp puncture have been used to elicit an acceleration but are less safe. Digital scalp stimulation (gentle stroking of the fetal scalp for 15 seconds) is the test with the best predictive accuracy among these four techniques [30]. There are currently **no RCTs that address the safety and efficacy of digital scalp or vibroacoustic stimulation used to assess fetal well-being in labor in the presence of NRFHT**.

Fetal scalp blood sampling

FSBS to measure scalp pH and lactate was introduced in 1962 in Berlin, Germany, as a standalone fetal status test, before the commercialization of EFM machines in 1968 [31].

It is important to understand fetal intrapartum physiology in order to interpret FSBS. The fetus reacts to intrapartum hypoxia by using anaerobic glycolysis, which leads to metabolic acidosis through conversion of pyruvate to lactate. Low pH can be a combined measure of both metabolic acidosis and the more labile component, respiratory acidosis [32].

Historically, a pH value >7.25 on FSBS is considered normal, with a low likelihood of fetal hypoxia. Values between 7.25 and 7.20 are considered subnormal, indicating the need for repeat sampling within 20–30 minutes. FSBS pH <7.20 (or <7.15 in the second stage of labor) requires intervention, such as intrauterine resuscitation or operative delivery. As for lactate concentration, normal values have been described as being <4.2 mmoL/L. Values between 4.2 and 4.8 are defined as intermediate, and values > 4.8 mmoL require intervention [33]. If the results are scalp pH <7.20 or lactate >4.8 mm/L, then delivery should be expedited [34].

The technical aspects of FSBS require ruptured membranes and a cervical dilatation greater than or equal to 3 cm. An amnioscope is then placed vaginally to allow adequate visualization of the fetal head. A small blood sample is then taken from the fetal scalp. Usually 30–50 microliters of blood are sufficient to perform the test. For testing lactate, a much smaller amount of blood is required [32]. To be beneficial, the scalp pH machine needs to be reliable and readily available with prompt results.

Observational data from a Cochrane review on continuous CTG monitoring with or without FSBS demonstrate that use of FSBS is associated with a decrease in neonatal acidosis (P = 0.04) but at the cost of more instrumental deliveries (P = 0.04) [35]. Retrospective studies have also failed to show a positive effect of FSBS on neonatal outcomes [36, 37].

The only level 1 evidence pertaining to FSBS are **two RCTs comparing lactate to pH in FSBS** [31]. The two RCTs [38, 39] enrolled a total of 3348 women in labor with NRFHT patterns and investigated maternal/fetal/neonatal/infant outcomes following FSBS-obtained pH or lactate. The Cochrane review noted that lactate sampling is more likely to be successful than pH sampling, but there were no differences between the two tests in terms of mode of birth or neonatal outcomes evaluated by umbilical cord blood gases, Apgar score, encephalopathy, or admission to the NICU [33].

Given these data, as well as the several risks of FSBS [31], ACOG has recommended **against the use of FSBS** [37, 40]. Others have also cautioned against its use [31, 34]. However, this procedure is still frequently performed in some countries.

Fetal electrocardiogram for fetal monitoring in labor

Use of the fetal electrocardiogram (ECG) has been evaluated **as an adjunct to continuous EFM in labor** [40–47]. Traditionally, fetal ECG has been obtained via internal monitoring with a fetal scalp lead. However, recent data suggest the feasibility of transabdominal ECG monitoring [48]. One study assessed PR intervals but was insufficient to make recommendations [45]. Six RCTs assessed the ST segment [38, 39, 41–44].

A meta-analysis of six RCTs including 26,529 laboring singletons at 34 weeks or more reported that **ST analysis (STAN) plus CTG** was associated with no difference in perinatal composite outcome (1.5% vs. 1.6%; RR 0.90, 95% CI 0.74–1.10), neonatal metabolic acidosis (0.5% vs. 0.7%; RR 0.74, 95% CI 0.54–1.02), admission to the NICU (5.4% vs. 5.5%; RR 0.99, 95% CI 0.90–1.10), perinatal death (0.1% vs. 0.1%; RR 1.71, 95% CI 0.67–4.33), neonatal encephalopathy (0.1% vs. 0.2%; RR 0.62, 95% CI 0.25–1.52), CD (13.8% vs. 14.0%; RR 0.96, 95% CI 0.85–1.08), or operative delivery (either cesarean or operative vaginal delivery) (23.9% vs. 25.1%; RR 0.93, 95% CI 0.86–1.01) compared to standard CTG only [4]. The Cochrane review confirms these findings, but also found an 8% decrease in operative vaginal deliveries associated with STAN [40].

As there is no difference in perinatal outcomes between STAN with CTG compared with CTG alone, this modality cannot yet be recommended for routine clinical care. Nonetheless, given the concerns of heterogeneity in inclusion criteria among RCTs, the learning curve for STAN, possible Hawthorne effect in the RCTs, different (three vs. four) tier classifications used in the RCTs, and limited power to address abnormal perinatal outcomes such as metabolic acidosis, more research is needed before the STAN technology can be deemed of no value for fetal monitoring in labor [46].

Fetal pulse oximetry

The use of fetal pulse oximetry (FPO) has been evaluated **as an adjunct to intrapartum continuous EFM** [49–54]. In this noninvasive form of monitoring, a fetal oxygen sensor lies against the fetal cheek. FPO showing fetal oxygen saturation ($FSpO_2$) <30% for at least 2 minutes is associated with an increased risk of declining fetal arterial pH and metabolic acidosis.

RCTs on FPO are at high risk of bias because of the impractical nature of blinding participants and clinicians. In RCTs not requiring FSBS prior to study entry, the use of FPO plus CTG decreased the risk of cesarean section for NRFHT (RR 0.65, 95% CI 0.46–0.90) compared to CTG alone; however, there was **no evidence of differences in the overall cesarean section rate** between those monitored with and without FPO or for whom the FPO results were masked (RR 0.99, 95% CI 0.86–1.13). There was evidence of a higher risk of cesarean section in the group with FPO plus CTG than in the group with fetal ECG plus CTG (one study only, *n* = 180, RR 1.56, 95% CI 1.06–2.29). No studies reported details of long-term disability [49].

No differences are seen for endometritis, intrapartum or postpartum hemorrhage, uterine rupture, low Apgar scores, umbilical arterial pH or base excess, admission to the NICU, or fetal/neonatal death [49, 50]. Given the evidence presented, **routine use of FPO in labor is not recommended**.

Management of abnormal EFM

The frequency with which EFM should be evaluated depends on the risk status of the pregnancy (see earlier). To correctly interpret intrapartum EFM, the clinician must be cognizant of the gestational age, labor progress, medications (Table 11.3) [55], prior fetal assessment, and obstetric and medical conditions. Since more than 80% of fetuses demonstrate category II EFM in labor, a standardized approach to EFM management in this group is important (Figure 11.7) [56]. The management of category II EFM, specifically recurrent late or variable FHR decelerations, is guided by the presence or absence of moderate variability or accelerations and intrauterine resuscitation. Category III EFM should prompt rapid assessment with

TABLE 11.3: Effect of Medications and FHR Patterns

Medications	Study Design	Effect on FHR
Butorphanol	Case control	Transient sinusoidal FHR pattern
Cocaine	Case control	No characteristic changes in FHR pattern
Corticosteroid	RCT	Decrease in FHR variability with betamethasone but not dexamethasone
Magnesium sulfate	RCT and retrospective	A significant decrease in the FHR baseline and variability; inhibits the increase in accelerations with advancing gestational age
Meperidine	RCT	No characteristic changes in FHR pattern
Morphine	Case control	Decreased number of accelerations
Nalbuphine	RCT	Decreased the number of accelerations, long- and short-term variations
Terbutaline	Retrospective	Abolishment or decrease in frequency of late and variable decelerations
Zidovudine	Case control	No difference in the FHR baseline, variability, number of accelerations or decelerations

Source: Adapted from Ref. [55].

Abbreviations: FHR, fetal heart rate; bpm, beats per minute; RCT, randomized clinical trial.

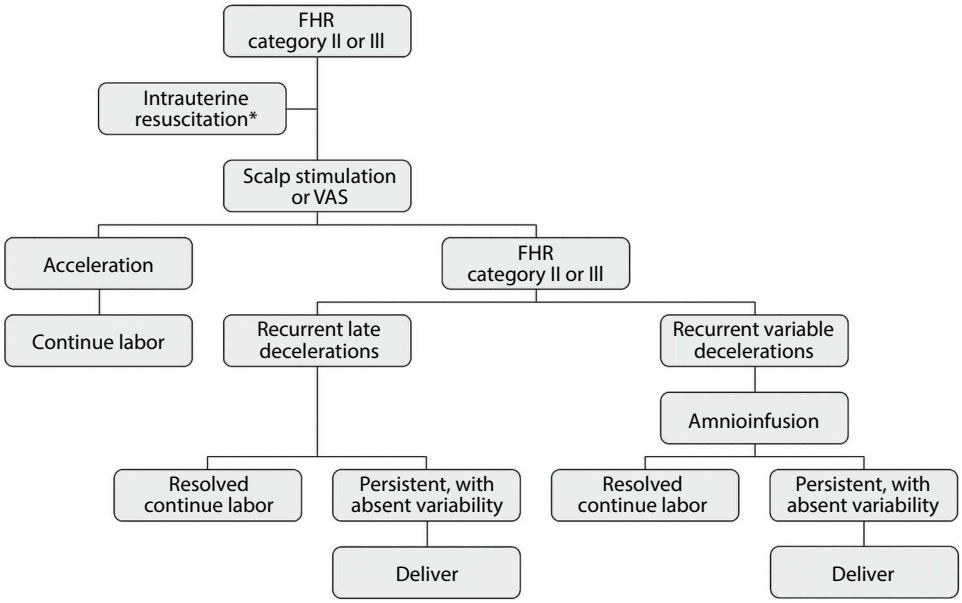


FIGURE 11.7 Algorithm for the management of Category II EFM in labor. (Adapted from ACOG Practice Bulletin 116.) *Uterine relaxation, hydration, maternal repositioning, and/or amnioinfusion.

scalp stimulation, vibroacoustic stimulation, and intrauterine resuscitation with movement toward expedited delivery if not resolved.

In an RCT investigating intrauterine resuscitation maneuvers in patients with reassuring EFM, **intravenous fluid (IVF) bolus of 1000 mL, lateral positioning, and oxygen administration at 10 L/minute via nonbreather face mask were the three techniques that increased $FSpO_2$ during labor** [57]. However, interpretation of these results is limited by a lack of supportive data for $FSpO_2$ as a marker of neonatal morbidity and the exclusion of patients with NRFHT from this study.

Intrauterine resuscitation

Amnioinfusion

Amnioinfusion is the process of infusing fluid into the amniotic cavity after ROM. The goal of amnioinfusion is to provide fluid and buoyancy in order to relieve possible umbilical cord compression, usually during labor after ROM. This technique consists of introducing normal saline or Ringer's lactate transcervically through a catheter into the uterine cavity. Intrapartum amnioinfusion is used in the setting of repetitive variable decelerations after ROM. Transcervical amnioinfusion can be done by bolus or continuous infusion technique, with similar ability to relieve recurrent variable decelerations. Either lactated Ringer's solution or normal saline can be used to place a crystalloid solution into the uterus without altering the neonatal electrolyte balance [58].

In a Cochrane review on use of amnioinfusion for suspected cord compression in labor, **transcervical amnioinfusion** was found to significantly **reduce the following outcomes**: **CD** (13 trials, 1493 participants, RR 0.62, 95% CI 0.46–0.83); **FHR decelerations** (7 trials, 1006 participants, RR 0.53, 95% CI 0.38–0.74); **Apgar score less than 7 at 5 minutes** (12 trials, 1804 participants; RR 0.47, 95% CI 0.30–0.72); **meconium below the vocal cords** (3 trials, 767 participants; RR 0.45, 95% CI 0.25–0.81); and **maternal stay longer than 3 days** (4 trials, 1051 participants, RR 0.45, 95% CI 0.25–0.78) [58].

ACOG recommends **amnioinfusion for management of recurrent variable decelerations** [56].

Uterine relaxation

Tocolysis is a possible tool in the management of recurrent FHR decelerations, particularly in the presence of tachysystole The rationale behind this is that uterine relaxation improves uteroplacental blood flow and therefore fetal oxygenation. Uterine relaxation can be performed by stopping or reducing the dose of oxytocin infusions or by administering a tocolytic. The most commonly studied tocolytics for intrapartum fetal resuscitation are betamimetic drugs (e.g. terbutaline 0.25 mg IV).

There are some important safety concerns regarding these drugs. The most serious side effects of beta-agonists are pulmonary edema and myocardial ischemia [59]. Six RCTs have been performed to evaluate the use of betamimetics for acute intrapartum fetal resuscitation [60–66]. When betamimetic administration was compared with no treatment, neonatal outcomes seemed to improve [61, 62]. Four RCTs assessed the efficacy of betamimetics by comparing these drugs with either magnesium sulfate (4.0 g IV) [63], atosiban (6.75 mg in 4.9 mL saline administered IV over a 1-minute period) [60, 64], or nitroglycerin (0.4 mg IV) [65]. Betamimetics provided a more effective tocolysis, with similar successful resuscitation rates [60].

ACOG recommends the **administration of tocolytic medications (e.g. terbutaline) when tachysystole is associated with FHR abnormalities** [56]. **Repetitive use of terbutaline is not recommended**. **There is insufficient evidence (no randomized trial) to assess the effect of labor stimulant discontinuation on fetal status**. Nonetheless, **labor stimulants such as oxytocin** should be discontinued in cases of NRFHT, especially in the setting of tachysystole.

Maternal position change

Maternal position change to improve fetal status in cases of intrapartum NRFHT **has not been independently studied in an RCT**. This intervention has only been studied in combination with IVF

and oxygenation supplementation (see earlier) [57]. Indirect evidence for position change comes from studies on maternal positioning during normal labor. There are two reports comparing the effects of right lateral, left lateral, and supine maternal positions on fetal oxygen status, each suggesting that lateral positioning is more favorable than a supine position [66, 67]. In 2013, a Cochrane review was published on the impact of maternal positions during the first stage of labor on peripartum outcomes. Twenty-five trials with a total of 5218 women were included. Upright and mobile positions were associated with a shorter duration of first stage of labor, a reduction in the risk of cesarean birth, less use of epidural as a method of pain relief, and a lower chance of babies being admitted to the neonatal unit [68]. However, this review does not answer directly the question of whether changing maternal position should be considered as a therapeutic measure for NRFHT in labor. Given that maternal repositioning is a low-risk intervention, it **should be considered as part of routine intrauterine resuscitation of category II EFM**.

Intravenous hydration

The rationale for intravenous (IV) fluid administration is that it optimizes maternal intravascular volume, thereby improving placental perfusion. In one randomized trial comparing 500 mL to 1000 mL IVF bolus, the 1000 mL was associated with an increase in $FSpO_2$ [57]. IV fluids are typically administered at the time of epidural placement, given the 10%–12% incidence of hypotension following neuraxial anesthesia. However, there is no evidence that routine preload of IV fluids reduces the incidence of hypotension [69]. Excessive administration of IV fluids may be harmful in those at risk of pulmonary edema such as patients with preeclampsia or cardiac disease. A 1500-mL IVF bolus may help reduce the risk of FHR abnormalities in patients with narrow pulse pressures indicative of hypovolemia [70]. There is **no evidence to suggest that routine, prophylactic IVF boluses are effective in the setting of NRFHT. A targeted approach of hydrating volume-depleted patients may be beneficial**.

Oxygen supplementation

Maternal oxygen administration is commonly administered for category II EFM, with the goal of increasing oxygen transfer to the fetus, although evidence of fetal benefit is lacking [71].

In the Cochrane review of two trials investigating *prophylactic* administration of oxygen to prevent NRFHT, oxygen was associated with a higher likelihood of abnormal cord blood pH <7.2 (RR 3.51, 95% CI 1.34–9.19) [72]. In the two RCTs that have investigated the *therapeutic* use of oxygen administration for abnormal FHT, oxygen was not associated with an improvement in umbilical artery pH or lactate, mode of delivery, or neonatal outcomes compared to room air [73, 74]. There is conflicting evidence on whether maternal oxygen supplementation improves abnormal EFM [74, 75].

Taken together, multiple RCTs have shown no benefit to fetal acid–base status or mode of delivery with maternal oxygen administration at the time of vaginal delivery or cesarean section [76, 77]. However, the impact of intrapartum oxygen supplementation on clinical measures of neonatal morbidity remains unknown.

The risks of hyperoxygenation should be considered. Excess oxygen exposure is associated with free radical–mediated oxidative stress and subsequent cell damage [75, 78]. Hyperoxygenation in nonpregnant adults and neonates is associated with morbidity [79]. In light of evidence suggesting harm with postnatal oxygen exposure, the American Academy of Pediatrics now recommends against neonatal resuscitation with 100% oxygen [80].

In the absence of benefit and concern for potential harm, **routine use of prophylactic or therapeutic maternal oxygen administration for intrauterine resuscitation should be reconsidered**.

Other interventions

Additional steps with the management of NRFHT might include (no trials available) the following:

- **Cervical examination**
  Assessment of cervical status can be helpful to assess rapid dilation or descent and to ensure that the umbilical cord has not prolapsed.
- **Maternal blood pressure assessment**
  Maternal blood pressure monitoring may be helpful, especially among those who have received regional anesthesia. If hypotension is present in conjunction with NRFHT pattern, ephedrine or phenylephrine may be utilized [9].
- **Piracetam for NRFHT in labor**
  Piracetam, a derivative of gamma-aminobenzoic acid, is thought to counteract the effects of hypoxia on the fetal brain by promoting metabolism. There is not enough evidence to evaluate the use of piracetam for NRFHT in labor. In one randomized trial of piracetam versus placebo for fetal distress in labor, the rates of cesarean section, low Apgar scores, and neonatal morbidity were similar between groups [81].
- **Operative delivery for NRFHT in labor**
  There are no contemporary trials of operative delivery versus conservative management of suspected NRFHT. In the only outdated (1959) trial, there is no difference in perinatal mortality [82].

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12

ANALGESIA AND ANESTHESIA

Michele Mele, Valentina Bellussi, and Laura Felder

Key points

- **In every hospital providing labor and delivery services, anesthesia personnel must be available on a 24-hour basis**, with the ability to perform a cesarean delivery (CD) within 30 minutes from decision.
- **Intravenous pain relief is inferior to neuraxial analgesia**, less effective, and associated with several maternal and fetal/neonatal side effects.
- **Neuraxial analgesia provides superior pain relief in labor** and should be **available to all laboring women upon request**.
- **Airway complications can occur during induction and emergence of general anesthesia, as well as in the postoperative period, and constitute the most common cause of anesthesia-related death**.
- Regarding parental opioids, remifentanil is an ultra-short-acting opioid, usually given as patient-controlled analgesia. Patients receiving remifentanil were more satisfied with their pain relief and had better pain relief at 1 hour; however, it is associated with maternal apneic episodes and should only be administered at institutions with the capability of increased maternal respiratory monitoring and appropriate nursing ratios.
- In the absence of a medical condition associated with coagulopathy, it is not necessary to obtain a platelet count before neuraxial techniques. In general, women with platelet counts of ≥70,000/μL can safely receive neuraxial analgesia.
- As there is no benefit to obstetric outcome from delaying neuraxial analgesia until an arbitrary cervical dilation has been reached, **the decision of when to initiate neuraxial analgesia should be made individually with each patient**.
- **Patients should be counseled regarding the benefits and risks of neuraxial analgesia in labor. These include the following**:
  - **Neuraxial anesthesia is associated with superior pain relief** compared with any other intervention for pain relief and with lower risk of umbilical cord pH <7.20 compared with systemic opioids.
  - **Neuraxial analgesia is associated with an increased incidence of hypotension, pruritus, urinary retention, and maternal fever; increased need for oxytocin administration; increased duration of the second stage (by about 15 minutes); and increased risk of operative vaginal birth**.
  - **Complications of neuraxial analgesia include postdural puncture headache (PDPH), respiratory depression from opioid use, and, rarely, epidural or spinal hematoma or abscess**.
- Discontinuation of neuraxial analgesia in the second stage does not affect obstetric outcome.
- Use of **a low-concentration local anesthetic epidural infusion, prophylactic prehydration**, and **phenylephrine or ephedrine** can **decrease** the incidence of **maternal hypotension and associated** nonreassuring fetal heart rate **(NRFHR)**.
- Compared with the standard epidural approach, combined spinal epidural **(CSE)** has been shown to **produce a quicker** (by about 6 minutes) **onset of analgesia**, result in a **lower total dose of local anesthetic** over the course of the labor, achieve a **lower median visual analog pain score earlier in labor**, **increase** the incidence of **maternal satisfaction**, and have a **lower incidence of incomplete block**, **but is associated with an increased likelihood of maternal pruritus**.
- **For CD, neuraxial anesthesia is the anesthetic technique of choice. Spinal (intrathecal) anesthesia has advantages over epidural anesthesia, including quicker onset of surgical anesthesia, simplicity, lower total drug dose, and superior abdominal muscle relaxation**. Compared with epidural anesthesia, the spinal technique is associated with a similar failure rate, need for supplemental intraoperative analgesia, need for conversion to general anesthesia intraoperatively, maternal satisfaction, need for postoperative pain relief, and neonatal intervention.
- **Hypotension** following spinal analgesia for CD can **be decreased by crystalloid or colloid administration, phenylephrine, or ephedrine**.
- **General anesthesia for CD should be avoided if at all possible**, as it is associated with a threefold risk of maternal death compared with neuraxial analgesia. Risks include inability to intubate or ventilate the patient at the induction of general anesthesia, as well as airway complications at emergence from anesthesia. There are no evident advantages to general anesthesia in the absence of a contraindication to a neuraxial approach.
- Transversus abdominus plane (TAP) block may be used at the time of CD in patients unable to receive long-acting intrathecal opioids to decrease postoperative pain.
- Postpartum analgesia after vaginal delivery is typically achieved with a combination of abdominal heating pads, perineal ice packs, topical lidocaine, nonsteroidal anti-inflammatory drugs (NSAIDS), and acetaminophen. Opioids should be reserved for severe or breakthrough pain.
- Following CD, a stepwise multimodal approach should be employed, with scheduled NSAIDS and acetaminophen as first-line analgesia, and oral or intravenous opioids reserved for breakthrough pain. Combination pain medications, such as oxycodone-acetaminophen, should be avoided, with acetaminophen administered standing and opioids used only as needed. The lowest effective opioid dose should be used for the shortest necessary duration.

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- For severe, refractory, postoperative pain, Ketamine may be used as an analgesic adjunct to decrease opioid requirements. Lidocaine patches, gabapentin, and pregabalin may also improve postoperative pain control.

Historic notes

Three months after the first successful public demonstration of the anesthetic properties of ether, on January 19, 1847, Dr. James Simpson Young of the University of Edinburgh used diethyl ether to deliver anesthesia for childbirth to a woman with a deformed pelvis [1]. Before this time, pain during labor and childbirth was seen by both medical professionals and the lay community as a necessary and indeed inseparable part of pregnancy. By 1860 anesthesia for parturition had become common practice thanks to a majority of women demanding it be a part of their medical care. The practice of obstetric anesthesia has changed markedly since. Women in labor now receive analgesia, rather than anesthesia, with the goal of enabling maternal mobility during labor. Refined anesthetic techniques for women requiring cesarean delivery (CD) have substantially decreased the number of maternal deaths directly related to anesthesia.

Definitions

Pain: An unpleasant sensory and emotional experience associated with actual or potential tissue damage
Analgesia (from the Greek: "no pain"): Loss of the ability to feel pain without the loss of consciousness
Anesthesia (from the Greek: "no sensation"): An induced, temporary state of analgesia, paralysis, amnesia, and unconsciousness

General comments

More than 60% of women in the United States choose to receive epidural or spinal anesthesia during labor [2]. **While not all laboring women desire the services of an anesthesiologist, maternal request is a sufficient medical indication for pain relief in labor** [3]. Hospitals providing labor and delivery services must have **anesthesia personnel available on a 24-hour basis**, with the ability to perform a CD within 30 minutes from decision [4]. Availability of licensed practitioners to administer anesthetics and support vital functions in emergencies is recommended [3, 4].

Physiology of labor pain

Labor is associated with two sources of pain: visceral pain at T10–L1 from uterine contractions and cervical dilatation during the first stage of labor and somatic pain transmitted by the pudendal nerve at S2–S4 from descent and consequent pressure of the fetal head on the pelvic floor, vagina, and perineum during the second stage of labor [5]. This pain is amenable to safe intervention, as the anesthesiologist can interrupt the transmission of peripheral afferents from the cervix, lower uterine segment, and perineum by use of neuraxial techniques that block spinal cord transmission of labor pain.

Maternal physiologic changes

Pregnancy is associated with **unique physiologic changes**. As a result of these changes, after the first trimester, parturients are at increased risk for aspiration of gastric contents, have decreased oxygen reserve, and are much more likely to be difficult to intubate than a nonpregnant woman (see also Chap. 3). Centers for Disease Control and Prevention (CDC) Surveillance Data on Pregnancy Related Mortality reveal anesthetic-related maternal mortality decreased nearly 60% when data from 1979 to 1990 were compared with data from 1991 to 2002. Although case-fatality rates for general anesthesia are falling, rates for regional anesthesia are rising. A subgroup comparison of data for CD showed that case-fatality rates for general anesthesia decreased from 16.8 per million in 1991–1996 to 6.5 per million in 1997–2002, whereas for regional anesthesia, there was a slight increase in mortality rates from 2.5 to 3.8 per million [6].

Whenever possible, pregnant patients should be positioned with **left uterine displacement** when supine after 20 weeks of gestational age. Left uterine displacement prevents aortocaval compression, which can result in a marked decrease in venous return and a subsequent drop in cardiac output. The ability to compensate for aortocaval compression is compromised in the presence of neuraxial analgesia or anesthesia.

When considering anesthesia or analgesia, one must take into account that pregnant women are **more sensitive to sedative hypnotics, local anesthetics, and the inhaled anesthetic agents** than nonpregnant women. In addition, the pregnant patient should be considered *two patients*, and occasionally the needs of one must be prioritized over the other. Informed consent should be obtained early in the course of labor in case of an emergency, and the patient's wishes for an unmedicated birth always respected. Successful initiation of breastfeeding is not affected by neuraxial analgesia.

Nonpharmacologic analgesic techniques

Increasingly, many pregnant women are seeking alternative approaches to labor pain relief such as water immersion, acupuncture, and aromatherapy. While these techniques may not provide complete pain relief, they may diminish labor pain, helping parturients delay or even avoid the use of pain relief medications if that is their goal.

Acupuncture and acupressure

Acupuncture and acupressure are therapeutic techniques based on the concept that energy flows throughout the body and strategic placement of needles or pressure can restore its balance and provide pain relief. Theories on its mechanism of action suggest it stimulates the release of endorphins in the muscles, brain, and spinal cord.

A Cochrane review including 28 trials with data reporting on 3960 women compared acupuncture with no intervention or placebo and found **acupuncture** for labor pain may be associated with **less intense pain and reduced use of pharmacologic analgesia**. Compared with no intervention or placebo, **acupressure** may be associated with **less pain intensity** [7]. Therefore, acupuncture and acupressure may have a minor role in reducing pain, increasing satisfaction with pain management, and reduced use of pharmacologic management.

Water immersion

Water immersion is a form of hydrotherapy in which water is used to relieve pain during labor. A Cochrane review suggests that immersion during the first stage of labor may be associated with a **reduction in the use of neuraxial anesthesia** compared to controls [8]. There were no differences in perineal trauma,

need for assisted vaginal deliveries, or CDs. There is no evidence that immersion improves perinatal outcome; however, there are case reports of rare but serious adverse effects in the newborn, including respiratory distress, when practiced during the second stage of labor. Given these rare but serious risks to the newborn, it is the opinion of the American Congress of Obstetricians and Gynecologists (ACOG) and the American Academy of Pediatrics that the practice of immersion in the second stage of labor (underwater delivery) should be avoided in routine obstetrical care [9]. See also Chaps. 8 and 9.

Biofeedback

Biofeedback is a therapy that allows women to gain control over their body's physiologic response to pain by controlling heart rate, blood pressure, and muscle tension. Despite some positive results shown in some very small trials, there is **insufficient evidence** that biofeedback is effective for the management of pain during labor [10].

Aromatherapy

Aromatherapy is the use of plant-derived aromatic essential oils to promote the sense of physical and psychological well-being. The limited evidence available **does not show benefit, or harm, from aromatherapy** for labor pain relief compared to no aromatherapy [11].

Hypnotherapy

Hypnotherapy is the use of hypnosis to deeply relax the body through focused concentration. For childbirth, hypnosis is often used to focus attention on feelings of comfort or numbness, as well as to enhance women's feelings of relaxation and sense of safety. In a review of nine studies (2954 women) there was **no significant difference** between women receiving hypnosis versus controls in terms of women's satisfaction with method of pain relief or women's sense of coping with labor. However, fewer women in the hypnosis group used pharmacologic pain relief [12].

Massage

There is **insufficient evidence** to assess the effect of massage therapy on labor pain. However, a meta-analysis involving 326 women found that women who used massage felt **less pain** when compared with women given usual care during first stage of labor [13].

Relaxation

A review of 19 randomized controlled trials, with data reported on 2519 women, found that **relaxation techniques, music, and yoga may help manage labor pain** [14].

Transcutaneous electrical nerve stimulation

Transcutaneous electrical nerve stimulation (TENS) units emit low-voltage electrical impulses and may be used to stimulate acupressure points. A systematic review of nine trials including more than 1000 women concluded that TENS did not reduce labor pain and did not reduce the use of additional analgesic agents [15].

Systemic analgesia

Parenteral opioids

Parenteral opioids continue to have a role in managing labor pain globally and are the most widely used of the systemic medications for labor analgesia. Opioids are low cost, easy to use, and do not require specialized personnel or equipment to be delivered safely. There are a variety of opioid agonist-antagonists in clinical use such as butorphanol (Stadol) or nalbuphine (Nubain) or pure opioid agonists such as meperidine, fentanyl, morphine, hydromorphone, or their derivatives. More recently, remifentanil, an ultra-short-acting opioid without active metabolites, has been utilized and is administered only as a patient-controlled intravenous (IV) infusion.

Characteristics of some of these drugs are shown in Table 12.1. Opioids may be delivered intramuscularly or intravenously. Intramuscular (IM) administration is easy for the health care provider, but painful for the patient. IV administration requires IV access, but allows faster onset of analgesia, predictable magnitude of peak plasma concentration, and titrating of dose to effect. IV opioids may be delivered as intermittent boluses or via patient-controlled analgesia (PCA) technology.

Efficacy

Meperidine is a commonly used opioid for labor analgesia administered by intermittent boluses intravenously or intramuscularly. In one small study, **compared** with **placebo, meperidine** (Demerol, pethidine) **100 mg IM in early labor is associated with a very modest** (17 mm) **reduction in** the visual analogue scale (VAS) **pain score at 30 minutes** [16, 17]. Request for epidural analgesia is delayed to 232 minutes compared with 75 minutes

TABLE 12.1: Intravenous or Intramuscular Opioid Agents for Maternal Pain Relief in Labor

Agent	Usual Dose (mg)	Frequency (Hour)	Onset (Minute)	Neonatal Half-Life (Hours)
Tramadol	50–100 mg	4		
Pentazocine	30 mg IV or IM	3–4		
Meperidine	25–50 IV	1–2	5	13–22
Remifentanil	0.15-0.5 μg/kg	Q 2 minutes as PCA	3–4 minute	
Fentanyl	50–100 μg IV	1	1	5
Nalbuphine	10 IV or IM	3	2–3 (IV) 15 (IM)	4
Butorphanol	1–2 IV or IM	Q 4–6	1–2 (IV) 10–30 (IM)	Not known
Morphine	2–5 IV 5–10 IM	4	5 (IV) 30–40 (IM)	7

Source: Adapted from Ref. [5].

Abbreviations: IV, intravenous; IM, intramuscular; Q, every; PCA, patient-controlled analgesia.

for parturients receiving placebo, with no further requests for analgesia in 32% versus 4% of women receiving meperidine or placebo, respectively [17]. In contrast, other studies have shown that meperidine provides limited labor analgesia and has less labor analgesia efficacy than other systemic opioids such as remifentanil [18]. Additionally, meperidine has an active metabolite, normeperidine, which has a prolonged duration of action and may result in neurobehavioral effects in the newborn.

Fentanyl is a synthetic opioid that is 50–100× more potent then morphine [19]. It is most commonly given intravenously by intermittent bolus administration or via PCA. It has a fast onset and relatively short duration of action of 45–60 minutes, making it a good option for labor pain relief. It has no active metabolites; however, larger doses are associated with longer duration of action and increased needs for neonatal resuscitation compared to remifentanil [20]. When compared to equianalgesic doses of meperidine, fentanyl is associated with less maternal nausea, vomiting, maternal sedation, and need for neonatal naloxone [21].

Remifentanil, an ultra-short-acting opioid without active metabolites, has been growing in use as an option for labor analgesia. Its pharmacokinetics allow for easy titration and for less risk of respiratory depression of the newborn. Remifentanil has a rapid peak analgesic effect <2 minutes after IV administration [22] and a short context-sensitive half-life of 2–3 minutes. Women who received PCA remifentanil were more satisfied with their pain relief, had better pain relief at 1 hour, and were associated with a reduced need for additional analgesia compared to women receiving other opioids either by IV or IM injection [23].

Maternal safety

There is not enough evidence to definitively evaluate the comparative safety of the various systemic opioids used to provide labor analgesia. Maternal side effects are largely dose dependent rather than drug dependent. Across all opioids there exists the potential for maternal nausea, histamine release and pruritus, delayed gastric emptying, constipation, urinary retention, dysphoria, drowsiness, apnea, hypoventilation, and hypotension. However, in a small randomized controlled trial, maternal apneic episodes occurred in 26% of women receiving remifentanil by patient-controlled IV analgesia [24]. Due to concerns of maternal respiratory depression, standardized protocols for administration and monitoring, including one-to-one nursing care, pulse oximetry, and capnography, as well as the immediate availability of anesthesiology personnel, should be standard of care at institutions where remifentanil PCA is used for labor analgesia [18].

There is weak evidence of more frequent adverse effects such as maternal nausea, vomiting, and drowsiness with meptazinol compared to meperidine. However, both **tramadol and pentazocine** have fewer maternal side effects when compared with meperidine [16], making these two agents the ones with the best evidence of **both moderate efficacy and lowest incidence of side effects among the opioid analgesic agents**. Respiratory and neurobehavioral depression can be reversed with the use of the pure opioid antagonist naloxone.

Fetal safety

IV opioids cross the placenta because of their low molecular weight and lipid solubility and as a result can affect the neonate. When compared with neuraxial analgesia, IV opioids are associated with **increased incidence of nonreassuring fetal heart rate (NRFHR), lower fetal base excess, and decreased fetal respirations and tone at birth**. Meperidine, the first synthetic opioid to be used for labor analgesia, is metabolized to normeperidine in the liver. This active metabolite has a prolonged half-life in adults and a half-life of up to 72 hours in the neonate, which is associated with neonatal sedation. The normeperidine effect cannot be reversed by naloxone. Because of this, meperidine must be used cautiously for intrapartum analgesia. Agonist/antagonists such as nalbuphine can result in both neonatal cardiac and respiratory depression, although there are no data that demonstrate adverse outcomes. Naloxone is a pure opioid antagonist and is the drug of choice in the treatment of neonatal respiratory and neurobehavioral depression secondary to opioid agonist agents. Repeated doses might be necessary, but excess use can be associated with neonatal withdrawal seizures. **Compared with neuraxial analgesic techniques, systemic medications are much less effective at decreasing visual analog pain scores** (see later).

Peripheral nerve blocks

Paracervical block

During the first stage of labor, pain from cervical dilation (but not uterine contractions) can be blocked by a **paracervical block**. Studies assessing the effectiveness of paracervical block in labor are small and of poor quality. The data suggest that this block is more effective for pain relief than placebo [25]. Risks include maternal local anesthetic toxicity from IV injection, fetal local anesthetic toxicity from inadvertent fetal injection, and a strong association with fetal bradycardia.

Pudendal block

During the second stage of labor, perineal pain can be blocked with a **pudendal block**. Studies assessing the effectiveness of pudendal block in labor are small and of low quality. The data suggest the pudendal block is more effective for pain relief than placebo [25]. There is a small risk of maternal local anesthetic toxicity in the event of accidental intravascular injection.

Lumbosacral sterile water injection

For patients who desire nonpharmacologic analgesic techniques, back pain during the first stage of labor can be reduced with lumbosacral sterile water injection. In a randomized controlled trial studying 128 term parturients, women receiving sterile water injection versus acupuncture reported greater pain relief and higher degrees of relaxation during labor [26]. In another study, for women with severe lower back pain, four **injections of sterile water**, either 0.1 mL intracutaneously or 0.5 mL subcutaneously **in the lumbosacral region**, has been shown to be **effective** in reducing severe back pain [27].

Neuraxial (regional) labor analgesia (epidural, spinal, or combined)

Background

Epidural, spinal, and combined spinal-epidural analgesia techniques are the most effective methods of providing pain relief to the laboring parturient. A large meta-analysis looking at over 300 studies comparing neuraxial analgesic techniques to a variety of other techniques, including systemic opioids, inhaled anesthetics, and nonpharmacologic agents, concluded that neuraxial techniques are superior to all other methods in terms of parturient pain relief [28]. In a jointly published opinion, both the ACOG and the American Society of Anesthesiologists (ASA) state: "In the absence of a medical contraindication, maternal request is

a sufficient medical indication for pain relief during labor" [29]. As labor results in severe pain for many women, neuraxial anesthesia, when available, should be offered to all women in labor, assuming no medical contraindication.

Overview of techniques

Neuraxial labor analgesia is also commonly called regional analgesia. It can be provided via the epidural space, the intrathecal (spinal) space, or both.

Medications injected into the epidural space have a relatively slow analgesic onset of 8–15 minutes. Block height is determined by the volume of medication injected into the epidural space. Injecting low-concentration local anesthetic produces analgesia, and injecting high-concentration local anesthetic produces anesthesia.

By contrast, medication injected into the intrathecal space has a quick onset of 2–5 minutes. Block height is determined primarily by the baricity (density relative to cerebrospinal fluid [CSF]) of the drug and, to some extent, the total volume of the drug.

Epidural analgesia

Technique

The epidural space is located using a loss of resistance (to air or saline) technique (Figure 12.1) [30]. A small catheter is placed into the epidural space through which local anesthetics and opioids can be intermittently injected (bolus) or given as a continuous infusion.

The most common local anesthetic choices include low-concentration, long-acting amides such as bupivacaine and ropivacaine in combination with a lipid-soluble opioid such as fentanyl and sufentanil. The addition of opioids to local anesthetics produces an additive effect that results in a lower concentration of local anesthetic being required to produce adequate labor analgesia. A lower concentration of local anesthetic increases maternal mobility and decreases the potential for maternal systemic toxicity. There is insufficient evidence comparing concentrations, type of anesthetic used, and several other technical aspects of epidural anesthesia in labor to recommend one specific drug combination [31, 32]; however, a meta-analysis of 23 randomized controlled trials comparing epidural ropivacaine and bupivacaine did not demonstrate significant difference between the two drugs in mode of delivery, maternal satisfaction or neonatal outcomes, although the incidence of motor blockade was less in the ropivacaine groups [33].

The epidural infusion rate can be controlled either by the anesthesiologist or by the patient. **Patient-controlled epidural analgesia** (PCEA) typically employs a background infusion of local anesthetic and opioid together with enabling the parturient to augment the infusion with a bolus dose every 10–15 minutes. This technique can also be used with a spinal catheter with appropriately reduced doses.

Indications

In its 2019 Practice Bulletin, *Obstetric Analgesia and Anesthesia*, ACOG confirmed an opinion published also by the ASA, which stated that "**in the absence of medical contraindication, maternal request is a sufficient medical indication for pain relief during labor**" [5]. However, numerous maternal conditions make neuraxial anesthesia the prudent choice. Examples of such conditions include anticipated difficult intubation, history of malignant hyperthermia, high risk for CD, the presence of a comorbidity that would benefit from the reduced catecholamine levels that result from adequate labor analgesia (e.g. selected respiratory or cardiac disease), and prophylaxis against autonomic hyperreflexia in the woman with a high spinal cord lesion. Functioning epidural catheters can also be used to provide anesthesia for instrumented delivery and extraction of a retained placenta.

In some cases, an epidural catheter can be intentionally inserted into the intrathecal space to provide continuous spinal analgesia. However, the resulting postdural puncture headache (PDPH) incidence may be high. Nonetheless, this risk may be acceptable in certain situations such as the presence of certain

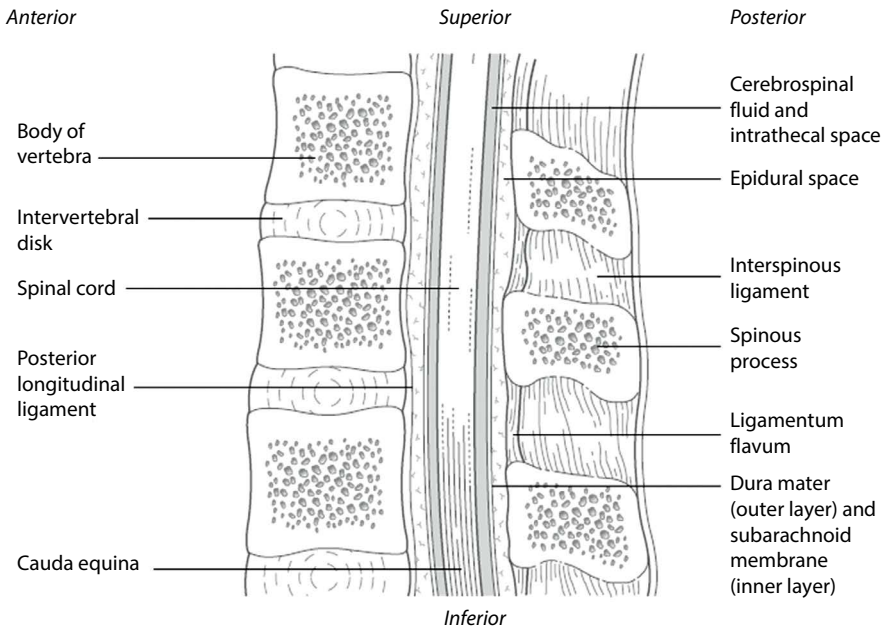


FIGURE 12.1 The epidural space. (From Pamela E. Macintyre and Stephan A. Schug, *Acute Pain Management: A Practical Guide*, Fifth Edition, CRC Press 2021, with permission.)

maternal comorbidities (typically cardiac), the morbidly obese parturient with an airway that appears extremely difficult or impossible to intubate, or following an inadvertent dural puncture during a difficult epidural placement.

Efficacy and advantages

Compared with nonepidural methods, epidural analgesia both reduces pain during labor and increases maternal satisfaction with pain relief. However, some women who undergo epidural versus nonepidural analgesia appear to have an increased incidence of assisted vaginal birth. These findings have not been seen in more recent studies, suggesting that modern approaches to epidural analgesia with lower concentration of local anesthetics do not affect this outcome [31]. In more than 85% of cases, the pain relief is optimal. **As labor results in severe pain for many women, and neuraxial analgesia is the most effective intervention to decrease or eliminate this pain, neuraxial analgesia should be offered, when available, to all women in labor (assuming no medical contraindication)**.

Compared with systemic opioids, **epidural anesthesia is associated with superior pain relief and lower risk of umbilical cord pH <7.20**. There is no evidence of a significant difference in the risk of CD. In addition, there is no evidence of a significant difference in the risk of long-term backache, and this did not appear to have an impact on neonatal status as determined by Apgar score or in admissions to neonatal intensive care [31]. No studies reported on rare but potentially serious adverse effects of epidural analgesia [31]. Neuraxial analgesia is the least depressant method of analgesia for the fetus/neonate, and it is important to note that initiation of breastfeeding is not affected by neuraxial analgesia.

Timing of initiation of neuraxial analgesia

There is no reason to delay epidural placement until an arbitrary cervical dilation has been reached. The traditional practice of delaying the placement of an epidural catheter until the cervix is dilated to 4–5 cm has been disproven. Data suggest that neuraxial analgesia can be offered as early as 2 cm or less without adversely affecting labor outcome or incidence of CD. Epidural placement at ≤2–5 cm is associated with similar maternal (instrumental delivery, CD, etc.) and neonatal outcomes compared with epidural placement at ≥3–5 cm in women in spontaneous labor or receiving oxytocin [34–38]. Subsequently, in the updated ACOG Committee Opinion, it is affirmed that early initiation of neuraxial analgesia does not increase the rate of CD [39]. Moreover in practice bulletin No. 209 *Obstetric Analgesia and Anesthesia* ACOG reaffirms that "consideration should be given to early placement of neuraxial catheter that can be used later for women undergoing labor after cesarean" [5].

The decision of when to place epidural analgesia should be made individually with each woman [5].

PCEA gives the patient control over her analgesia. Patients receive less local anesthetic overall (and therefore have less motor blockade) and receive fewer manual boluses from the anesthesiologist ("top-offs") [31, 40]. As patient satisfaction is high with epidural analgesia, PCEA is not associated with additional improvement in maternal satisfaction.

There is insufficient evidence to support the hypothesis that discontinuing epidural analgesia late in labor (e.g. at the beginning of the second stage) reduces the rate of instrumental delivery. There is evidence that it increases the rate of inadequate pain relief in the second stage of labor [41].

Safety, disadvantages, and complications

Compared with non-neuraxial analgesia, epidural analgesia is associated with an increased risk of mild maternal **fever, hypotension**, and **urinary retention; increased need for oxytocin administration; increased duration of the second stage by an average of 15 minutes; and increased risk of operative vaginal birth (forceps or vacuum-assist)** [31]. A recent noninferiority trial assessed the effects of routine epidural analgesia during labor versus epidural upon maternal request and suggests that routine epidural analgesia was associated with a statistically significant increase in the rate of operative deliveries (difference 8.1%, 95% confidence interval [CI] −0.01 to −16.3) [42].

The etiology of the occasional **increase in maternal temperature** associated with epidural use is uncertain. This effect can lead to increased maternal and neonatal antibiotic treatments, as well as neonatal sepsis evaluations, but with no difference in the corresponding rate of neonatal infection or sepsis [43]. In centers with structured protocols for neonatal sepsis workups, there are no increases in the incidence of neonatal sepsis workups in babies born to mothers with epidural analgesia.

The incidence of maternal **hypotension** following neuraxial analgesia during labor is approximately 14%. Hypotension is associated with an increased incidence of nonreassuring fetal heart rate tracing (NRFHT) that **rarely (1%–2%) necessitates** CD. Left uterine displacement should be maintained whenever possible, as it will increase maternal preload and increase uterine perfusion. Measures such as fluid preloading and concurrent administration of phenylephrine or ephedrine can mitigate or prevent maternal hypotension.

Although the risk of long-term **backache** in women who utilize epidural analgesia is similar to controls (IM meperidine), it is quite common for a woman to experience soreness or tenderness at the site of epidural insertion for 2–3 days [44].

Disadvantages of epidural analgesia include a slower onset compared with intrathecal (spinal) injection, incomplete blockade of pain (in about 10%–15% of patients), and inadvertent intrathecal or intravascular catheter placement. While the PCEA gives the patient more control and requires less intervention from anesthesiologists, this can lead to underdosing and therefore inadequate analgesia: for example, if the patient does not self-administer a bolus (if she is asleep) or if there is a pump malfunction.

Other complications include a 1%–2% chance of **PDPH** following accidental lumbar puncture and, rarely, epidural **hematoma, respiratory arrest** due to the unrecognized injection of an epidural dose of opioid into the intrathecal space, systemic local anesthetic toxicity due to unrecognized IV injection, or total spinal anesthesia from an unrecognized intrathecal injection of a dose of local anesthetic meant for the epidural space. See sections on spinal analgesia and anesthesia emergencies for further details on these complications and strategies for their prevention and treatment. **Women should be counseled about these risks before labor** [43].

Interventions to avoid some disadvantages and complications of epidural analgesia

Preloading with IV fluids to prevent hypotension: Preloading with IV fluids (500–1000 mL or weight-based formula 10–20 mL/kg) prior to traditional high-dose local anesthetic blocks may have some beneficial fetal and maternal effects in healthy women [45]. When using **low-concentration** analgesic solutions for epidural techniques, preloading with IV fluids is associated with **no significant difference in maternal hypotension**, although only a

very large effect was excluded. There is, however, a **trend toward less frequent fetal heart rate** abnormalities [45]; therefore, some fluid preloading may be beneficial.

Prophylactic ephedrine to prevent NRFHR: Compared with no ephedrine, ephedrine 10 mg IV bolus, followed by a 20-mg continuous infusion over 60 minutes, started in the first minutes after the epidural test dose significantly **decreases the incidence of NRFHT** from 15% to 3% [46]. However, this evidence is insufficient to make a recommendation.

In summary, epidural analgesia remains one of the most effective and safe methods of intrapartum analgesia, and, in most cases, maternal request for pain relief is sufficient indication for its placement. A lower-concentration local anesthetic (e.g. bupivacaine 0.0625%–0.125%) with the addition of a lipid-soluble opioid (fentanyl 1–2 mcg/mL) allows excellent analgesia while reducing the total dose of local anesthetic and minimizes the side effects (i.e. the severity of motor block). While there is no superior method of dosing (continuous infusion vs. PCEA), PCEA allows the patient to titrate the neuraxial blockade, which can result in less breakthrough pain. Epidural analgesia can be given in early labor (cervical dilation <4 cm) and does not increase the rate of CD or prolong the duration of labor.

Spinal analgesia

Technique

Using a small-bore spinal needle (typically a pencil-point design that minimizes trauma to the dura, thereby reducing the incidence of PDPH), a dural puncture is made and proper location confirmed by CSF aspiration (Figure 12.1). A single injection of an analgesic dose of an opioid such as fentanyl or sufentanil, with or without a local anesthetic such as bupivacaine or ropivacaine, is administered.

Indications

Indications for single-injection spinals include advanced labor where delivery is imminent, forceps deliveries in women without epidurals, and for patients with retained placentas.

Advantages

Advantages for single-injection spinals include ease and speed of onset, completeness of block, and lower incidence of PDPH compared with epidural analgesia.

Disadvantages and complications

The main disadvantage for single-injection spinals is an inability to redose.

Postdural puncture headache

PDPH occurs with a frequency of approximately 1%–2% after either spinal or combined spinal-epidural (CSE) analgesia when administered using a small-gauge pencil-point needle. PDPH is thought to be caused by leakage of CSF through the punctured dura. The leak of CSF and subsequent decreased spinal fluid pressure leads to downward traction or stretch on the meninges with resulting symptoms. PDPH is characterized by a positional frontooccipital headache that is exacerbated by the upright position (with gravity worsening stretch on the meninges), with improvement in symptoms when the patient is supine. Diplopia, tinnitus, nausea, and vomiting caused by stretch on the cranial nerves are also common symptoms. Although **pencil-point-design spinal needles have significantly reduced the incidence of PDPH following spinal analgesia**, there are no proven interventions to prevent PDPH following inadvertent dural puncture with an epidural needle. Conservative early interventions include **analgesics, supine positioning, caffeine, and hydration**. In about one-third of cases, the headache persists and is severe enough to require an epidural blood patch procedure. An epidural **blood patch** is performed by injecting 10–25 mL of autologous blood into the patient's epidural space at the level of the dural puncture using meticulous sterile technique. If the level of the dural puncture is unknown, a more caudad interspace should be chosen. After the procedure, the patient should rest in the supine position for 1–2 hours. Resolution of symptoms with blood patch occurs in 70%–85% of women. Expected side effects following epidural blood patch include transient backache and leg pain [47].

Respiratory depression or arrest

Respiratory depression or arrest due to intrathecal opioids occurs rarely: 1 in 5000–10,000 patients. Naloxone reverses this complication and should be readily available, along with airway management equipment, when administering labor analgesia.

Hematoma

Hematoma after epidural or spinal analgesia is an extremely rare complication of neuraxial anesthesia (1/150,000–250,000). Symptoms include bilateral leg weakness, urinary incontinence, and back pain. Prolonged motor paralysis without regression of block should raise suspicion. If suspected, the patient should undergo prompt definitive imaging (magnetic resonance imaging [MRI]) of her neuraxis, followed by surgical decompression after diagnosis. Surgical decompression within 6 hours following the onset of symptoms often prevents permanent neurologic injury. The risk of persistent neurologic injury from epidural is about 1/240,000 [30].

Combined spinal epidural

Technique (Figure 12.1)

The epidural space is identified with the loss-of-resistance technique. A spinal needle is then introduced into the intrathecal space. An intrathecal dose of local anesthetic and opioid is injected through the spinal needle, which is then removed, leaving the epidural needle in place. An epidural catheter is inserted, and an epidural local anesthetic and opioid infusion is started. The intrathecal dose generally lasts about 2 hours, after which the epidural catheter will provide continuous analgesia.

Indications

The CSE technique provides the benefit of immediate onset of spinal analgesia coupled with the indefinite duration of an epidural catheter technique. This technique is particularly useful for women in advanced labor requesting pain relief. There are data that associate CSE with an increased rate of cervical dilatation and shorter length of labor compared with both IV opioid and epidural analgesia [48–50]. Indications for a CSE are the same as those for both epidural and spinal techniques.

Advantages

Both CSE and epidural techniques provide effective pain relief in labor. The type of opioid and concentration of local anesthetic used in the CSE or epidural technique affect maternal mobilization and other outcomes more than the technique itself [51]. **A CSE results in faster onset of pain relief when compared to a traditional epidural** [52], and in a randomized controlled comparison of epidural and CSE analgesia, CSE may provide better subsequent labor analgesia with reduced need for

additional doses for breakthrough pain [53]. There is some evidence that CSE compared with an epidural is associated with a faster rate of cervical dilatation in nulliparous women less than 5 cm [49], and women close to imminent birth may benefit from the speed of onset a CSE offers. There is no difference in ability to mobilize, obstetric outcome, or neonatal outcome [51]. However, there is a statistically significant difference in risk of instrumental delivery between CSE and epidural analgesia, with CSE having decreased rates of instrumentation (relative risk [RR] 0.81; 95% CI 0.67–0.97) [51].

Disadvantages

The disadvantages of CSE are similar to epidural and spinal techniques. Although data are limited, no differences are reported between IV preloading and no preloading to prevent hypotension [45]. Women who receive intrathecal opioids experience **more pruritus** than with a standard epidural [51]. However, pruritus is quite common after both spinal and epidural opioids and results from mu-opioid receptor stimulation in the brainstem. Naloxone and nalbuphine are effective interventions. Diphenhydramine and other antihistamines are not effective in treating opioid-induced pruritus because opioids administered via the intrathecal or epidural route do not cause histamine release. **The significantly higher incidence of urinary retention, instrumental deliveries, and rescue analgesia interventions with traditional high-concentration epidurals would favor the use of low-dose epidurals** [51]. An additional disadvantage is that the correct placement of the catheter in the epidural space cannot be verified until the spinal analgesia regresses. It is not possible to draw any meaningful conclusions as to possible differences between CSE and epidurals in producing rare complications such as nerve injury and meningitis.

In summary, CSE is an ideal technique when rapid-onset analgesia with good sacral coverage in advanced labor is needed. In addition to rapid pain relief, an advantage of this technique is the visualization of CSF flow through the spinal needle, which can provide confirmation that the epidural space has been reached successfully. An additional benefit of a CSE is the block can be extended with the epidural catheter if the duration of the spinal anesthetic is inadequate.

Contraindications to regional anesthesia

Coagulopathy

A routine platelet count is not necessary before administering neuraxial analgesia in the healthy parturient; however, the decision to order a platelet count should be individualized and based on the patient's history, physical examination, and clinical signs [3]. Indications for platelet count may include hypertensive disorders of pregnancy, history of thrombocytopenia (gestational, immune thrombocytopenia [ITP]), abruption, and disorders of coagulation. Thrombocytopenia is a relative contraindication to neuraxial anesthesia, but a safe lower limit for platelet count has not been clearly defined. In the absence of disseminated intravascular coagulation (DIC), a platelet count of $\geq 100 \times 10^9$/L has historically been considered safe; however, there are no data to support a specific minimum platelet count for neuraxial anesthesia. The literature reports mostly retrospective data on this issue. In a recent retrospective cohort study of 84,471 obstetric patients from 19 institutions combined with a review of the medical literature suggests that epidural or spinal anesthesia is considered acceptable, and the **risk of epidural hematoma is low in patients with platelet counts of 70×10^9/L or more**, provided that the platelet count is stable and there is no other acquired or congenital coagulopathy, the platelet function is normal, and the patient is not receiving any anticoagulation [54, 55]. In a recent statement by the Society for Obstetric Anesthesia and Perinatology (SOAP) (endorsed by the American Society of Regional Anesthesia and Pain Medicine [ASRA], ACOG, and Society for Maternal-Fetal Medicine [SMFM]) through a systematic review and modified Delphi method, they concluded that **the risk of spinal epidural hematoma associated with a platelet count $\geq 70{,}000 \times 10^6$/L is likely to be very low** in obstetric patients with thrombocytopenia secondary to gestational thrombocytopenia, ITP, and hypertensive disorders of pregnancy in the absence of other risk factors [56].

Anticoagulation

Recently updated guidelines from the ASRA from 2018 address the use of neuraxial anesthesia in the setting of anticoagulation [57]. These updated guidelines now include prophylactic unfractionated heparin in the dosing regimens that are considered to increase the risk for major complications of neuraxial anesthesia. These new ASRA recommendations are reflected in the SOAP consensus statement from 2018 and the updated ACOG Practice Bulletin No. 196 *Thromboembolism in Pregnancy* [58, 59]. When administering any form of anticoagulation to a parturient, whether in the antepartum or postpartum period, in the setting of neuraxial anesthesia use, clinicians must be knowledgeable of these recommendations to minimize the risk of major complications from neuraxial anesthesia, including spinal epidural hematoma.

Intrapartum recommendations regarding thromboprophylaxis

These recommendations are adapted from the SOAP Consensus Statement on the Anesthetic Management of Pregnant and Postpartum Women Receiving Thromboprophylaxis or Higher Dose Anticoagulants) [58].

Low-dose aspirin

Women receiving prophylactic low-dose aspirin are not at increased risk for spinal epidural hematoma from neuraxial anesthesia.

Unfractionated heparin

For low-dose unfractionated heparin (UFH) thromboprophylaxis (i.e., 5000 U SQ twice daily or three times daily), consider holding the dose for 4–6 hours before placing the neuraxial anesthetic or assessing coagulation status as per ASRA recommendations.

For intermediate-dose UFH thromboprophylaxis (i.e., 7500 U SQ twice daily or 10,000 U SQ twice daily), consider holding the dose for 12 hours and assessing coagulation status before placing a neuraxial anesthetic.

For high-dose UFH thromboprophylaxis (i.e., individual dose >10,000 U SQ per dose, or >20,000 U SQ total daily dose), consider holding the dose for 24 hours and assessing coagulation status before placing the anesthetic.

For IV heparin, consider stopping the infusion for 4–6 hours and then assessing coagulation status before placing a neuraxial anesthetic.

Low-molecular-weight heparin

For low-dose low-molecular-weight heparin (LMWH) thromboprophylaxis (i.e., enoxaparin ≤40 mg SQ once daily or 30 mg SQ

twice daily, or dalteparin 5000 U SQ once daily), consider holding the dose ≥12 hours before placing a neuraxial anesthetic, as recommended by the Food and Drug Administration (FDA) and ASRA.

For intermediate-dose LMWH thromboprophylaxis (i.e. enoxaparin >40 mg SQ once daily or 30 mg SQ twice daily and <1 mg/kg SQ twice daily, or 1.5 mg/kg SQ once daily or dalteparin >5000 U SQ once daily and <120 U/Kg SQ twice daily, or 200 U/kg SQ once daily), there are insufficient published data to recommend a specific interval between 12 and 24 hours to wait before proceeding with neuraxial anesthesia.

For higher-dose LMWH (i.e. enoxaparin 1 mg/kg SQ twice daily or 1.5 mg/kg SQ once daily; dalteparin 120 U/kg SQ twice daily or 200 U/kg SQ once daily), consider holding the dose ≥24 hours before placing a neuraxial anesthetic as recommended by the FDA and ASRA.

General considerations

The safest way to prepare the pregnant patient on thromboprophylaxis for delivery is through advanced planning and thorough communication between the obstetric and anesthesia teams. Consideration should be given to converting women who require anticoagulation from LMWH to UFH as they approach term.

The coagulation status of parturients with medical conditions associated with coagulopathy, such as the HELLP syndrome (hemolysis, elevated liver enzyme levels, and low platelet levels), should be thoroughly evaluated before initiating a neuraxial block. Patients with thrombocytopenia should be examined for stigmata of coagulopathy (easy bruising, bleeding from the IV site, etc.) before instrumentation. A fibrinogen level and a D-dimer level are useful to assess the presence of DIC if suspected. A bleeding time is not indicated. Patients with known platelet dysfunction, including those on antiplatelet medication (e.g. clopidogrel), should not receive neuraxial analgesia. Aspirin therapy is considered an acceptable risk [57].

Infection

Systemic: Patients with suspected meningitis (bacterial or viral) or sepsis should not receive neuraxial blockade. Patients with suspected chorioamnionitis can receive neuraxial analgesia/anesthesia following the administration of appropriate IV antibiotics. Chronic herpes simplex virus (HSV) outbreak is not a contraindication to neuraxial techniques. However, a primary outbreak places the parturient at risk for herpetic viremia and the theoretical risk for central nervous system (CNS) infection and should be weighed against the risk of alternative methods of analgesia. HIV/AIDS is not a contraindication to spinal or epidural anesthesia or epidural blood patch.

Localized: Patients with localized skin or soft tissue infections should not be instrumented at those sites.

Anesthesia and maternal comorbidities

Hypertensive disorders

Advantages of neuraxial analgesia

Pregnant women with hypertension may benefit from neuraxial analgesia, as it may improve uterine perfusion through several pathways (localized neuraxial vasodilatory effect, reduced catecholamine release). **Neuraxial analgesia is the analgesia of choice in hypertensive pregnant women, as it allows clinicians to avoid the possibility of difficult intubation and the severe hypertension that accompanies endotracheal intubation**.

Disadvantages

Patients with gestational hypertension, preeclampsia, and eclampsia are at increased risk for hemodynamic instability during both labor and surgical anesthesia. Neuraxial techniques can be used safely with increased vigilance for maternal hypotension. In one focused review, marked hypotension after spinal anesthesia in women with preeclampsia did not occur, lending support to the safety of the technique in these women [60].

Women with preeclampsia may have thrombocytopenia, which increases the risk of neuraxial hematoma formation. A recently published SOAP consensus statement considers a platelet count above 70,000/mm^3 to be adequate for the administration of neuraxial anesthesia in patients with thrombocytopenia secondary to hypertensive disorders of pregnancy [56].

Cautions

Caution must be taken in fluid management in this patient population, as there is altered vascular leaking, decreased oncotic pressure, and a higher incidence of pulmonary edema. Also, there can be an exaggerated hypertensive response to ephedrine and phenylephrine. The prevention, rather than treatment, of hypotension has been associated with better outcomes for the fetus. Women with severe preeclampsia who must undergo general anesthesia are at risk for an exaggerated hypertensive response to intubation and often benefit from pretreatment with an antihypertensive such as labetalol immediately prior to induction. Treatment with magnesium sulfate for preeclampsia/eclampsia can potentiate neuromuscular blockade in patients receiving general anesthesia, so care must be taken when using nondepolarizing muscle relaxants.

Maternal cardiac disease

Heart disease in the parturient is the leading cause of maternal mortality outside of obstetric complications. Understandably, the risk increases with severity of maternal disease. The normal changes in maternal cardiac physiology resulting from pregnancy can either unmask subclinical disease or worsen clinical cardiac disease. Every effort should be made to care for these patients in facilities equipped to provide the multidisciplinary approach that is required to ensure the best possible outcome for mother and neonate. Goals of anesthetic management for parturients with heart disease are: (1) maintain a normal heart rate, sinus rhythm, and adequate systemic vascular resistance (SVR); (2) maintain intravascular volume and venous return; (3) avoid aortocaval compression; and (4) avoid myocardial depression during general anesthesia.

Valvular heart disease

Patients with acquired valvular disease (rheumatic fever, mitral valve prolapse, artificial valves, and endocarditis) are at increased risk for arrhythmias, pulmonary edema, and cardiac ischemia from the increased heart rate, cardiac output, metabolic demand, and decreased oxygen reserve associated with pregnancy and the pain of labor. Patients with arrhythmias or artificial valves may also be on heparin or LMWH.

Advantages of neuraxial analgesia: Epidurals and CSE block the pain and stress of contractions, therefore reducing tachycardia and increased cardiac output. Ablation of the bearing-down reflex can be advantageous in patients with aortic or mitral regurgitation.

Disadvantages: Hypotension is the largest disadvantage with neuraxial analgesia; even transient hypotension can lead to

coronary hypoperfusion, ischemia, arrhythmias, or arrest. This is especially dangerous in patients with moderate to severe aortic stenosis. However, parturients with aortic stenosis have safely undergone both neuraxial labor analgesia and anesthesia for CD. Meticulous anesthetic technique and allowing adequate time to slowly administer the requisite medication is the key to safe provision of neuraxial anesthesia in these patients. Inadvertent IV injection of local anesthetics is also a significant risk in patients with underlying arrhythmias due to impairment of cardiac automaticity and conduction (especially with bupivacaine).

Congenital heart disease

Women with congenital heart disease (e.g., tetralogy of Fallot, hypoplastic left ventricle, transposition of the great vessels, and septal defects) are now surviving to childbearing years. Depending on the adequacy of their surgical repair, pregnancy may or may not severely affect these patients with underlying cyanotic heart disease. The increased cardiac output, oxygen consumption, changes in systemic and pulmonary resistance, and aortocaval compression can exacerbate preexisting right-to-left shunts, increasing the risk of maternal cyanosis and death.

Advantages of epidural analgesia: Although the hypotension of large-dose spinal anesthesia can be associated with risk of shunting and cyanosis, slowly administered epidural, low-dose spinal, and continuous spinal analgesia are advantageous to these patients by reducing catecholamine levels and preventing maternal expulsive reflexes. Additionally, if an instrumented delivery or CD is required, a surgical anesthetic level can be slowly produced, avoiding the risks of general anesthesia in these patients.

Disadvantages: The largest disadvantage of neuraxial analgesia is the risk of hypotension. Hemodynamic management of these patients should be aggressive and tailored to the underlying cardiac defect.

Previous lumbar surgery

Previous lumbar surgery (e.g., discectomy, placement of Harrington rods) is not a contraindication for lumbar epidural or spinal analgesia or anesthesia. One case series found that successful block can be achieved, although at a lower rate (55%) than in the control population. There were no cases of spine infection, low back pain, or headaches [61].

Maternal obesity

The incidence of maternal obesity has been rapidly increasing worldwide. Obese parturients have higher rates of hypertension, diabetes, preeclampsia, chorioamnionitis, and cesarean section compared with normal-weight women. Obese patients are also more at risk for hypoventilation and apnea after administration of opioids, complicating postpartum and postoperative pain control. Relative immobility also increases the risk of thromboembolic events [62]. Most importantly, obesity increases the risk for death during pregnancy. The report of *Confidential Enquiries into Maternal Deaths in the United Kingdom* for the 2006–2008 triennium showed that 49% of maternal deaths were overweight or obese [63]. The risks of low Apgar scores, neonatal intensive care unit admission, fetal death, and perinatal death are increased [64]. Respiratory, gastrointestinal, and anatomic changes of pregnancy significantly increase the **risk of a failed intubation and aspiration, which is as high as 15%–33% in obese pregnant women**. Venous access can be difficult, increasing the need for central venous access. Bony landmarks and increased adipose and soft tissue can complicate placement of neuraxial analgesia and anesthesia with initial **epidural failure as high as 42%**. Despite this increase in technical difficulty, neuraxial anesthesia is the technique of choice in the obese parturient.

Cesarean delivery anesthesia

Current guidelines recommend a fasting period for solids of 6–8 hours prior to scheduled CD. Parturients without complications may drink clear liquids for up to 2 hours before induction of anesthesia for planned CD [3]. For laboring patients with additional risk factors (i.e. morbid obesity, diabetes mellitus) or patients at increased risk for CD (NRFHR pattern), consider further restrictions of oral intake [3]. See also Chap. 8 for food intake in labor.

Epidural

Epidural anesthesia can be used for CD and for most urgent or emergent deliveries if a functioning catheter is in place. Patients with existing labor epidurals can have their block extended to an adequate level for surgery using a large volume of high-concentration local anesthetic solution containing opioids and epinephrine (which is thought to produce analgesia via α2 receptors in the spinal cord).

Advantages

There are numerous advantages to using epidural anesthesia for CD, including avoiding instrumentation of the maternal airway, the ability to redose the epidural in the event of a delayed or prolonged surgery, the ability to administer long-acting epidural opioids to augment postoperative pain control, and the avoidance of a dural puncture. Opioids administered via the neuraxial approach are associated with a 35%–55% incidence of maternal pruritus severe enough to require treatment [65]. An additional advantage is that the patient is awake and can experience the birth. The epidural catheter should be removed after 24 hours to reduce urinary retention, pruritus, and infection risks.

Disadvantages

Disadvantages of an epidural for CD include longer onset time for surgical block compared with spinal anesthesia and the possibility of incomplete or patchy block, making epidural anesthesia a less attractive option than spinal anesthesia in emergent situations (when an epidural catheter is not already in place). The higher doses of local anesthetics used in epidural blocks (compared with spinal) increase the risk of maternal systemic toxicity.

Spinal

Spinal anesthesia can be used for both planned CDs and in most emergencies. Intrathecal opioids can be added to augment postoperative pain control.

Advantages

Spinal anesthesia is a reliable form of anesthesia that is technically easier to perform and produces adequate anesthesia significantly faster than epidural anesthesia [66]. Other advantages are its simplicity, lower drug doses, and superior abdominal muscle relaxation. **Compared with epidural, spinal technique is associated with similar failure rate, need for additional intraoperative analgesia, need for conversion to general anesthesia intraoperatively, maternal satisfaction, need for postoperative pain relief, and neonatal intervention** [66]. Compared with epidural, spinal anesthesia for cesarean section is associated with

reduced time, by about 8 minutes, from start of the anesthetic to start of the operation.

Compared with general anesthesia, women with neuraxial anesthesia have less intraoperative blood loss but significantly more nausea. In a review of randomized clinical trials, no differences in umbilical cord arterial blood pH were found among general and neuraxial anesthetic techniques [67].

Disadvantages

Hypotension, possibly profound, is increased in incidence 23% with spinal versus epidural anesthesia [66]. A number of strategies can be used to mitigate hypotension. No intervention reliably prevents hypotension due to spinal anesthesia for CD, but five interventions have been found to reduce the incidence of hypotension: (1) **crystalloid** preload, (2) **preemptive colloid administration**, (3) **ephedrine**, (4) **phenylephrine**, and (5) **lower limb compression** [45, 68, 69]. No differences were detected for different doses, rates, or methods of administering colloids or crystalloids. High doses of ephedrine may increase the incidence of hypertension and tachycardia and are associated with fetal acidosis of uncertain clinical significance. Patients who receive intrathecal bupivacaine with prophylactic IV phenylephrine infusion have less hypotension than those without phenylephrine [68]. One systematic review showed that **phenylephrine** is as safe as ephedrine; in fact, fetal pH is higher and the incidence of maternal nausea is lower with phenylephrine [70]. Given the efficacy of phenylephrine and better umbilical cord pH, many anesthesia providers now use phenylephrine as a first-line agent for the treatment and prevention of maternal hypotension. Different methods of compression appeared to vary in their effectiveness. In summary, **interventions such as crystalloids, colloids, ephedrine, phenylephrine, or lower-leg compression can reduce the incidence of hypotension**, but none have been shown to eliminate maternal hypotension during spinal anesthesia for CD.

Limited duration is another disadvantage of spinal anesthesia. CSEs and spinal catheters combine the advantages of the rapid onset of spinal anesthesia with the ability to redose in the case of prolonged surgical time.

The rate of **PDPH** after spinal anesthesia ranges between 1.5% and 11.2%. To reduce this risk, this technique should be performed using a small-gauge (24 g or smaller), pencil-point spinal needle when possible.

In summary, both spinal and epidural techniques are shown to provide effective anesthesia for cesarean section. Both techniques are associated with moderate degrees of maternal satisfaction. Spinal anesthesia has a shorter onset time, but treatment for hypotension is more likely if spinal anesthesia is used. Because of its safety and effectiveness, **spinal anesthesia has evolved as the regional technique of choice for CD** due in particular to rapidity of anesthetic onset, quality of anesthesia, and ease of performance of block.

General anesthesia

While neuraxial techniques are clearly the preferred anesthetic for CD, general anesthesia is indicated in the case of failed regional anesthesia, an obstetric emergency preventing placement of a neuraxial technique, a contraindication for regional anesthesia, or objection by the patient to regional anesthesia.

Precautions

If a general anesthetic is chosen, patients must receive aspiration prophylaxis that may include a nonparticulate oral antacid within 30 minutes of surgery and/or metoclopramide. Time permitting, an H2 blocker can be given 30–50 minutes before induction of anesthesia to confer additional protection. Airway protection with **endotracheal intubation** is mandatory.

There is insufficient evidence to assess prevention of aspiration during general anesthesia. When compared with no treatment or placebo, there is a significant reduction in the risk of intragastric pH <2.5 with antacids, H2 antagonists, and proton pump antagonists [71]. H_2 antagonists are associated with a reduced risk of intragastric pH <2.5 at intubation when compared with proton pump antagonists, but compared with antacids, the findings were unclear. The combined use of "antacids plus H2 antagonists" is associated with a significant reduction in the risk of intragastric pH <2.5 at intubation when compared with placebo or compared with antacids alone (RR 0.12, 95% CI 0.02–0.92, 1 trial, 119 women). In general, the quality of the evidence is insufficient to make a recommendation. None of the studies assessed potential adverse effects or substantive clinical outcomes [71].

Advantages

There are *few advantages* to general anesthesia in the absence of a contraindication to a neuraxial approach. One possible advantage is the relaxation properties halogenated anesthetics have on uterine muscle. This property can be useful in the management of uterine inversion, fetal entrapment, or retained placenta. IV nitroglycerine and terbutaline are other options in these situations.

Disadvantages

Compared with neuraxial anesthesia, general anesthesia is associated with a threefold risk of maternal death [72]. The **greatest risk is from the inability to intubate or ventilate the patient**. Parturients have increased upper airway edema, lower pulmonary functional residual capacity, increased metabolic oxygen consumption, decreased lower esophageal sphincter tone, and delayed gastric emptying. These conditions increase the risk of both hypoxemia and aspiration. Airway edema can also make anesthetizing the airway for awake fiber-optic intubation more difficult. The incidence of failed intubation in the obstetric population is approximately 1 in 300, nearly eight times that of the general population [72, 73].

CD is considered a high-risk procedure for intraoperative recall. Concern about neonatal depression and uterine atony has led to minimal use of benzodiazepines and low-dose intraoperative halogenated anesthetics intraoperatively. **Compared with nonobstetric surgery, the risk of maternal awareness under general anesthesia is increased (0.4% vs. 0.2% for nonobstetric surgery)** [74]. Although benzodiazepines and opioids can depress the fetus, they are pharmacologically reversible, and administration should be considered if their use would benefit the mother. For instance, the judicious use of preintubation opioids can be considered to blunt the sympathetic response to direct laryngoscopy in the hypertensive parturient. The ultra-short-acting synthetic opioid remifentanil can provide this benefit with minimal effect on the neonate.

General anesthesia is also associated with **higher incidence of postoperative nausea and vomiting, maternal sedation, and increased time to breastfeeding**.

General anesthesia's **effect on the fetus** depends on the length of time from induction to umbilical cord clamp; length of time from hysterotomy to cord clamp is also important. Fetal exposure to inhaled anesthetics of >5–8 minutes is associated with **neonatal depression**. General anesthesia compared with neuraxial

anesthesia has been shown to increase the incidence of **fetal acidosis, drug exposure, and lower Apgar scores**. IV induction agents, opioids, and hypnotics readily cross the placenta, while neuromuscular blocking agents do not [75].

Post–vaginal delivery analgesia

After a vaginal delivery, women may experience pain from uterine cramping or perineal laceration. Typical first-line analgesic methods include abdominal heating pads for uterine cramps, perineal ice packs, and topical lidocaine applied to the perineum. The data to support these methods is limited [76–78]. Oral analgesics such as nonsteroidal antiinflammatory drugs (NSAIDs) and acetaminophen may be used as needed or scheduled. NSAIDs have been shown to be superior to acetaminophen [79]. Oral or IV opioids should be reserved for severe or breakthrough pain, and these medications should be limited to the lowest effective dose for the shortest necessary duration.

Post-CD analgesia

Pain management following CD is important for patient and provider experiences, bonding with the newborn, minimizing the risk of postpartum depression, and improving breastfeeding [80–82]. However, studies have shown that a significant number of women become persistent users after opioid prescription at the time of CD [83]. Optimizing alternative analgesic methods after CD is therefore a priority. Preservative-free **morphine** hydrochloride administered **at the time of spinal** anesthesia **or** following cord clamp when using **epidural** anesthesia provides effective pain relief in the first 12–24 hours after surgery and has been shown to limit opioid use in this period [5, 84].

For patients unable to receive regional anesthesia with long-acting opioids**, the transversus abdominis plane (TAP) block** may be utilized. It is performed by injecting local anesthetic between the internal oblique and transversus abdominis muscles to block the plexus of nerves supplying the anterior abdominal wall. In a randomized controlled trial comparing intrathecal opioid to TAP block after CD, intrathecal opioid was superior, and patients receiving TAP block had increased opioid consumption in the immediate postoperative period [85]. The TAP block is a reasonable alternative in a patient with a contraindication to a neuraxial block [86, 87].

Following surgery, **scheduled NSAIDs and acetaminophen** have been shown to decrease opioid use and improve pain scores [88–90]. While the optimal dose and route of these medications are unclear, IM or IV administration of NSAIDs does appear to be more effective than oral administration [91]. Acetaminophen may also be administered intravenously, although there is conflicting data on the efficacy of the IV route when compared to oral or rectal administration [92–96]. Because IV acetaminophen is significantly more expensive than other formulations, many institutions opt to use oral acetaminophen. In general, medications that combine acetaminophen with an opioid should be avoided. Compared to scheduled acetaminophen, combination medications, such as oxycodone-acetaminophen (Percocet), have been shown to increase opioid consumption overall [97], and such medications are known to have higher associated street value, making them more prone to abuse by other community members.

Opioids should be reserved for breakthrough pain that is not controlled with around-the-clock acetaminophen and NSAIDs. In general, the **lowest possible dose of opioids, if needed, should be used on an as-needed basis, and these medications should be administered orally if the patient is able to tolerate oral intake**. Women should be aware of an FDA advisory warning not to breastfeed when using tramadol or codeine [98]. Opioid PCA may be required by some individuals, such as in cases where regional anesthesia with a long-acting opioid was not used. An opioid PCA is not required for most patients and should not be the default order in the postoperative period.

These methods may not be effective for adequate post-cesarean pain control in some situations. This includes women with allergies to NSAIDs and acetaminophen, women with substance use disorder, and those undergoing cesarean hysterectomy. **Ketamine** is an adjunct that has been shown to improve postoperative pain scores and decrease opioid use that may be used when pain is not optimally controlled [99]. Additional analgesics, such as a **lidocaine patch, pregabalin, and gabapentin**, are also options; however, there are limited data on their efficacy following CD [100–103]. Finally, an epidural catheter may be left in place for women at risk of poor pain control or those undergoing more extensive surgery. This can be titrated for an analgesic effect, rather than anesthesia.

Anesthetic emergencies

An anesthetic emergency in the obstetric patient necessitates clear and precise communication and cooperation between the anesthesia and obstetric teams. The goal is to stabilize the mother while, if necessary, safely and quickly delivering the neonate.

Total spinal

A total spinal occurs with cephalad spread of local anesthetic to the breathing centers of the brainstem. This can result from unintentional intrathecal placement of an epidural dose of local anesthetic or from subdural catheter placement with subsequent migration of the catheter. Agitation, difficulty speaking, and profound hypotension are signs of a total spinal. Control of the airway with endotracheal intubation, blood pressure support with fluid, vasopressors, and left uterine displacement should be performed immediately. Once the airway has been secured, assessment of the fetus should be facilitated. If the fetus is stable, delivery can safely await maternal recovery.

Local anesthetic systemic toxicity

IV injection of local anesthetics can lead to systemic toxicity, including seizures and cardiovascular collapse. The mother's airway should be controlled immediately, and delivery of the fetus is often indicated because of maternal instability. Seizures can be quickly terminated with administration of diazepam. The pharmacologic treatment of local anesthetic systemic toxicity (LAST) is different from other cardiac arrest scenarios. Management of cardiac arrest includes treatment according to the American Heart Association/Advanced Cardiac Life Support (AHA/ACLS) guidelines with adjustment of medications and possibly prolonged effort as per ASRA guidelines [104]. Administration of Intralipid, a 20% fat emulsion, has been shown to increase the survival rate of patients who experience cardiac arrest secondary to LAST [104, 105].

Failed intubation

The risk of failed intubation is increased in the parturient at approximately 1 in 300—nearly eight times that of the general population (1:2330) [72, 73]. Increased edema in the upper airway, increased breast size, and increased friability of the mucosa increase chance of failure. In addition, parturients have

decreased functional residual capacity that decreases their apneic oxygen reserve and are at higher risk for aspiration secondary to decreased gastric emptying and increased abdominal pressure. In patients where intubation was difficult, it is important to note that emergence is an equally high-risk event. This is emphasized by the number of anesthetic deaths in parturients involving loss of airway, the majority of which occurred during emergence from anesthesia or in the postanesthesia period [106]. Open communication between the obstetric team and anesthesia team is crucial, and all decisions should incorporate multidisciplinary communication and cooperation.

Maternal hemorrhage, resuscitation, and massive transfusion

Maternal hemorrhage can lead to exsanguination and the need for massive transfusion, defined as the need for 10 or more units of packed red blood cells (PRBCs) in 24 hours. Volume resuscitation with crystalloid, nonbiologically active colloid, and PRBCs can lead to a dilutional coagulopathy necessitating the transfusion of clotting factors and platelets. Recent retrospective studies from both military and civilian trauma have shown improved outcomes using an empiric ratio of fresh frozen plasma:red blood cells (FFP:RBCs) 1:1 in settings that require massive transfusion. Cryoprecipitate may also be needed in patients with low fibrinogen levels. Parturients may acquire a dilutional thrombocytopenia; thus, transfusion of platelets may also be warranted; however, the optimal ratio of platelet units to other factors is not known. Risks of massive transfusion include transfusion reactions, viral infection, fluid overload, pulmonary edema, and transfusion-related acute lung injury (TRALI) [107]. Intraoperative cell salvage is an addition to the previous armamentarium and is gaining acceptance. The ASA Practice Guidelines on Obstetric Anesthesia recommend "in case of intractable hemorrhage when banked blood is not available or the patient refuses banked blood, intraoperative cell salvage should be considered if available" [3].

Cardiopulmonary resuscitation in the pregnant patient

Cardiac arrest during late pregnancy occurs in approximately 1 in 30,000 pregnancies. ACLS protocols apply to pregnant women with a few important adjustments. Pregnant women should be intubated promptly to facilitate oxygenation and protect the airway from aspiration. Left uterine displacement is essential to relieve aortocaval compression. The AHA states the resuscitation team leader should consider delivery of the fetus after 4 minutes to improve cardiopulmonary resuscitation of the mother by relieving aortocaval compression [108]. The AHA further notes improved survival for infants occurs when the delivery occurs no more than 5 minutes after maternal cardiac arrest [108].

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13

OPERATIVE VAGINAL DELIVERY

Adeeb Khalifeh and Megan Piacquadio

Key points

- **Vacuum- and forceps-assisted deliveries** have the **same indications**. There are **no circumstances where operative vaginal delivery is definitely indicated**. Alternatives, including allowing the patient to labor longer, oxytocin augmentation, and cesarean delivery, should always be considered.
- **When used by experienced operators, operative vaginal delivery is safe for both mother and baby** and **effective in obtaining vaginal delivery**, with **forceps having slightly higher success rates**.
- Ultrasound before operative vaginal delivery is more accurate than digital examination (>99% versus 80% accuracy, respectively).
- **Forceps achieve a vaginal delivery more often than vacuum, 91% versus 86%, respectively. Complication rates differ between vacuum and forceps**, with the predominant differences being that **maternal third- and fourth-degree perineal (14% versus 7.5%) and vaginal wall (26% versus 8%) injuries are more common with forceps-assisted delivery. Neonatal facial injury is uncommon with operative delivery, 1.7% with forceps and 0.2% with vacuum**. The choice of instrument is decided after appropriate counseling and depends also on operator experience.
- There is insufficient evidence to compare different types of forceps.
- **Soft vacuum cups fail at attaining vaginal delivery more often than by rigid cups** but have a lower rate of significant fetal scalp trauma. Rigid cups may be better for occiput posterior and other more difficult deliveries, while soft cups may be better suited for less complicated, routine deliveries.
- If attempted, **delivery with a vacuum should ideally be achieved within 5 minutes from vacuum application** and, in general, should be **discontinued if the vacuum cup pops off the fetal head three times**.
- **Attempting to use a different extraction instrument after failing with one should be avoided due to increased incidence of fetal injury**.

Historical perspectives

Operative vaginal delivery (OVD) has been practiced for centuries. Its initial function was fetal extraction during prolonged dysfunctional labor in an attempt to preserve the life of the laboring woman. The invention of modern forceps can be traced back to the Chamberlain family in Europe during the 16th century. Vacuum extraction was first described by Dr. James Yonge in 1705. The modern evolution of vacuum delivery (also called ventouse) can be attributed to Malmström's metal cup vacuum system developed in 1954. OVD has evolved significantly and today implies a mechanism for facilitating vaginal delivery of a healthy infant while minimizing maternal risk.

In modern obstetrics, OVD, whether forceps or vacuum, is used to expedite safe vaginal delivery for maternal or fetal indications. Despite wide variations in different countries [1], in appropriate circumstances, OVD has a crucial role in safely avoiding primary cesarean delivery (CD). Emphasis should be placed on indications, contraindications, and prerequisites for an OVD, with instrument choice based on clinical circumstances and operator skill to minimize maternal and neonatal morbidity.

Incidence

Rates of OVD (forceps and vacuum) have been declining in the United States. The rate of OVD decreased from 9.01% in 1992 to 3.30% in 2013. In 2013, forceps-assisted deliveries accounted for only 0.59% of live births [2].

Indications

Both forceps and vacuum have the same indications. Use should depend mostly on proper evaluation of the patient's labor, risk factors, clinical pelvimetry, estimated fetal weight, and operator experience. There are **no circumstances where OVD is definitely indicated. Alternatives, including allowing the patient to labor longer, oxytocin augmentation, and CD, should always be considered**. OVD is usually considered for the following [3]:

- Maternal:
  - **Prolonged second stage**: At least 3 hours in nulliparous women and at least 2 hours in multiparous women (longer duration are possible on individualized basis, e.g. with the use of epidural analgesia) [4] (See also Chap. 9)
  - **Shortening of the second stage of labor for maternal benefit (e.g. underlying medical condition precluding pushing)**
  - **Inefficient maternal effort** (e.g. exhaustion or underlying medical condition precluding pushing)
- Fetal:
  - **Suspicion of fetal compromise**

"Elective" forceps delivery, that is, without an indication, is associated with increased maternal perineal trauma and, given the other potential maternal and neonatal complications, should not be preferred to spontaneous vaginal delivery [5].

Contraindications to operative vaginal delivery

Contraindications to OVD are listed in Table 13.1. Severe scalp trauma and unexplained active bleeding may be relative contraindications in individual cases. OVD should be used with

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TABLE 13.1: Contraindication to Operative Vaginal Delivery

- Nonvertex presentation
- Unengaged fetal head
- Unknown fetal head position
- Fetal prematurity such as <34 weeks (vacuum)
- Known fetal coagulation disorders (e.g. hemophilia, NAIT, von Willebrand disease)
- Known fetal bone demineralization conditions (e.g. osteogenesis imperfecta)

Source: From data in Ref. [3].
Abbreviation: NAIT, neonatal alloimmune thrombocytopenia.

extreme caution in women with maternal diabetes, prolonged labor, and fetal macrosomia, with appropriate preparations due to an increased risk of shoulder dystocia.

Risks for failed operative vaginal delivery

Risks for failed vacuum or forceps vaginal delivery include increased maternal age, increased body mass index, diabetes, polyhydramnios, macrosomia, occiput posterior (also increases rates of third- and fourth-degree perineal lacerations), dysfunctional labor, and prolonged labor [6, 7].

Classification of operative vaginal delivery [3]

- **Outlet:** Scalp is visible at introitus without separating the labia, fetal skull has reached pelvic floor, sagittal suture is anteroposterior (AP) diameter or right or left occiput anterior or posterior position, fetal head is at or on perineum, and rotation ≤45 degrees.
- **Low:** Leading point of the fetal skull is at station ≥+2 cm and not on the pelvic floor, rotation is ≤45 degrees (left or right occiput anterior to occiput anterior or left or right occiput posterior to occiput posterior), or rotation is >45 degrees.
- **Mid:** Station is above +2 cm but head is engaged.

Originally devised for forceps, this classification is valid for any OVD, including vacuum [8].

Types of forceps

There are many different designs for forceps, but all consist of two separate halves that each have the same four basic components: Blade, shank, lock, and handle. **There is insufficient evidence to compare different types of forceps, and it is recognized that the choice is often subjective**. In the only small trial performed, severe facial abrasion was decreased from 4.1% to 1.9% from the regular forceps compared with soft forceps, as were minimal markings (from 61% to 34%, respectively) [9]. Unfortunately, successful delivery rates for the two different forceps were not reported, and the soft forceps were self-made. Given the paucity of data, **choice of forceps type is operator dependent**.

- **Classical forceps:** These have cephalic and pelvic curvatures. Usually indicated when no rotation of the fetal head is necessary before delivery. Common types include the following: Simpson forceps (fenestrated blades and nonoverlapping shanks), Tucker-McLane forceps (nonfenestrated blades and overlapping shanks), and Elliot forceps (fenestrated blades, overlapping shanks, and largest cephalic curvature). Many of these forceps have been modified with a Luikart pseudofenestration of the blade.
- **Rotational forceps:** These have a cephalic curvature but lack a pelvic curvature. Also have a sliding lock to allow forceps to slide to correct asynclitism of the fetal head if present. After rotation of the fetal head is accomplished, classical forceps should be used to complete the delivery. Types include Kielland, Luikart, Barton, and Salinas forceps.
- **Forceps for breech delivery:** These are indicated to help with the aftercoming head in a breech delivery. These forceps lack a pelvic curvature and have blades that are beneath the plane of the shank. Types include Piper and Laufe forceps.

Types of vacuum extractors

Vacuum extractors were originally designed with a rigid metal cup. Subsequently, soft cups have been developed. **Several types of rigid (metal or plastic) and soft (silicone plastic or rubber) vacuums are in clinical use** [10–12]. Among different types of vacuums, **the metal cup is more likely to result in a successful vaginal birth** than the soft cup (9% versus 17%), with **more cases of scalp injury** (41% versus 30%) **and cephalohematoma** (14% versus 8%). The handheld ventouse is associated with more failures than the metal ventouse and a trend to fewer than the soft ventouse [10–13].

Rigid cups may be better for occiput posterior and other more difficult deliveries, while **soft cups are better suited for less complicated, routine deliveries** [10]. Maternal injury, low Apgar scores at 1 or 5 minutes, umbilical artery pH <7.20, hyperbilirubinemia/phototherapy, retinal/intracranial hemorrhage, and perinatal death do not differ between soft and rigid vacuum cups [10, 13]. Soft vacuum cups have largely replaced the rigid cup in routine clinical practice. For a comprehensive review of vacuum delivery, see Ref. [14].

Possible complications of operative vaginal deliveries

1. **Maternal**
   - **Forceps** use is associated with a **sixfold increase in third- and fourth-degree perineal tears** compared to a spontaneous vaginal delivery [15].
   - **Vacuum** use is associated with a **twofold increase in third- and fourth-degree lacerations compared to spontaneous vaginal deliveries** [15].
   - **Forceps delivery** has an increased risk of **anal sphincter injury compared to vacuum delivery** [10].
   - **Urinary, flatus, liquid, and solid incontinence is similar at 1 year in women who had OVD compared to women who had a second-stage CD** [16].
   - **Pelvic floor and sexual function do not differ at 1 year postpartum compared to women who had CD** [17].
   - **In the absence of anal sphincter injury, anal incontinence rates at 5–10 years are similar to those in women who had a spontaneous vaginal delivery** [18].
2. **Neonatal**
   - **Intracranial hemorrhage** rate is increased in OVD, but the absolute risk is low [19].
   - **The rates of intracranial hemorrhage and neonatal encephalopathy compared to second-stage CD are similar** [19, 20].

- **Cephalohematoma, fetal scalp lacerations, retinal hemorrhages, subgaleal hematoma, and intracranial hemorrhages** have been reported in **vacuum deliveries**.
- **Facial lacerations, facial nerve palsy, and corneal abrasion** are more common **with forceps delivery**.
- **Long-term cognitive outcomes are similar to spontaneous vaginal deliveries** [21, 22].
- **Recent data show that the duration of OVD, more specifically vacuum duration, is correlated to a greater risk of adverse neonatal outcomes** [23].

Comparison of forceps- versus vacuum-assisted delivery [10]

Safety/Complications

Maternal

- **There is a trend for less regional (37% versus 40%) and significantly less general anesthesia (1% versus 10%) with vacuum-assisted** compared to forceps-assisted deliveries. We do not use general anesthesia for operative delivery.
- **Third- and fourth-degree perineal** (14% versus 7.5%; relative risk [RR] 1.89, 95% confidence interval [CI] 1.51–2.37) **and vaginal wall lacerations** (26% versus 8%; RR 2.48, 95% CI 1.59–3.87) **(maternal trauma) are significantly increased with forceps** compared with vacuum.
- **Severe perineal pain at 24 hours is decreased (9% versus 15%) with vacuum-** compared to forceps-assisted deliveries.
- Flatus incontinence or altered continence is more common with forceps compared to vacuum in a small trial (59% versus 33%; RR 1.77, 95% CI 1.19–2.62). **In one randomized controlled trial (RCT) comparing forceps and vacuum delivery, there was no difference in either bowel or urinary dysfunction 5 years postpartum** [24].
- Rates of moderate/severe pain at delivery, endoanal ultrasound abnormalities [24], and other maternal outcomes are similar.
- Rotational forceps does not increase adverse maternal outcome compared to rotational vacuum delivery [25].

Fetal/Neonatal

- **Facial injury** is more likely with **forceps** (1.7% versus 0.2%; RR 5.10, 95% CI 1.12–23.25).
- Using a random effects model because of heterogeneity between studies, there was a trend toward **fewer cases of cephalohematoma with forceps** (5% versus 9%; RR 0.64, 95% CI 0.37–1.11). Rates of cephalohematomas occur in about 10% versus 4% in vacuum and forceps, respectively [10]. Cephalohematomas have an overall rate of 2.5% in the general population [26]. However, the diagnosis of cephalohematoma can be falsely positive in up to 75% of cases [27].
- **Retinal hemorrhages** tended to be **less common in forceps** than vacuum deliveries (5% versus 8%; RR 0.68, 95% CI 0.43–1.06) [12]. One study found retinal hemorrhages occurred in 18% in spontaneous vaginal deliveries [28]. The clinical significance of retinal hemorrhages remains unclear [26].
- Rates of scalp/face injury other than cephalohematoma, use of phototherapy, perinatal death, readmission to hospital, and hearing or vision disability are similar between forceps- and vacuum-assisted vaginal deliveries [10, 29].
- Other possible uncommon fetal complications associated with OVD include facial nerve injury, corneal abrasions, facial bruising, and lacerations. Very rare findings include facial nerve palsy, skull fractures, cervical spine injury, and intracranial hemorrhage. **With vacuum-assisted delivery,** life-threatening neonatal injuries include **subgaleal (subaponeurotic) hematoma** (0%–4%). **Intracranial hemorrhage** is a **rare** complication of OVD (0%–2.5%).

Efficacy

Both vacuum- and forceps-assisted delivery have high delivery success rates (with vacuum from 83% to 94% and with forceps from 78% to 92%) [10, 27]. **Forceps are less likely than the vacuum to fail to achieve a vaginal birth with the allocated instrument** (9% versus 14%; RR 0.65, 95% CI 0.45–0.94) [10].

CD occurred in 4.5% of forceps and 2.6% of vacuum deliveries, as in these studies unfortunately, failed vacuum would at times be followed by forceps, which, in general, should not be done [10].

Alternatives to operative vaginal delivery

Alternative management should always be discussed with the patient. This includes continued **expectant management for prolonged second stage in the presence of a reassuring fetal status, oxytocin augmentation, or proceeding with a CD**. However, the appropriate use of OVD is encouraged by the American Congress of Obstetricians and Gynecologists (ACOG) to safely prevent the primary CD [4].

Summary

There is a recognized place for forceps and all types of vacuums in clinical practice [10]. The role of operator training with any choice of instrument must be emphasized. The **increasing risks of failed delivery with the chosen instrument from forceps, to metal cup, to handheld, to soft cup vacuum** and the **trade-offs between the risks of maternal and neonatal trauma** (see Table 13.2) need to be considered when choosing an instrument. **Overall, forceps or the metal cup appears to be most effective at achieving a vaginal birth, but with increased risk of maternal trauma with forceps and neonatal trauma with the metal cup** [10].

TABLE 13.2: Comparison of Forceps versus Vacuum for Operative Vaginal Delivery

Fetal		Maternal	
Favors Forceps	**Favors Vacuum**	**Favors Forceps**	**Favors Vacuum**
	Less facial injury (0.2% versus 1.7%)	Less likely to fail to deliver vaginally the baby (9% versus 14%)	Fewer third- and fourth-degree perineal tears (7.5% versus 14%) and vaginal wall (8% versus 26%) lacerations
			Less severe perineal pain postpartum (9% versus 15%)

Source: From data in Ref. [10].

Management

Preoperative assessment

Counseling

Review with the patient the indication, risks (possible complications) and benefits, and type of instrument to be used for OVD. The option of CD, including its risks and benefits, should also be reviewed. Obtain verbal or written informed consent prior to OVD.

Preparation/Documentation (Table 13.3)

Maternal: Sufficient analgesia, clinical assessment of pelvis, lithotomy position, ± empty bladder.

Fetal: Vertex presentation, head engaged (lower part of bony vertex—not caput—at or lower than level of ischial spines), knowledge of the position of the head, asynclitism, and estimated fetal weight. Suboptimal instrument placement increases maternal and neonatal morbidity [30].

Ultrasound: Several studies have investigated the role of ultrasound in OVD. In one RCT, the use of ultrasound significantly decreased the incidence of incorrect **diagnosis of fetal head position** [31]. The measurement of ultrasound **distance between the perineum and fetal skull** has been shown to be a reproducible and predictive measure of the difficulty of OVD [32]. Another study demonstrated ultrasound measurements of **head circumference** and **angle of fetal head progression** as predictors of OVD complications, defined as the need for three or more tractions, third- and fourth-degree lacerations, hemorrhage during episiotomy repair, and/or neonatal trauma [33]. However, an RCT demonstrated ultrasound did not show any benefits in reducing the risk of failed operative delivery or maternal and fetal morbidity. Moreover, patients randomized to the transabdominal ultrasound arm were noted to have a higher rate of episiotomy [34]. See figures in Chap. 9.

Uteroplacental: Cervix completely dilated, ruptured membranes, absence of placenta previa, or other contraindications.

Other: Alert nursing, anesthesia, and neonatology of plan for OVD. Be prepared for possible shoulder dystocia. Willingness to discontinue the procedure if it does not proceed as planned [2].

Episiotomy

There is insufficient evidence (no trials) to assess the benefits and risks of episiotomy in operative deliveries. Lateral episiotomy has been shown to be protective against anal sphincter injuries in vacuum deliveries, compared to mediolateral and median episiotomies, in a meta-analysis [35]. In a large observational study, mediolateral episiotomy protected significantly against anal sphincter damage in both vacuum extraction (odds ratio [OR] 0.11, 95% CI 0.09–0.13) and forceps delivery (OR 0.08, 95% CI 0.07–0.11), compared with no episiotomy. The number of mediolateral episiotomies needed to prevent one sphincter injury in vacuum extractions was 12, whereas 5 mediolateral episiotomies could prevent one sphincter injury in forceps deliveries [36, 37]. Episiotomy should not be routinely performed, as it is associated with perineal lacerations in nonoperative vaginal deliveries. However, episiotomy should not be used as an obstetric quality measure in assisted vaginal deliveries, as this could decrease further the use of OVD and increase the CD rate [38].

Antibiotic prophylaxis

OVD increases the risk for postpartum infection and readmission to hospital when compared to spontaneously vaginal delivery. Two grams of cefotetan IV at the time of vacuum or forceps delivery are associated with a nonsignificant decrease (0% versus 3.5%) in endometritis [39]. A more recent RCT, the ANODE trial, showed patients in the United Kingdom who received a single dose of co-amoxiclav (1 g amoxicillin/200 mg clavulanic acid) following OVD were at significantly decreased risk for infection within 6 weeks of delivery. However, aspects of the ANODE trial may make these findings ungeneralizable to U.S. patient populations. For example, 89% of patients in the study received an episiotomy (majority mediolateral), which is routinely performed in the United Kingdom [40]. Therefore **a single dose of co-amoxiclav at the time of delivery may be reasonable in patients with OVD and concomitant episiotomy**. However, **antibiotic prophylaxis cannot be recommended solely for the indication "operative vaginal delivery."** Of note, there is an increased risk for wound infections and complications in patients with third- and fourth-degree lacerations; thus, one may consider prophylactic antibiotics in this setting [3].

Vacuum application

Vacuum application, if performed, should begin with low suction and be slowly increased to vacuum of about 0.7–0.8 kg/cc^2 (500–600 mmHg). Compared with stepwise negative pressure for vacuum delivery, rapid negative pressure application is associated with reduced duration (by 6 minutes) of vacuum procedure, but no other maternal or perinatal effects, in a small trial [25]. No torque or rocking motions should be applied to the vacuum. Traction should only be in the direct line of the vaginal canal. The risk of cephalohematoma increases as the time of vacuum application increases. There is no evidence that reducing pressure between contractions decreases the risk of fetal injuries [41]. Most deliveries are achieved with one to three pulls, with increased neonatal trauma (45%) after three pulls [42]. The risk of cephalohematoma is increased after 5 minutes of vacuum application [43].

TABLE 13.3: Preoperative Checklist before Operative Delivery

Maternal Criteria	Fetal Criteria	Uteroplacental Criteria	Other Criteria
Sufficient analgesia	Vertex presentation	Cervix fully dilated	Obtain patient's informed consent Alert nursing, anesthesia, and neonatology
Patient in the lithotomy position	The fetal head must be engaged in the pelvis	Membranes ruptured	An experienced operator who is fully acquainted with the use of the instrument
Bladder has been emptied	The position of the fetal head must be known with certainty; perform ultrasound before OVD	No placenta previa	Ability to monitor fetal well-being continuously
Clinical pelvimetry must be adequate in dimension and size to facilitate an atraumatic delivery	The station of the fetal head must be +2 or more		The capability to perform an emergency cesarean delivery if required

Failed operative delivery

Attempting to use a different extraction instrument after failing with one should be avoided, as cephalopelvic disproportion may be present, and the highest incidence of neonatal intracranial hemorrhage, as well as other neonatal injuries, is highest among infants delivered using forceps and vacuum sequentially [29, 44–46]. At that point, cesarean is usually offered and performed.

Postpartum

It is essential to examine carefully both the fetus and the maternal perineum after OVD.

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14

CESAREAN DELIVERY

A. Dhanya Mackeen and Meike Schuster

Key points

- **A cesarean delivery on maternal request (CDMR) or a planned repeat CD without other indication should not be performed before 39 weeks**.
- **The optimal CD rate is unknown, though ≥19% is the CD rate associated with lower maternal and neonatal mortality**. CD rates of less than 15–19% have been associated instead with higher neonatal mortality rates.
- **Prophylactic antibiotics should be administered before every CD**. The evidence suggests the use of a **single dose of cefazolin (e.g. 1 gram) or ampicillin IV be given 30–60 minutes prior to skin incision. Higher doses (e.g. 2–3 grams) are appropriate for patients with greater body mass indexes (BMIs). If performing CD in labor or after rupture of membranes (ROM) >4–6 hours, add azithromycin**.
- **All women undergoing CD should receive mechanical venous thromboembolism (VTE) prophylaxis with either pneumatic compression devices or compression stockings**. These should be **applied preoperatively and continued until full ambulation. In women with a history of VTE or inherited thrombophilia, pharmacologic prophylaxis with subcutaneous enoxaparin 40 mg daily (preferred) or UH 5000 units every 8–12 hours should also be initiated and continued for 6 weeks postpartum. In women with these risk factors and class III obesity, enoxaparin 40 mg every 12 hours should be considered**.
- Manual displacers may be better than left lateral tilt for maternal positioning.
- If opting to remove pubic hair, an electric clipper applied the morning of the surgery is preferred to shaving.
- **The use of chlorhexidine (preferred) or povidone-iodine is recommended for skin cleaning before skin incision at CD**.
- **Vaginal cleansing with chlorhexidine or povidone-iodine before CD is recommended**.
- **Active warming decreases maternal and neonatal hypothermia**.
- **Adhesive drapes** should be avoided at CD due to their association with a **higher incidence of wound infection**.
- **The fascia can be transversely incised initially with the scalpel and the incision extended bluntly or sharply with scissors**.
- **Routine development of a bladder flap is not necessary for CD**.
- **The uterus should be incised transversely with a scalpel and the incision expanded bluntly with the fingers in a cephalocaudal direction**.
- **Misoprostol plus oxytocin or carbetocin was more effective than oxytocin alone at preventing postpartum hemorrhage (PPH) ≥ 500 mL in the setting of CD**.
- **Tranexamic acid should be used prophylactically preoperatively, particularly in women at increased risk for PPH**.
- **Gentle cord traction with uterine massage for spontaneous placental removal is recommended**.
- **Continuous, full-thickness, one-layer uterine closure is recommended if the woman is planning no more pregnancies (e.g. receives tubal ligation). For women planning future pregnancies, especially after primary CD, the uterus can be closed in two layers**.
- **Routine intraabdominal irrigation is not recommended**.
- **Routine use of adhesion preventions barriers is not recommended**.
- **There is no evidence to justify the time taken and the cost of peritoneal closure, so it should be avoided**.
- **Continuous nonlocking fascial closure with delayed absorbable suture at about 5- to 10-mm intervals should be considered**.
- **Subcutaneous tissue should be irrigated and closed with sutures, especially if ≥2 cm in thickness. Routine drainage should be avoided**.
- **The low transverse cesarean skin incision should be closed with suture, regardless of obesity status**.
- **Gum chewing after CD, typically three times/day for at least 30 minutes each time, is associated with earlier return of bowel sounds, passage of flatus and stool, and less ileus**.
- **Early oral fluids and even food within 6–8 hours after CD is recommended**.
- **Nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen should be administered around the clock for post-CD pain relief**. Wound infiltration with local analgesia and abdominal nerve blocks can also be utilized. **Narcotics should only be used if and when these interventions do not control the pain**.
- **Reclosure of the disrupted laparotomy wound with adhesive tape or surgically** is associated with success in >80% of women, faster healing times, and fewer office visits as compared to healing by secondary intention.

Historic notes

The word cesarean is probably derived either from the "Lex Regia," later called "Lex Cesarea," which allowed the postmortem abdominal delivery of the child in ancient Rome, or from the Latin "caesare," which means "to cut." Until the late 1800s, most cesarean deliveries (CDs) were done after maternal death for attempt at fetal salvage. In 1882, the era of modern CD began when Saenger advocated closing all uterine incisions immediately after surgery. The lower uterine segment incision was introduced by Kronig in 1912 and popularized in the United States by DeLee in 1922. The transverse uterine incision was described by

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Munro-Kerr in 1926 [1]. CD has been associated with relatively low maternal mortality for about 100 years. Safety has improved in the last 50 years, especially with the introduction of antibiotics and improvement of surgical techniques.

Diagnosis/Definition

Birth via abdominal route by laparotomy.

Epidemiology/Incidence

CD is now the most common surgical procedure in the United States, with over 1.2 million performed each year. Its incidence has increased to 32% of all deliveries in the United States in 2018 [2]. This increase has been fueled, at least in part, by increased multifetal gestations and decreased trial of labor after cesarean (TOLAC) and vaginal breech deliveries.

Indications

Commonly accepted indications for CD are **failure to progress** (aka arrest of dilation, arrest of descent, suspected cephalopelvic disproportion [CPD], dystocia, etc.), **nonreassuring fetal heart rate tracing**, **nonvertex presentation**, etc. (Figure 14.1). See specific chapters for details.

Cesarean by maternal request

Cesarean delivery by maternal request (CDMR) indicates that the sole reason for CD is the woman's preference for CD and her refusal to labor in the case of a cephalic, singleton gestation. Although the true rates are unknown, it is estimated that the incidence of CDMR is approximately 2% in the United States and less in low-income countries [3, 4]. CDMR has increased as cesarean complications diminish, women have fewer children, and fear or concerns about vaginal delivery persist. This practice is supported by the American Congress of Obstetricians and Gynecologists (ACOG), the Society of Obstetrics and Gynecology of Canada, the Brazilian Medical Association, and the National Institutes of Health State-of-the-Science Conference on Cesarean Delivery on Maternal Request [4–7]. Uniformly, these medical authorities recommend **shared decision-making between patient and provider** and that the provider explore the patient's motivation for CDMR to help determine the most appropriate mode of delivery. Two meta-analyses found increased risks of bleeding, infections, and respiratory complications associated with unindicated CD [6, 8], while two other meta-analyses found increased urinary incontinence and pelvic organ prolapse, but not anal incontinence [9, 10], associated with vaginal delivery.

There is insufficient evidence to assess the benefits and risks of a policy of CDMR compared with trial of labor in women with term singleton gestations in cephalic presentation. The most common reason for CDMR is fear of labor pain. CDMR should not be motivated by the unavailability of effective pain medication. There is also no randomized controlled trial (RCT) to evaluate the obstetrician's recommendation for CD without indication. With the absence of strong trials, **the short- and long-term outcomes after CDMR versus trial of labor cannot be assessed**. There is insufficient evidence on the impact of counseling during pregnancy with the aim of reducing the incidence of CDMR, but counseling reduces anxiety and concerns related to pregnancy and birth [11]. A practitioner is not obligated to perform a CDMR, but should appropriately refer the woman as necessary. Although CDMR and elective CD are commonly used synonymously, CDMR is the preferred term and should not be referred to as elective CD.

A CDMR or a planned repeat CD without any other indication should not be performed before 39 weeks.

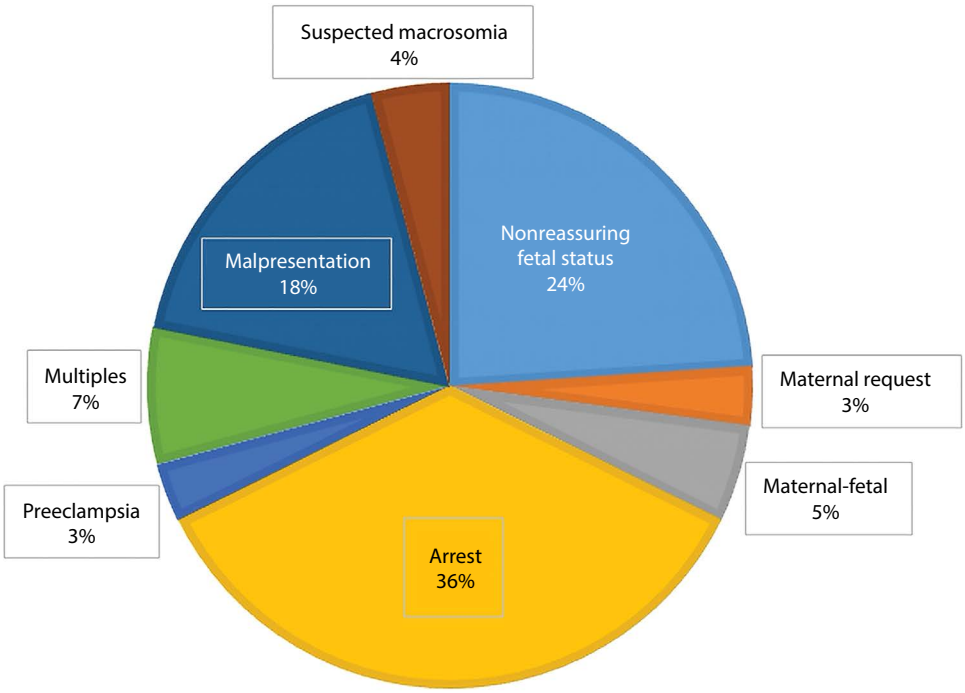


FIGURE 14.1 Primary cesarean delivery indications. (Adapted from Refs. 15, 347.)

Optimal CD rate

The optimal CD rate is unknown. Per the World Health Organization (WHO), there were no reductions in maternal and neonatal mortality with CD rates higher than 10% [12]. However, it is important to note that this is based on an ecological analysis at the population level and does not provide information that can be used at an institutional or individual physician level [12]. **Maternal and neonatal morbidity and mortality are the important outcomes, not CD rate per se**. A recent study on the relationship between CD rate and maternal and neonatal mortality in 194 WHO member states revealed that about **19% was the CD rate associated with lower maternal and neonatal mortality** [13]. **CD rates of less than 15–19% have been associated instead with higher neonatal mortality rates** [14]. **What is most important is that a woman/fetus who needs a cesarean can have one**.

In centers with higher CD rates, strategies to decrease the rate should focus on the three main indications for CD: Arrest (or dystocia, CPD), nonreassuring fetal heart rate tracings, and malpresentation. These strategies include using 6 cm to define active labor, not performing CD for arrest before 6 cm or for protracted disorders, reserving consideration of CD for arrest in the first stage of labor only for women ≥6 cm dilation with rupture of membranes (ROM) who failed to progress despite ≥4 hours of adequate uterine activity, or ≥6 hours of inadequate uterine activity and no cervical change, calling a failed induction in the latent phase one which requires ≥18–24 hours of oxytocin *after* ROM, using secondary means (e.g. scalp stimulation) to assure normal fetal status in cases of nonreassuring fetal heart rate tracings, routine use of external cephalic version for nonvertex presentations, use of operative vaginal delivery as appropriate, offering trial of labor after CD, and others [15, 16].

There are **limited data of nonclinical interventions aimed at decreasing the unnecessary CD rate** [17]. Implementation of guidelines with peer review [18], including precesarean consultation, **mandatory second opinion**, postcesarean surveillance, and audit, can lead to a 1–2% reduction in CD rates [19], predominately in cases of **intrapartum CD** [20]. Conversely**, guidelines** disseminated with endorsement and support from local opinion leaders resulted in a 13% decrease in CD rate (see Chap. 15) [19]. **Nurse-led relaxation classes and birth preparation classes** may reduce CD rates in low-risk pregnancies [19]. **Primary midwifery antenatal** [21] **and labor care** in low-risk patients may help decrease CD, but results are inconsistent [22–25]. Continuous labor support, such as a doula or nurse midwife, has been associated with reduced rates of CD, lower rates of epidural use, and more positive feelings about childbirth [25].

There is insufficient evidence that prenatal education and support programs, computer-based patient decision aids, decision-aid booklets, and intensive group therapy are effective. There is insufficient evidence that training public health nurses, insurance reform, and legislative changes are effective.

Timing of delivery

In a study of 23,794 women, planned repeat CD at 37 or 38 weeks' gestation has a significantly increased risk of adverse neonatal outcomes when compared with planned repeat CD at 39 or 40 weeks' or expectant management [26]. A planned repeat CD should, in general, be performed at $39^{0/7}$–$39^{6/7}$ weeks, unless there is a medical indication for earlier delivery (Table 23.1, Chap. 23).

Preoperative considerations

See Table 14.1 for summary of recommendations on how to perform a CD.

Counseling should include a discussion of indications, benefits, risks (including possible complications), and alternatives.

TABLE 14.1: Evidence-Based Recommendations for Cesarean Delivery (CD[a])

CD Technical Aspect	Comment
Prophylactic antibiotics	
Yes or no	Yes for all CDs
Antibiotic type	First-generation cephalosporin or ampicillin preoperatively; add azithromycin if in labor or ROM >4–6 hours
Route of administration	IV
Single dose	Generally sufficient
Timing	Administer 30–60 minutes before skin incision
Prophylaxis for VTE	Mechanical prophylaxis with graduated compression stockings or pneumatic compression devices applied preoperatively and continued until ambulation In women with a history of VTE or inherited thrombophilia, pharmacologic prophylaxis should also be initiated
Lateral tilt	Manual displacers may be better than left lateral tilt, which is better than right lateral tilt
Indwelling bladder catheterization	No complications with its avoidance; if placed, remove right after CD
Hair removal	Pubic hair does not need to be removed; if the decision is made to remove hair, use hair clippers (not razors) on the morning of the surgery
Skin cleansing	Use chlorhexidine-alcohol (preferred) or povidone-iodine
Vaginal irrigation	Use chlorhexidine-alcohol (preferred) or povidone-iodine
Active warming	Consider performing
Adhesive drapes	Avoid; use nonadhesive drapes

(*Continued*)

TABLE 14.1 (Continued): Evidence-Based Recommendations for Cesarean Delivery (CD)

CD Technical Aspect	Comment
Skin incision	
Type	Transverse, Pfannenstiel, or Joel-Cohen
Changing to a second knife	No need to change knife after skin incision
Subcutaneous dissection	Blunt dissection is preferred
Fascial incision	Transversely incise and extend bluntly or sharply
Rectus muscle cutting	Avoid
Dissection of fascia off rectus	Often unnecessary
Opening of peritoneum	Bluntly
Bladder flap	Avoid
Uterine incision	
Type	Low transverse uterine incision
Stapling device	Not recommended
Expansion of uterine incision	Bluntly in cephalocaudad direction with fingers
Fetal delivery	Manual delivery of head preferred; reverse breech extraction recommended for delivery of impacted head
Skin-to-skin	Recommended
Prevention of uterine atony[a]	
Choice of agents	Misoprostol plus oxytocin, or carbetocin
Oxytocin route	IV
Oxytocin infusion rate	Optimal rate unclear
Carbetocin	Carbetocin superior or equivalent to oxytocin; should be used if available but associated with higher cost
Misoprostol	Best if used in conjunction with oxytocin
Tranexamic acid	Use prophylactically (especially in high-risk patients) to prevent postpartum hemorrhage[a]
Uterine massage	No evidence of benefit
Placental removal	
Spontaneous	Spontaneous placental removal with gentle cord traction; avoid manual removal
Uterine exteriorization	Either exteriorization or in situ repair is acceptable
Cleaning of uterus	Can be performed, but may not be necessary
Cervical dilation	Avoid
Closure of uterine incision	
Two layers versus one layer	Double layer generally, though single layer can be considered if bilateral tubal ligation performed concurrently for closure of transverse incisions; double- or triple-layer closure for vertical incisions
Intraabdominal irrigation/drain	Not recommended
Peritoneal closure	Not recommended (for either parietal or visceral)
Reapproximation of rectus muscles	Not recommended
Glove change	Consider prior to closure of fascia
Fascial closure	Recommended with continuous nonlocking delayed absorbable suture at 5- to 10-mm intervals
Subcutaneous irrigation	Consider; if done, perform with 200 cc saline
Subcutaneous tissue closure	Close subcutaneous space, especially if ≥2 cm
Subcutaneous tissue drain	Not recommended
Closure of skin	
Staples versus subcuticular suture	Close transverse skin incision with suture, even in obese gravida
Negative pressure wound therapy	Routine use not recommended

[a] See text for more details.

Abbreviations: CD, cesarean delivery; IV, intravenous; ROM, rupture of membranes; VTE, venous thromboembolism.

Informed consent should always be obtained *after* counseling. A checklist, including pre-, intra-, and postoperative steps aimed at preventing complications, has been associated with benefits in general surgery [27] and should probably be implemented prior to CD [28].

Prophylactic antibiotics

Surgical site infection (SSI) is a common complication after CD (2–10%) and is associated with increased pain, morbidity, cost, and more frequent office visits [29]. Many of the studies discussed later have been directed at attempting to decrease SSI, blood loss, and other CD morbidity [30].

Whom to give

Prophylactic antibiotics should be administered before every CD [31, 32]. They are associated with decreased incidence of endometritis by 62%, wound infection by 60%, fever by 55%, and serious maternal infectious complications by 69%. Urinary tract infections (UTIs) are also markedly decreased [33].

What to give

The **efficacy of first-generation cephalosporins, such as cefazolin (Ancef) 1 gram, appears equivalent to that of ampicillin** [34–37]; however, the former is preferred [38]. These are the recommended agents to use unless the patient reports allergies. A seemingly equally efficacious alternative is penicillin [39], though sample size may have been too small to show differences. A large meta-analysis reviewing multiple penicillin regimens was unable to show sufficient evidence as to which regimen was most beneficial [40]. Later-generation (e.g. second or third) cephalosporins, or more expensive broad-spectrum agents, do not improve efficacy further [39]. A multiple-dose regimen for prophylaxis appears to offer no added benefit over a single-dose regimen [32, 36, 41–43]. If ampicillin or a first-generation cephalosporin has been given in labor (e.g. for chorioamnionitis), there may be no need for additional prophylactic antibiotics at CD [38]. If preoperative antibiotics were not given, prophylaxis should include an extended-spectrum regimen involving azithromycin or metronidazole in the setting of chorioamnionitis [44]. **Obese women may benefit from higher doses (e.g. Ancef 2–3 grams** [38, 45–49]) and longer courses (i.e. 48-hour postoperative course of metronidazole and cephalexin PO [orally]) in addition to routine preoperative prophylaxis to further reduce the risk of SSI within 30 days after CD (see Chap. 3 in *Maternal-Fetal Evidence Based Guidelines*) [50]. **For unplanned (e.g. in labor) CD or patients with ROM >4–6 hours, there may be an additional reduction in infectious morbidity with the addition of azithromycin** [51–53].

When to give

Compared with after cord clamp, **administration of antibiotics within 1 hour (optimally about 30 minutes) before skin incision is associated with a lower incidence of endometritis (by 46%) and wound infection (by 41%)** [31, 54–62]. Pharmacokinetic studies demonstrate that adequate cefazolin tissue concentration is attained 30 minutes after administration [31, 63, 64]. Systemic administration after cord clamping versus lavage routes of antibiotic administration seem to have similar efficacy to each other [32, 41, 65], but are inferior to administration prior to skin incision.

Summary

Prophylactic antibiotics should be administered before every CD. The evidence suggests the use of a **single dose of cefazolin (e.g. 1 gram) or ampicillin IV be given 30–60 minutes prior to skin incision. Higher doses (e.g. 2–4 grams) are appropriate for patients with greater body mass indexes (BMIs). If performing CD in labor or after ROM >4–6 hours, add azithromycin**.

Venous thromboembolism prophylaxis

There is insufficient evidence to give strong recommendations for thromboprophylactic methods or agents during pregnancy and the early postpartum period [66]. A large meta-analysis (60 trials) showed an odds ratio (OR) of 3.7-fold increased risk of venous thromboembolism (VTE) associated with CD versus vaginal delivery [67]. European guidelines recommend the use of VTE pharmacologic prophylaxis for at least 6 weeks post-CD for very high-risk patients, but can be limited to at least 7 days postcesarean in medium-risk patients. The only group not significantly at risk were healthy pregnant women with planned procedures who had early ambulation and the absence of infection [68]. The three most commonly used interventions are pneumatic compression devices, compression stockings, and anticoagulants such as unfractionated heparin (UH) or low-molecular-weight heparin (LMWH).

Pneumatic compression devices have been recommended based on retrospective data [69–72] and appear to be safe and effective [73]. While there are two RCTs on UH versus placebo, two RCTs of LMWH versus placebo, and four RCTs on LMWH versus UH given antenatally, the RCTs are, in general, small and the data are insufficient to make any recommendation [70, 71]. A meta-analysis that included seven RCTs showed no additional benefit with LMWH over UFH or control with respect to risk of VTE, but was associated with a higher risk of bleeding and hematomas [74]. It is not possible to assess the effects of any of these interventions on most outcomes, and especially on rare outcomes such as VTE, death, and osteoporosis, because of small sample sizes. There was some evidence of side effects associated with thromboprophylaxis. In summary, given the higher risk of VTE at CD compared with vaginal delivery, **all women undergoing CD should receive at least mechanical VTE prophylaxis with either pneumatic compression devices or compression stockings** [71]. These should be **applied preoperatively and continued until full ambulation**.

In women with a history of VTE or inherited thrombophilia, pharmacologic prophylaxis with subcutaneous enoxaparin 40 mg daily (preferred) or UH 5000 units every 8–12 hours should also be initiated and continued for 6 weeks postpartum. In women with these risk factors and class III obesity, enoxaparin 40 mg every 12 hours should be considered [71]. This pharmacologic prophylaxis can start 12–24 hours (depending on enoxaparin dose) after block was performed, after concerns for hemorrhage have decreased [71].

Summary

All women undergoing CD should receive mechanical VTE prophylaxis with either pneumatic compression devices or compression stockings. These should be **applied preoperatively and continued until full ambulation**. In women with a history of VTE or inherited thrombophilia, pharmacologic prophylaxis with subcutaneous enoxaparin 40 mg daily (preferred) or UH 5000 units every 8–12 hours should also be initiated and continued for 6 weeks postpartum. In women with these risk factors and class III obesity, enoxaparin 40 mg every 12 hours should be considered.

Fetal heart monitoring

1. *If external monitoring* has been employed, it should be continued until the abdominal prep has begun. This includes the time when regional anesthesia is administered. If continuous fetal monitoring is not possible, reapply the external monitor for 2–3 minutes (if feasible) after completion of the regional anesthesia to determine the postanesthesia fetal status.
2. *If internal monitoring* has been employed, the scalp electrode can be kept on until delivery of the fetal head, at which point the lead can be cut and the fetus delivered, or the fetus delivered with the electrode attached. The operating room team will be responsible for documenting on the count sheet the location of the scalp electrode after delivery.
3. If the CD is done for **nonreassuring fetal status**, all attempts should be made to perform continuous fetal monitoring until the delivery occurs. This may not apply when the CD is done in an emergent manner.

There is no trial regarding optimal **time from "decision to incision"** for CD. Thirty minutes for CD for nonreassuring fetal status and 60 minutes for CD for dystocia and most other indications have been proposed, but are not based on trials [75, 76].

Additionally, studies have shown that while many CDs are not performed within this time frame, neonatal outcomes are not adversely affected by longer intervals from decision to delivery [77, 78], unless significant neonatal compromise is suspected (such as with fetal bradycardia).

Steroids for fetal maturity

If CD is necessary before 37 weeks, **betamethasone** 12 mg IM × 2 doses, 24 hours apart **(or dexamethasone** 6 mg IM × 4 doses, 12 hours apart) should be given for fetal maturity, when indicated (see Chap. 19) [79, 80]. Betamethasone at 37 weeks or beyond before planned CD has also been shown to reduce the incidence of respiratory distress syndrome (RDS), to 0.2% from 1.1% [81–83]. However, these data are insufficient for a definitive recommendation.

Music

Playing music preoperatively significantly increases positive emotions and decreases negative emotions [84–86]. Playing music during planned CD under regional anesthesia may improve pulse rate and birth satisfaction score, as well as reduce maternal stress and anxiety [85, 86]. Preoperative exposure to Mozart decreased baseline anxiety (3.5 versus 4.6) and postoperative pain (0.6 versus 1.4) compared to no music; patient-selected music did not result in benefit as compared to no music [87]. While the magnitude of these benefits is small and the methodological quality of trials is questionable [85, 86], this is a relatively simple intervention with possibility of benefit. **In summary, the clinical impact of music seems promising** [88, 89].

Preparations on the operative table

Maternal position

There is **insufficient evidence to support or clearly disprove the value of tilting or flexing the table, the use of wedges and cushions, or mechanical displacers at CD** [90]. Most of the results presented here are from small RCTs. The incidence of air embolism is not affected by head up versus horizontal positioning [90]. Left **lateral tilt** involves tilting the woman toward her left side 10–15 degrees to avoid inferior vena caval compression by the gravid uterus. There is no change in systolic blood pressure or incidence of hypotensive episodes when comparing various positions, including left lateral tilt, right lateral tilt, head-down tilt, and right lumbar pelvic wedge with horizontal positions or when comparing full lateral tilt with 15 degrees tilt [90]. Umbilical artery base excess was also not affected by 15 degrees lateral tilt versus supine position [91]. **Hypotensive episodes are decreased with manual displacers** (relative risk [RR] 0.11, 95% confidence interval [CI] 0.03, 0.45) and increased 1.64-fold with right lumbar wedge compared to right pelvic wedge (95% CI 1.07, 2.53) and increased 3.30-fold with right lateral tilt (95% CI 1.20, 9.08) versus left lateral tilt [90]. Manual displacers showed a decreased fall in mean systolic blood pressure compared with left lateral tilt. The mean diastolic pressure is 7 mmHg lower in head-down tilt when compared with horizontal positions. There are no statistically significant changes in maternal pulse rate, 5-minute Apgar, maternal blood pH, or cord blood pH when comparing different positions [90]. **In summary, manual displacers may be better than left lateral tilt**; left lateral tilt is better than right lateral tilt.

Indwelling bladder catheterization

Compared with the use of indwelling urinary catheters inserted pre-CD and removed at 12 hours after CD, a systematic review of three trials showed that nonuse is associated with a lower incidence of UTI (RR 0.08, 95% CI 0.01, 0.64), lower rate of discomfort at first voiding (RR 0.06, 95% CI 0.03, 0.12), less time to first voiding (by 16 minutes), and less time until ambulation (by about 6 minutes) [92, 93]. No differences in intraoperative difficulties, complications (including urinary retention), or operative time were seen [92]. Given that both studies were not powered to assess differences in bladder or ureteral injury, were performed in developing countries, and did not report important confounders such as use of prophylactic antibiotics, there is insufficient evidence to determine whether bladder catherization decreases complications such as injury. In summary, **avoidance of bladder catherization does not seem to be associated with complications**. **If bladder catheterization at CD is performed, the catheter should be removed at the end of the CD** (see later).

Hair removal

Based on a meta-analysis of 1343 patients, shaving was associated with twice the number of SSIs when compared to clipping. Hair removal is not necessary or beneficial at CD. **In summary, if opting to remove pubic hair, an electric clipper applied the morning of the surgery is preferred to shaving** [94, 95]. (See Chap. 7.)

Skin cleansing

Skin is impossible to sterilize. Chlorhexidine-alcohol scrub results in less wound infections than povidone-iodine (p-i) scrub (9.5% versus 16.1%, RR 0.59; 95% CI 0.41, 0.85) in patients undergoing clean-contaminated surgeries [96]. A large RCT of 1356 patients undergoing CD examined the use of chlorhexidine cloths versus placebo and found no difference in rates of SSI at 6 weeks [97]. One small study showed that chlorhexidine scrub is associated with less bacterial contamination of the cesarean skin incision 18 hours later and lower rates of SSI as compared to p-i scrub [98]. Large RCTs have demonstrated superiority of chlorhexidine-gluconate over p-i with respect to overall SSI (RR 0.55, 95% CI 0.34, 0.90; $p = 0.02$; $n = 1147$ [99]; RR 0.72, 95% CI 0.52, 0.98; $n = 3059$ [100]), but this effect was lost when rates of superficial and deep SSI were analyzed separately (3.0% versus 4.6%, $p = 0.10$, and 1.0% versus 2.7%, $p = 0.07$, respectively) [99]. Other large RCTs recruiting almost 1500 and 932 patients showed similar rates of SSI (ranging from 3.9% to 4.6%) with the use of chlorhexidine-gluconate versus p-i or both [101, 102]. In a recent RCT, p-i with alcohol, chlorhexidine with alcohol, or both were associated with similar and low (3.9–4.6%) incidences of SSIs [101]. While meta-analyses have shown no significant differences between various antiseptic agents [103], a more recent Cochrane review showed a slightly decreased SSI rate (RR 0.72; 95% CI 0.58, 0.91; 8 trials, 4323 women) with the use of chlorhexidine compared to p-i (however, the results were no longer significant when removing trials with high risk of bias [104]). **In summary, the use of chlorhexidine is slightly preferred compared to iodine solution for skin cleansing before skin incision at CD**.

Vaginal irrigation

Compared with no scrub, **vaginal irrigation with chlorhexidine or p-i immediately before CD** significantly reduces the incidence of endometritis [105–107]. Vaginal cleansing for patients in labor and those who have ruptured membranes undergoing CD resulted in lower rates of postoperative endometritis (8.1% versus 13.8%; RR 0.52, 95% CI 0.28, 0.97; 4.3% versus 20.1%, RR 0.23, 95 CI 0.10, 0.52, respectively) and postoperative fever (9.4% versus 14.9%;

RR 0.65, 95% CI 0.50, 0.86) [106]. The effect remained significant even for elective CD with reduction in postoperative infectious morbidity (24.5% versus 8.8%) and endometritis (13.2% versus 2.9%), though the rates in the control group were higher than expected [108]. A small trial showed a reduction in C-reactive protein and postoperative pain in patients who received preoperative p-i vaginal cleansing [109]. A secondary analysis showed no difference in SSI between vaginal prep versus control with use of standard prophylactic antibiotics and adjunct azithromycin [110]. No adverse effects were reported with the p-i vaginal cleansing [105, 111]. Most, but not all, of these studies used p-i skin cleansing and prophylactic antibiotics, so **it is difficult to determine if vaginal preparation is necessary in women who receive the current recommendations for preoperative antibiotics and adequate skin cleansing**; however, as a simple and generally inexpensive intervention, providers should consider implementing preoperative vaginal cleansing. In 2019 an RCT including 1114 patients showed that the use of 4% chlorhexidine-gluconate reduced the risk of wound infection (0.6% versus 0.2%; RR 0.28, 95% CI 0.08, 0.98) compared to the use of p-i, but rates of endometritis and postoperative fever were similar [112]. A meta-analysis of 23 trials showed that p-i is superior to cetrimide, metronidazole, and saline solution/no treatment in prevention of endometritis [111]. A recent Cochrane review supports the use of chlorhexidine-gluconate or p-i for vaginal prep prior to CD for laboring and nonlaboring patients [105]. **In summary, vaginal cleansing with chlorhexidine or p-i before CD is recommended compared to no vaginal cleansing, even in women who have antibiotic prophylaxis prior to the skin incision**.

Warming the patient

Maternal and neonatal hypothermia are decreased by active warming at the time of CD under regional anesthesia [113]. However, studies were heterogeneous with respect to methods of warming (intravenous [IV] fluids, forced air, mattress [114], increased ambient temperatures [115]), as well as assessment of body temperatures [113]. **In summary, active warming decreases maternal and neonatal hypothermia; however, the optimal method of warming has not been established**.

Cell salvage

There were no clinically significant differences in rates of transfusion when cell salvage techniques were routinely deployed; however, there was a higher rate of feto-maternal hemorrhage in Rh-negative mothers when cell salvage was used (adjusted odds ratio [aOR] 5.63) [116]. **In summary, cell salvage cannot be recommended at every CD**.

Adhesive drapes

Adhesive drapes for CD are associated with a **higher incidence of wound infection** (13.8%) compared with the control group (10.4%) [117, 118]. **In summary, adhesive drapes should be avoided at CD due to their association with higher incidence of wound infection**.

Oxygen administration

A Cochrane review of supplemental oxygen in adult surgical patients found no firm evidence that a high fraction of inspired oxygen (60–90%) reduces all-cause mortality or SSI as compared to 30–40% inspired oxygen [119]. An RCT of 585 women showed no difference in the rate of infectious morbidity when comparing 2 L oxygen via nasal cannula versus 10 L oxygen by nonrebreather during CD [120]. An RCT of 831 women showed no difference in rate of SSI or endometritis when comparing 30% versus 80% supplemental oxygen after cord clamp and for 1 hour post-CD [121]. **In summary, there is no evidence that supplemental oxygen improves outcomes** at CD.

Anesthesia

For anesthesia, see Chap. 12.

Surgical technique

Skin incision

Skin incision techniques for CD have been evaluated separately from other aspects of CD in limited studies [122, 123]. In general, a **transverse skin incision** is recommended, since this is associated with less postoperative pain and improved cosmesis compared with a vertical incision. The **Pfannenstiel** (slightly curved, 2–3 cm or 2 fingerbreadths above the symphysis pubis, with the midportion of the incision lying within the shaved area of the pubic hair) and **Joel-Cohen** (straight, 3 cm below the line joining the anterior superior iliac spines, slightly more cephalad than the Pfannenstiel) are the preferred transverse incisions. Most RCTs do not only evaluate type of skin incision but also other technical aspects of CD, making it often impossible to evaluate the effect of only the type of skin incision [124]. The better designed, larger trial revealed no differences in total operative time (32 versus 33 minutes), intra- and postoperative complications, and neonatal outcomes, with the extraction time 50 seconds shorter for the Joel-Cohen group [122]. In contrast, a smaller study [123] showed significantly shorter operating times, reduced blood loss, and postoperative discomfort associated with the Joel-Cohen incision compared with the Pfannenstiel incision [125]. Considering the absence of clinical benefits to the mother and fetus, **there is no clear indication for preferring either a Pfannenstiel or a Joel-Cohen incision for CD**.

There are probably **no absolute indications for performing a vertical skin incision**. Compared with the transverse skin incision, the vertical skin incision is associated with slightly shortened incision-to-delivery intervals of about 1 minute for primary and about 2 minutes for repeat CD [126, 127]. One underpowered study showed no differences in outcomes when comparing Pfannenstiel versus vertical skin incisions in women with class III obesity [128].

Skin incision length has not been studied in a trial. Abdominal surgical incision size should probably provide about 15 cm (size of a standard Allis clamp) of exposure to assure optimal outcome of both mother and term fetus [1, 129].

Skin/subcutaneous tissue incision with diathermy as compared to scalpel results in a shorter incision time and less postoperative pain; however, the study was underpowered to determine a difference in wound complications between these techniques [130].

Changing to a second scalpel after skin incision versus no such change has never been evaluated in a trial or in any obstetric literature. From general surgery data, one scalpel is probably adequate to use throughout the whole surgical procedure.

In summary, a transverse skin incision with either a Joel-Cohen or a Pfannenstiel incision is recommended for CD skin incision.

Subcutaneous tissue opening

There are limited data on whether the subcutaneous tissue should be opened with blunt or sharp technique. Blunt dissection has

been associated with shorter operating times. In one RCT, use of diathermy ("Bovie") for CD abdominal wall opening from subcutaneous tissue to the peritoneum was associated with less blood loss, skin-to-peritoneum incision time, and post-CD pain compared with the use of no. 22 disposable scalpel blade [131]. **In summary, blunt dissection of subcutaneous tissue is preferred**.

Fascial incision

Fascial incision has **not been studied separately in a trial**. A transverse incision is usually performed with the scalpel and then extended with scissors. Digital extension can alternatively be accomplished by inserting the forefingers into a small, midline transverse fascial incision and then separating the forefingers in a cephalad-caudad direction. In an RCT evaluating entry into the abdomen, **blunt entry with rectus sheath incision extended manually** and parietal peritoneum entered and extended bluntly (manually) was associated with less blood loss, shorter operative time, and less post-CD fever and pain, compared to sharp entry [132] and no difference in risk of abdominal hernias 3 years after delivery [133]. **In summary, the fascia can be transversely incised initially with the scalpel and this incision extended bluntly or sharply with scissors**.

Rectus muscle cutting

Rectus muscle cutting with the Maylard technique is not associated with any difference in operative morbidity, difficulty with delivery, or postoperative complications compared with the Pfannenstiel (no muscle cutting) technique [129, 134, 135], but abdominal muscle strength at 3 months was better in the Pfannenstiel group [135]. Pain scores did not differ between the groups, but this may have been due to a sample size of only 97 women [135]. **In summary, cutting the rectus muscle is probably not necessary** [125].

Dissection of fascia off the rectus muscles

Nondissection of the fascia off the rectus muscles inferiorly may result in less pain and similar blood loss as compared to dissection of the rectus sheath inferiorly during cesarean [136]. **In summary, dissection of the fascia off the rectus muscles is often unnecessary**.

Extraperitoneal versus transperitoneal CD

Extraperitoneal cesarean was used in the first half of the 20th century to decrease infectious morbidity. However, with the introduction of antibiotic prophylaxis, this benefit was eliminated. When performed by one of two experienced surgeons, one study demonstrated that extraperitoneal CD is associated with decreased postoperative pain and analgesia and increased oral tolerability, without significant differences in time to delivery [137, 138]. However, as the current standard is to perform CD transperitoneally, these findings are of limited clinical applicability. **In summary, extraperitoneal CD is not recommended**.

Opening of the peritoneum

Opening of the peritoneum has not been studied separately in a trial. The peritoneum is usually carefully opened with blunt or sharp dissection and blunt expansion, high above the bladder, avoiding injury to organs below. As compared to sharp entry, blunt entry and extension of the rectus sheath incision and parietal peritoneum was associated with less blood loss, shorter operative time, and less post-CD fever and pain [132]. **In summary, blunt peritoneal opening and extension is recommended**.

Retractors

A meta-analysis of 1669 women (six RCTs) noted that use of O-ring retractors at CD reduced the need for uterine exteriorization (RR 0.48, 95% CI 0.33–0.69), but did not reduce the risk of SSI, operating time, estimated blood loss, transfusion, or postoperative analgesia [139]. **In summary, there is insufficient evidence to recommend any particular type of retractor at CD**.

Bladder flap

Four RCTs of 581 women compared development of a bladder flap versus direct uterine incision above the bladder fold [140]. There were no differences in the rate of bladder injury, estimated blood loss, or length of hospitalization. However, one study was unpublished, two were judged to be of poor methodological quality, populations were heterogeneous, emergency cesareans were excluded from analysis, and **the majority of fetuses were >32 weeks' gestation** [140]. Based on the trial that was of better quality, there is some evidence that omission of the bladder flap shortened incision to delivery time in primary CD by 1 minute, though there was no difference in total operating time [141]. Creation of a bladder flap does result in an increase in dysuria symptoms postpartum (42% versus 13%) [142]. As bladder injury at CD is an uncommon event (1–3/1000), a sample size over 33,000 women would be required to show a difference in this outcome [143]. The use of a bladder blade to protect the bladder has not been studied separately in a trial. **In summary, routine development of bladder flap is not necessary for CD**. There is limited evidence to guide creation of a bladder flap in preterm and emergency CD.

Uterine incision

Uterine incision type has not been studied separately in a trial. The **transverse incision of the lower uterine segment** is usually recommended because there is less blood loss and it allows for TOLAC in subsequent pregnancies [1, 144]. Some experts advocate the classical vertical or at least low vertical incision if the lower uterine segment is not large enough to allow a transverse incision, e.g. for the very preterm (<25 weeks) uterus, and leiomyoma, but this has been associated with increased blood loss compared with low transverse incision [145].

Women without a history of cesarean who underwent emergency CD in labor were randomized to hysterotomy performed 2 cm above versus 2 cm below the plica vesicouterina [146]. More women in the low-incision group (41%) had myometrial thickness over the uterine incision of ≤2.5 mm noted during saline contrast sonohysterography 6–9 months after delivery as compared to those with high incisions (7%). Half the women had a subsequent delivery, and there were no differences in complications.

Use of the uterine stapling (autosuture) device for opening and closing of the uterus has been assessed in a meta-analysis of two trials of 300 women: There was no difference in febrile morbidity [147] and a nonsignificant increase in the duration of the procedure (by about 3 minutes) [148]. **There is not enough evidence to justify the routine use of stapling devices** to extend the uterine incision of the lower segment, especially since there is a possibility that stapling **could cause harm** by prolonging the time to delivery. **In summary, the uterus should be incised transversely with a scalpel. There is insufficient evidence to recommend the exact level of where this incision should be made and whether it should be slightly curved or straight**.

Expansion of uterine incision

Blunt expansion of the uterine incision with fingers is associated with significantly decreased unintended extension (8.8% versus 4.8%), blood loss (by about 189 mL) [149], estimated blood loss (EBL) >1000 mL (11.4% versus 6.8%) [149], and need for transfusion (RR 0.24; 95% CI 0.09–0.62) [147]. As it is also quicker and associated with less risk of inadvertently cutting the neonate or cord, **blunt should be preferred to sharp expansion of the uterine incision** [150].

Compared with transverse expansion, **cephalocaudal expansion** of the low transverse uterine incision is associated with significantly lower incidence of blood loss >1500 mL (0.2% versus 2%) [151], fewer unintended uterine extensions (3.7% versus 7.4%) [151], and less blood loss overall [152]. A meta-analysis of these two RCTs showed that women who were randomized to the cephalocaudal group had less postpartum blood loss (mean difference [MD] −67.64 mL, 95% CI −102.85 to −32.43), hemoglobin drop (MD −0.26 g/dL, 95% CI −0.37 to −0.14) and hematocrit drop 24 hours after CD (MD −1.20 g/dL, 95% CI −1.87 to −0.53), unintended extension (4.8% versus 8.9%; RR 0.51, 95% CI 0.30–0.88), injury of uterine vessels (1.5% versus 2.8%; RR 0.52, 95% CI 0.20–1.37), blood loss >1500 mL (0.2% versus 1.7%; RR 0.12, 95% CI 0.02–0.99), and need for additional stiches (20.3% versus 29.2%; RR 0.60, 95% CI 0.44–0.82). **In summary, the uterine incision should be expanded bluntly and in a cephalocaudal direction with the fingers** [153].

Instrumental delivery

Instrumental delivery of the fetal head by either vacuum or forceps compared with manual means has been insufficiently evaluated for a firm recommendation in women with cephalic [154] or breech presentation undergoing CD. As instrumentation has been associated with maternal (especially for forceps) or fetal (especially for vacuum) harm in vaginal deliveries, the principle of "primum non nocere" ("first do no harm") should be applied in this setting, therefore **favoring manual delivery of the fetal head whenever possible** until further data are available. **In summary, manual delivery of the fetal head at CD is recommended**.

Tocolysis

Tocolysis for assisting in delivery of the fetal head at CD has been insufficiently studied [155].

Delivery of the impacted/floating fetal head

Though a strong recommendation cannot be made based on the available evidence, in cases where the fetal vertex is wedged into the maternal pelvis, vaginal displacement of the presenting part upward ("push) has been associated with longer operating time, more extension of the uterine incision, increased postoperative infections, and increased EBL (approximately 300 cc) as compared to **reverse breech extraction ("pull" method)** in a meta-analysis of RCT and non-RCT data [156]. When the fetal head is noted to be high/floating, internal podalic version results in fewer maternal and fetal complications as compared to the use of forceps or vacuum for delivery [157].

Family-oriented CD

One study showed that allowing the parents to directly visualize delivery of the baby's body (after the head is delivered), to cut the umbilical cord, and to perform early skin-to-skin contact improves birth satisfaction without increased blood loss [158]. Early skin-to-skin contact is beneficial for both mothers and babies and can be performed at the time of CD [158–160]. Professional supervision is warranted to ensure neonatal well-being. **In summary, family-oriented CD, including transparent drapes to allow the mother and support person to directly visualize the baby's delivery, as well as early skin-to-skin contact after birth, is recommended**.

Collection and drainage of cord blood

At CD, drainage of fetal blood from the umbilical cord is associated with less incidence of feto-maternal transfusion (measured by Kleihauer-Betke test) compared with no drainage [161]. The clinical significance of this finding is unknown.

Delayed cord clamping (DCC) for 30–120 seconds increases neonatal blood volume by approximately 30% and decreases morbidity, including intraventricular hemorrhage, in preterm infants [162, 163]. In term infants, it is associated with higher hematocrit, but also higher bilirubin levels [164]. **In summary, DCC is recommended routinely in preterm infants**.

Prevention of uterine atony and postpartum hemorrhage

Prevention of uterine atony and postpartum hemorrhage (PPH) has been comprehensively studied for both vaginal delivery and CD (see Chap. 10). A Cochrane review from 2018 examined this topic extensively by reviewing 140 RCTs with a total of 88,947 women predominantly at term and having vaginal deliveries [175]. In this study 15 trials examined various agents for PPH ≥500 mL in the setting of CD and found that either **misoprostol plus oxytocin or carbetocin performed the best**. Oxytocin as a single agent ranked third; however, ergotamines or ergotamines plus oxytocin were unable to be studied, as no studies using those agents were able to be included in the subanalysis of CD [165].

Oxytocin

In the setting of vaginal delivery, **both IV and IM oxytocin effectively reduce postpartum hemorrhage** and the need for therapeutic uterotonics by at least 40% compared with placebo or no routine prophylactic agent [166]. One study combined oxytocin with methergine after CD and found a significantly lower rate of blood loss and higher postoperative hemoglobin as compared to oxytocin alone without increased risk of hypertension or cardiac ischemia; but larger studies are needed to further evaluate this, especially in patients who are at risk, such as smokers, diabetics, and hypertensives [167].

The adequate rate of oxytocin is unclear; many different regimens are used and appear to be provider and institution dependent. Rates of 1 IU [168], 3 IU [169], 15 IU [170], 20 IU, 30 IU [171], and 40 IU [172] administered after delivery of the infant have similar outcomes with respect to uterine tone, blood loss, and use of other uterotonics. Higher doses of oxytocin tended to be administered as a one-time dose, while some of the lower doses were used as an ongoing infusion. Patients required fewer additional uterotonics (19% versus 36%) when treated with 80 IU oxytocin/500 mL infused over 30 minutes as compared to those who received 10 IU/500 mL infused over 30 minutes [173]. **The optimal infusion rate for oxytocin at CD is still unclear**. One RCT of 200 women compared oxytocin administered prior to uterine incision versus after umbilical cord clamping and showed a similar rate in blood transfusion, but a significant reduction in intraoperative blood loss (432.7 +/− 90.6 versus 588 +/− 96.3 mL, respectively, $p = 0.001$) and the need for additional uterotonics (7 women versus 19 women, $p = 0.002$) [174].

Carbetocin

In one RCT of 263 women, carbetocin and oxytocin were comparable to each other and superior to misoprostol with respect to prevention of uterine atony [175]. For CD, **carbetocin (as a single 100-microgram dose) is associated with more effective prevention of uterine atony, less need for additional uterotonics, PPH, and transfusion** [176] **compared with oxytocin 8- or 16-hour infusions, but may be associated with a greater cost** [177–183]. A higher dose might be necessary for women with BMI ≥40 kg/m^2, but further studies are needed to establish the ideal dose [184]. Higher doses also appear to be associated with tachycardia, hypotension, and arrythmias and should be used with caution [185]. With regard to improved uterine tone, a lower dose (20 micrograms) has been shown to be effective [186]. Carbetocin (where available) may be equivalent [187] or recommended over oxytocin [188] or oxytocin and ergotamine [189] for the prevention of uterine atony.

Misoprostol

There is **insufficient evidence** to compare misoprostol to oxytocin for prevention of uterine atony and PPH at CD, as the seven RCTs compared different regimens of misoprostol and oxytocin. In single RCTs, **either sublingual misoprostol or rectal misoprostol was associated with equivalent blood loss** [190] **and less need for additional uterotonics (10% versus 40%, RR 0.16, 95% CI 0.06, 0.44)** [191–195]. A large single-institution RCT found sublingual misoprostol superior to rectal misoprostol with respect to intraoperative blood loss (357.8 +/– 129.7 versus 457.5 +/– 140.7, $p < 0.001$) [196]. Given that misoprostol and oxytocin appear equally efficacious based on this limited evidence and that side effects such as shivering and pyrexia [191, 194, 197] are more common with misoprostol, oxytocin remains preferred [198].

Misoprostol combined with oxytocin (e.g. 200 µg, 400 µg, or 600 µg sublingual, or rectal, after cord clamping) was associated with **less post-CD blood loss, fall in hematocrit, and need for additional uterotonic agents** (7 versus 21 patients; $P < 0.001$) when compared to oxytocin alone [197, 199–201]. In women at high risk for post-CD hemorrhage, the combination of both misoprostol and oxytocin may be considered.

Tranexamic acid

Tranexamic acid (TA) inhibits fibrinolysis that potentiates the clotting system and can be used to prevent bleeding. Its **half-life is 2–10 hours, and it typically works immediately after IV administration**. Side effects include gastrointestinal upset, but additional rare complications have been reported, including VTE, cerebral ischemia, and anaphylaxis. TA was administered precesarean, though the time frame varied among trials (four out of nine studies administered TA 10 minutes prior to skin incision). There was significantly less PPH (OR 0.43), mean blood loss (–72 mL), need for blood transfusion (OR 0.23), and need for uterotonics (OR 0.48) in those treated with TA compared to those that were not [202]. In the most recent meta-analysis of 21 RCTs (3852 patients), all women received standard oxytocin prophylaxis; in addition, the TA group received **TA 1 gram or 10 mg/kg IV 10–20 minutes before skin incision or spinal anesthesia** [203]. Compared with controls, women who received TA experienced **less intraoperative blood loss** (MD –155.23 mL, 95% CI –195.64, –111.81, $p < 0.01$), postoperative blood loss (MD –26.67 mL, 95% CI –32.98 to –20.36; $p < 0.01$) and total blood loss (MD –184.88 mL, 95% CI –218.83, –150.94; $p < 0.01$), less need for additional uterotonics (RR 0.40, 95% CI 0.30–0.55, $p < 0.01$), fewer blood transfusions (RR 0.29, 95% CI 0.18, 0.49; $p < 0.01$), a **lower drop in hemoglobin** (MD –0.80 g/dL, 95% CI –1.07, –0.53; $p < 0.01$) and hematocrit (MD –2.05, 95% CI –3.09, –1.01; $p < 0.01$), **lower incidence of EBL** >500 mL, (3.9% versus 41.9%; RR 0.06, 95% CI 0.04, 0.10), **and EBL >1000 mL** (RR 0.39, 95% CI 0.30, 0.51; $p < 0.01$) compared to controls [203]. There was no difference in the incidence of thromboembolic events between the two groups [204]. Therefore, **prophylactic administration of TA should be recommended to prevent PPH in women undergoing CD who are suspected to have a high risk of PPH** [202, 203, 205–208].

Postoperative bleeding and decrease in hemoglobin were similar when comparing TA to prostaglandin analogue to manage PPH caused by uterine atony; therefore, TA can potentially be used (instead of prostaglandins) for patients with uterine atony after vaginal delivery or CD [209].

In summary, oxytocin (IV route preferred) and misoprostol (e.g. 400–600 mcg per rectum or oral) or carbetocin alone are associated with less PPH compared to oxytocin alone. Carbetocin (not available in the United States), although more expensive, appears superior to oxytocin alone for prevention of PPH if one agent is used. TA should be used prophylactically preoperatively, particularly in women at increased risk for PPH.

Magnesium sulfate

A meta-analysis of five trials looking at 8909 patients showed a similar incidence of PPH for patients treated with magnesium sulfate versus those that were not (17% versus 18%, RR 0.97, 95% CI 0.88–1.06) (210). The magnesium sulfate group had a significantly lower rate of eclampsia (0.7% versus 1.9%, RR 0.4, 95% CI 0.3, 0.6), and therefore, women who require magnesium sulfate for seizure prophylaxis should remain on this medication during CD, as it decreases seizure risk, but does not affect overall blood loss or PPH [210]. **In summary, magnesium sulfate, if indicated (for maternal or neonatal neuroprophylaxis), does not have to be stopped during CD**.

Uterine massage

Uterine massage has not been studied by itself in an RCT for CD. Uterine massage, associated with cord traction, is associated with less blood loss compared with no such interventions [211]. **In summary, uterine massage in addition to cord traction should be performed at CD**.

Placental removal

A meta-analysis of 4694 women showed that manual removal of the placenta is associated with greater morbidity than spontaneous expulsion with gentle cord traction: Increased endometritis (RR 1.64, 95% CI 1.42, 1.90) and PPH (RR 1.81, 95% CI 1.44, 2.28), greater blood loss (by 94 mL), and decreased hematocrit after delivery (by 1.6%) [211]; these findings were confirmed by a more recent RCT [212]. Therefore, **gentle cord traction resulting in spontaneous expulsion should be utilized for delivery of the placenta**, given the significant decrease in blood loss and endometritis as compared to manual placental removal. Less intraabdominal hemorrhagic fluid was noted with extraabdominal placental removal as compared to intraabdominal removal, though intraoperative blood loss, infectious morbidity, and pain did not differ [213]. **In summary, gentle cord traction resulting in spontaneous placental expulsion is recommended**.

Change of gloves

Changing the operator's gloves before manual removal of the placenta does not alter the incidence of endometritis [214].

Uterine exteriorization

Meta-analyses have showed there are no significant differences in blood loss, intraoperative hypotension, nausea/vomiting, pain, blood transfusion, endometritis, or wound infection with uterine exteriorization (extraabdominal uterine incision repair) versus repair in situ [215–217]; bowel function was noted to return 3 hours sooner with in situ repair [217]. There is no difference in fertility or ectopic pregnancy 3 years post-CD [133]. The Cochrane review showed less febrile morbidity (RR 0.41; 95% CI 0.17–0.97) and 0.24-day longer hospital stay with extraabdominal closure [215]; however, recent RCTs showed decreased operating room time (by 10 minutes), postoperative pain and analgesia requirements [218], and nausea/vomiting and uterine atony in those repaired intraabdominally [219]. So, **the balance of the benefits and harms is too close to justify a strong recommendation**, but many obstetricians subjectively prefer to exteriorize the uterus for easier uterine incision repair. **In summary, either uterine exteriorization or repair in situ is acceptable**.

Uterine cooling

Uterine cooling after uterine exteriorization and during uterine closure is associated with a decrease in blood loss and PPH in one RCT [220]. **In summary, there is insufficient evidence to recommend uterine cooling**.

Cleaning the uterus

Cleaning any placental remnants or blood clots from the uterus with a dry laparotomy sponge (versus no cleaning) after placental removal was studied in one small RCT that showed no differences in rates of endometritis or other outcomes [221]. **In summary, cleaning the uterus after baby and placental delivery can be performed, but may not be necessary**.

Cervical dilation

Routine cervical dilation at CD is not associated with decreased PPH, endometritis, or febrile morbidity, even in women with a closed cervix [222, 223]. **In summary, cervical dilation is not recommended at CD**.

Closure of the uterine incision

At least one-layer uterine closure is always done, as the uterus should not be left open. Closure of the uterine incision involves several decisions, including use of blunt versus sharp needles, type of suture, full- versus split-thickness repair, continuous versus interrupted sutures, locking versus nonlocking of sutures, and whether to imbricate the second layer, if it is even closed.

Blunt needles for closure of the uterus, peritoneum, and rectus sheath are associated with similar outcomes compared with sharp needles in one RCT [224]. In another RCT, glove perforation was significantly less with the use of blunt compared to sharp needles, especially for the assistant surgeon. However, physicians reported decreased satisfaction performing CD with blunt needles [225]. In summary, there is **still limited evidence to recommend blunt versus sharp needles at CD**.

In one RCT, the assistant surgeon pulled the suture caudally with the left hand and used the right hand to hold the uterine wall to prevent upward tissue tension; this was associated with lower need for additional sutures, shorter operative times, and less decrease in hemoglobin compared with pulling the suture cephalad with the right hand [226].

There are several RCTs comparing different **sutures** for uterine closure. Polyglactin-910 was associated with generally similar outcomes compared to chromic catgut [132]. Knotless barbed sutures as compared to polyglactin-910 braided sutures resulted in shorter uterine closure time (103–119 seconds), less need for hemostatic sutures, and less EBL during incision closure (47 mL) [227, 228]. Monofilament suture resulted in higher residual myometrial thickness (5.5 ± 2.24 versus 4.18 ± 1.76) than multifilament suture [229].

Compared with split-thickness repair (avoiding the endometrium), **full-thickness uterine incision repair** is associated with a lower incidence of incomplete healing of the uterine incision after CD (documented by a split in uterine muscle seen on transvaginal ultrasound about 40 days after the CD) [147, 230] and a lower incidence of niche prevalence (a triangular anechoic area noted at the uterine incision site) [231].

Continuous single-layer closure may save operating time and reduce blood loss compared with interrupted single-layer closure [232]. **Locking of sutures** in the first layer has been insufficiently studied [233]. Compared with two (double) layers, one (single) layer of suture for low transverse uterine incision repair is associated with no differences in febrile morbidity (13,980 women; RR 0.98). Although there was a **reduction in mean blood loss for single-layer closure**, there were no differences in blood transfusion, and heterogeneity was high for included studies [132, 147]. Unfortunately, there were too few women who followed up to be able to detect a significant difference in rare, but extremely important, long-term outcomes, such as rates of rupture in the next pregnancy [133], with contradictory results noted in retrospective studies [232, 234–236]. Meta-analyses showed thinner residual myometrial thickness and decreased healing ratio (residual thickness/adjacent myometrial thickness) with single-layer closure as compared to double-layer closure, especially when locked sutures were used [231]; additionally, there was increased dysmenorrhea with single-layer closure (RR 1.23, 95% CI 1.01, 1.48) and no differences in uterine rupture [231]. Thinner residual myometrium was noted after single-layer closure as compared to double (MD –2.19 mm) [237], especially in those who underwent primary CD [238]. Since there is, as of yet, no trial demonstrating consistent benefit from two- versus one-layer uterine closure, **it might be reasonable to omit the second layer if the woman is planning no more pregnancies (e.g. receives tubal ligation). For women planning future pregnancies, especially after primary CD, the uterus can be closed in two layers** [239]. Vertical uterine incisions require a double- or triple-layer closure [231, 240].

In summary, continuous, full-thickness, one-layer uterine closure is recommended if the woman is planning no more pregnancies (e.g. receives tubal ligation). For women planning future pregnancies, the uterus can be closed in two layers.

Intraabdominal irrigation

Intraabdominal irrigation with 500–1000 mL of normal saline before abdominal wall closure **should not be routinely performed**, since it provides no significant differences in infectious or other complications but does increase intraoperative nausea and vomiting and postoperative nausea [241]. **In summary, routine intraabdominal irrigation is not recommended**.

Adhesion formation prevention

There is **insufficient evidence** to assess if any intervention is effective at adhesion prevention at CD. In one RCT, a hyaluronate

carboxymethylcellulose (Seprafilm) adhesion barrier applied at CD did not reduce adhesion formation at the subsequent CD [242]. Evidence from non-CD abdominal surgery shows that oxidized regenerated cellulose (Interceed) and hyaluronate carboxymethylcellulose (Seprafilm) safely reduce clinically relevant consequences of adhesions [243]. **In summary, routine use of adhesion preventions barriers is not recommended**.

Intraoperative interventions to reduce postoperative pain

One study of 370 patients who underwent primary CD showed that intraperitoneal instillation of 10 mL of 2% lidocaine significantly decreased persistent postoperative pain from 21% to 11%; the parietal peritoneum was closed [244]. **In summary, there is insufficient evidence to recommend routine use of lidocaine for intraperitoneal instillation**.

Appendectomy

Performing a planned appendectomy without indication at CD is not associated with inpatient morbidity in a small RCT [245]. However, no clear benefits were shown. **In summary, the evidence is insufficient to recommend routine appendectomy at CD**.

Intraabdominal drain

There is insufficient evidence to evaluate the effect of placing a drain in the abdominal cavity at CD. In one RCT, liberal use of a subrectus sheath drain was not associated with any effect compared with the restricted use of such intervention [246]. **In summary, a routine intraabdominal drain is not recommended**.

Peritoneal nonclosure

Observational studies have shown that the peritoneum regenerates in 5–6 days. Compared with closure, **peritoneal nonclosure** is associated with a reduction in operating time, whether both or either visceral or parietal peritoneal layers were not sutured. While nonclosure of visceral peritoneum versus closure of both peritoneal surfaces showed an increased risk of adhesion formation, one of the two included studies had a high risk of bias. Peritoneal nonclosure is also associated with significantly **less postoperative pain and shorter operative time** (by 6 minutes) [247, 248] as compared to closure of both layers. Nonclosure of the visceral peritoneum when the parietal peritoneum is closed is associated with **decreased urinary symptoms of urgency, frequency, and stress incontinence** [247].

Long-term follow-up after 3 years showed no difference in fertility [133] and in 7 years [249] showed no differences in pain, fertility, urinary symptoms, and adhesions. A review of general surgery and gynecologic data concluded that "we encourage clinicians not to close both parietal and visceral peritoneum" [250]. The hypothetical benefits of closing these layers for anatomic barrier protection, reduction of wound dehiscence, and minimization of adhesion have not been proven, and in fact have been invalidated by trials. **In summary, there is no evidence to justify the time taken and the cost of peritoneal closure, so it should be avoided**.

Reapproximation of the rectus muscles

Reapproximation of the rectus muscles results in increased postoperative pain and increased analgesic requirements [251]. **In summary, reapproximation of the rectus muscles is not recommended**.

Glove changing

Changing gloves prior to closure of the peritoneum/fascia decreases the rate of composite wound morbidity, especially skin separation (13.6% versus 6.4%, $p = 0.008$) [252]. **In summary, glove changing prior to fascial closure can be considered, but the evidence is limited**.

Fascial closure

Techniques of fascial closure have not been studied extensively in CD RCTs. Most experts suggest continuous nonlocking closure with delayed absorbable suture at about 10-mm intervals. Recent non-CD evidence has shown that small fascial tissue bites of 5 mm every 5 mm are associated with prevention of incisional hernia in midline incisions and are not associated with a higher rate of adverse events compared to large fascial bites of 10 mm every 10 mm [253]. **In summary, continuous nonlocking fascial closure with delayed absorbable suture at about 5- to 10-mm intervals** should be performed.

Subcutaneous tissue

Irrigation

Irrigation of the subcutaneous tissue with 200 cc normal saline (NS) reduces hematoma and seroma but does not decrease SSI [254, 255]. No differences in SSI were noted with p-i irrigation. **In summary, subcutaneous irrigation decreases hematoma and seroma formation**.

Closure

Suture closure of subcutaneous fat in women with any subcutaneous thickness is overall associated with less wound disruption versus nonclosure, likely secondary to decreased seroma formation (OR 0.53) [256], but inclusion of both women with <2-cm and ≥2-cm thickness (which can have differing outcomes) and inability to blind represent possible sources of confounding and bias [257].

Greater than or equal to 2-cm subcutaneous thickness: Suture closure of subcutaneous fat in women with ≥2-cm thickness is associated with a significant decrease in wound disruptions, defined as any wound complication that required intervention, and seromas, compared with nonclosure [256, 258]. The evidence supports routine subcutaneous suture closure in women with a subcutaneous tissue depth ≥2 cm.

Drainage

Some RCTs have evaluated drainage of subcutaneous tissue, compared with no drainage, or compared with tissue closure.

In meta-analyses of all RCTs, there is no difference in the risk of wound infection, other wound complications, febrile morbidity, or endometritis in women who had wound drains compared with those who did not [259, 260]. Wound drainage of subcutaneous tissue (in women who did not receive prophylactic antibiotics) with a 2-cm corrugated rubber drain (typically a 7-mm Jackson-Pratt drain) extruding from one end of the incision, left open to drain, and removed the following day is associated with a trend toward increased wound infection [259]. Drainage is less effective than tissue closure for women with ≥2 cm of subcutaneous fat. Therefore, **routine subcutaneous tissue drainage in women undergoing CD cannot be recommended** [246]. These trials do not answer the question of whether wound drainage is of benefit when hemostasis is not felt to be adequate.

In summary, the subcutaneous tissue should be irrigated and closed with sutures, especially if ≥2 cm in thickness. Routine drainage should be avoided.

Closure of skin

Closure of the skin incision at CD has been most commonly performed with either absorbable sutures or nonabsorbable metal staples. In a meta-analysis of 3112 women, compared with sutures, staple closure is associated with higher rates of wound complications (13.0% versus 4.8%), separation (9.4% versus 2.5%), and a shorter duration of surgery by 7 minutes [261–263]. This decrease in wound complications persists even when only examining the 1030 obese patients, as sutures were still associated with fewer complications (6.7% versus 12.8%) [262]; however, one small study showed no difference in wound complications in class III obese patients [264]. Though the incidences were small, there were no significant differences in hematoma, seroma, and readmission between groups [262]. Additionally, there were no significant differences between groups with regard to pain perception, patient satisfaction, and incision cosmesis [262, 265, 266]. One small study showed decreased wound complications with interrupted instead of continuous subcuticular sutures [267]. **Therefore, the low transverse cesarean skin incision should be closed with sutures, regardless of obesity status**.

The suture most commonly used in the RCTs showing superiority of sutures was **poliglecaprone** [262]. No differences in wound complications were noted when comparing skin closure with braided versus monofilament suture when analyzed by actual suture received [268]. Polyglycolic acid sutures have been associated with greater hypertrophic scarring compared to interrupted nylon sutures [269]. Barbed sutures were associated with similar rates of wound dehiscence, infection, and other adverse outcomes compared to 3-0 polydioxanone suture [270]. There were no differences in patient or physician assessments of scars at 8 weeks when comparing skin closure with suture versus with glue [271]. No differences were noted regarding wound complications when comparing tissue adhesive with sterile strips applied after suture closure of the skin incision [272].

Absorbable staples were associated with similar outcomes as metal staples, except for a longer skin closure time [273]. If staples are used, they should be removed on or after day 7, as early (day 3) removal is associated with a nonsignificant trend for higher rate of wound dehiscence (15.2% versus 11.5%) compared to delayed removal on days 7–10 [274]. There is insufficient evidence to evaluate the effectiveness of the Leukosan Skinlink wound closure device, though it may have similar cosmetic results as prolene suture closure [275].

In summary, the CD skin incision should be closed with sutures.

Dressings

There is no RCT comparing placing or not placing a wound dressing at CD. One RCT compared dialkylcarbamoyl chloride (DACC, Cutimed Sobatec) to standard surgical dressing and found a lower rate of SSIs (1.8% versus 5.2%, respectively, $p = 0.04$) [30]. This type of dressing also resulted in fewer outpatient visits, readmissions, and reduced health care costs [276]. Silver nylon dressing has also been investigated, but showed no risk reduction in SSIs as compared to standard dressing [277]. With regard to optimal timing of dressing removal, the evidence is limited. One RCT of 320 patients compared 6-hour removal to 24-hour removal and found no detrimental effects with early removal [278]. **In summary, the wound dressing at CD can be removed at 6 hours**.

Negative pressure wound therapy

Previously used in the treatment of postoperative wounds, more recently, negative pressure wound therapy (NPWT) has been applied prophylactically with success to decrease SSI. A large meta-analysis compared NPWT to standard care in obese women, and although the studies were heterogenous, there was a reduction in SSI (RR 0.45, 95% CI 0.31, 0.66) and overall wound complications (–6.0%, 95% CI –10.0%, –3.0%, number needed to treat [NNT] 17) [279]. This risk reduction was confirmed in a subsequent RCT that also demonstrated cost-effectiveness (>30,000 Euros per quality-adjusted life years [QALY]), especially in those patients with pre-pregnancy BMI >35 kg/m^2 [280, 281]. However, other meta-analyses on obese women found that NPWT did not reduce SSI [282–285]. **It appears that evidence is mixed regarding the usefulness of NPWT to reduce SSI in obese women. In summary, routine NPWT, even in obese women, cannot be recommended at CD**.

Incision treatment

A small RCT explored the placement of bupivacaine-soaked gelatin sponges subcutaneously and was able to demonstrate lower pain scores, narcotic use, blood pressure, and heart rate postoperatively, as well as less anxiety and depression [286, 287]. Another small RCT explored the use of topical scar gel (Contratubex) applied twice daily and showed improvement in Patient Observer Scar Assessment Scale (POSAS) scores with respect to color, stiffness, and irregularity of CD scars after 6 weeks of treatment [288]. One RCT compared the use of aloe vera gel to standard dressing and showed improved wound healing scores using the Redness, Edema, Ecchymosis, Discharge, and Approximation (REEDA) scale 24 hours postoperatively, but scores were equivalent 8 days postoperatively, and therefore, unnecessary, though not harmful [289]. Silicone gel or sheets have been demonstrated to improve scar healing when applied twice daily; when compared head-to-head, they appear to have similar Vancouver Scar Scale (VSS) scores, but the silicone sheets had higher Visual Analogue Scores (VAS) with respect to itching [290]. Another method investigated for improved scar cosmesis is tranilast 8% liposomal gel. When applied twice daily to the scar for 3 months, POSAS scores were lower (i.e. better) at 9 months compared to placebo [291]. Grapeseed extract ointment 5% has also been shown to improve REEDA scores at 6 and 14 days postoperatively [292]. **There are no comparative trials to evaluate which of these treatments are associated with the best cosmetic outcomes. In summary, no specific recommendations can be made regarding CD incision treatment; the individual treatments are safe options that can be considered.**

Postoperative care

Gum chewing

Compared with no gum chewing, **gum chewing after CD, typically three times a day for at least 30 minutes each time, is associated with earlier return of bowel sounds (by 4.4 hours), passage of flatus** (10.4 hours, 95% CI –11.9, –8.9) [293] **and stool** (12.7 hours, 95% CI –14.5, –10.9) [293], **less ileus (OR 0.36)** [294, 295], and shorter hospital stay (0.7 days, 95% CI –0.8, –0.5) [293, 296]. Since this large review, many other RCTs and systematic reviews have confirmed these findings [294, 295, 297–303]. **In summary, gum chewing starting immediately after CD three times a day for at least 30 minutes each time is recommended**.

Early oral fluids and feeding

A meta-analysis of 11 somewhat heterogeneous studies showed that compared with delayed (usually after 8 hours or upon passage of flatus) oral fluids or food, **early oral fluids or food** is associated with reduced time to return of bowel sounds (by about

8.8 hours), flatus (7.3 hours), and bowel movement (6.3 hours) [304]. It has also been associated with earlier ambulation, greater maternal satisfaction, shorter length of stay, and lower rates of narcotic use [305–309]. No significant differences were identified with respect to nausea, vomiting, abdominal distention, and mild ileus [304, 308, 310]. Typically, feeding was initiated within 2–8 hours with water, clear liquids, or solid foods [311–313]. **In summary, early oral fluids and even food within 6–8 hours after CD are recommended**.

Ambulation

There is limited RCT evidence regarding walking after CD. A small RCT showed that patients utilizing a pedometer had an increased number of steps in the first 48 hours postoperatively and reported a significantly easier physical and mental recovery [314]. **Early ambulation starting 4 hours after CD is recommended**.

Other interventions to reduce postoperative ileus

One RCT demonstrated decreased time to bowel sounds, first bowel movement, and time in bed with the use of **acupuncture** (20-minute sessions at 1 hour and 4 hours postoperatively) [315]. Similar results were seen with the administration of 10 mg of **metoclopramide** intraoperatively [316]. Another trial utilized **ginger capsules**, which helped decrease abdominal distension and allowed patients to eat quicker but did not affect the time to flatus or maternal satisfaction [317]. Another RCT showed that combining **dexamethasone 8 mg and ondansetron 4 mg** compared to just Zofran significantly decreased postoperative nausea and vomiting (9% versus 37%, p <0.01) [318]. **In summary, these interventions are options to decrease postoperative nausea and vomiting**.

Removal of Foley catheter

A small RCT randomized patients to removal of Foley catheter in 2 hours versus 12 hours and showed reduced urinary frequency ($p = 0.04$), microscopic hematuria ($p = 0.04$), postoperative mobilization time ($p = 0.01$), and length of hospital stay ($p = 0.009$) in the group whose Foley was removed earlier [319]. Results were similar in another RCT with removal of the Foley immediately postoperatively [320]. **In summary, the Foley catheter, if utilized during CD, can be removed right after CD**.

Postoperative anxiety

CD can be associated with significant anxiety, especially for those patients who underwent emergency surgery. Various interventions have been studied to reduce stress and anxiety postoperatively. One small RCT compared **hand and foot massage** to standard postoperative management and observed reduced pain intensity, lower blood pressure and respiratory rate, and increased rates of breastfeeding [321]. Another RCT evaluated the utilization of 30 minutes of **Reiki**, a Japanese form of healing with energy (3 minutes for each area, 10 areas total) within the first 24–48 hours postoperatively and found significantly lower use of analgesics and less anxiety in the treatment group [322]. **Auricular acupressure** (applied twice a day) has also been tested and shown to reduce cortisol levels, heart rate, anxiety, and fatigue when used postoperatively [323]. **Although there is insufficient evidence based on small sample size, these nonpharmacologic interventions have no expected harmful side effects and can be recommended to those patients who would like to utilize them**.

Pain relief after CD

See also Chap 12. **Nonsteroidal antiinflammatory drugs** (NSAIDs, e.g. ketorolac intraoperatively followed by ibuprofen 600–800 mg every 6–8 hours) and/or **acetaminophen** (325–650 mg every 4–6 hours) **around the clock (rather than upon patient demand)** should be recommended for post-CD pain relief. Narcotics such as morphine and codeine should be used only if NSAIDs and acetaminophen, both at maximal safe dosing and around the clock, do not control the pain. There is limited evidence evaluating oral narcotic use versus oral NSAIDs use after CD.

Wound infiltration with local analgesia and **abdominal nerve blocks** as adjuncts to regional and general anesthesia seem to be of benefit in reducing opioid consumption after CD in small RCTs. NSAIDs (even as a wound infiltration) as an adjuvant may confer additional pain relief [324]. In women who had CD performed under regional analgesia, wound infiltration is associated with a decrease in morphine consumption at 24 hours compared with placebo. In women with regional analgesia in addition to a local anesthetic, wound infiltration with an NSAID cocktail is associated with less morphine use compared with local anesthetic infiltration. Women who have regional analgesia with abdominal nerves blocked have decreased opioid consumption. In women under general anesthesia, CD wound infiltration and peritoneal spraying with local anesthetic reduce the need for opioid rescue [324].

Post-CD, persistent opioid use is as high as 1 in 50 to 1 in 300 in previously opioid-naïve women [325, 326]; therefore, it is important that obstetricians judiciously use narcotics for postpartum pain control. One potential framework is the WHO analgesic ladder endorsed by ACOG [327]. **In summary, NSAIDs and acetaminophen should be administered around the clock for post-CD pain relief. Wound infiltration with local analgesia and abdominal nerve blocks can also be utilized. Narcotics should only be used if and when these interventions do not control the pain**.

Discharge

A study of almost 3000 women who were randomized to be discharged with their newborn after 24 hours versus 72 hours postcesarean showed that **those discharged after 24 hours were more likely to report mood swings and have less success with breastfeeding**. Additionally, although there was no difference in maternal readmission, there were **increased neonatal admissions (typically due to jaundice) in those discharged after 24 hours** [328]. A recent smaller RCT showed that discharge on the first as compared to the second day is not associated with any difference in maternal or perinatal outcomes, either immediately or at 6 weeks [329]. As part of an enhanced recovery after surgery (ERAS) protocol with early feeding, catheter removal, and ambulation, patients with shorter hospital stay (–1.95; 95% CI –3.80, –0.029) [330], had lower pain scores and hospital expenses compared with those with a longer hospital stay without increased febrile or infectious morbidity [331]. For women who are discharged early, a home health nurse visit is advised. **In summary, discharge on day 2 or 3 after CD can be considered**.

Management of complications

Disrupted (open) laparotomy wound

Compared with healing by secondary intention, **reclosure of the disrupted laparotomy wound is associated with success in >80% of women, faster healing times** (16–23 versus 61–72 days), **and fewer office visits** [332]. No serious morbidity or mortality

is associated with either method. There is insufficient evidence to assess optimal timing (probably 4–6 days after disruption if noninfected) and technique (superficial vertical mattress or "en bloc" reclosure of entire wound thickness with absorbable sutures or adhesive tape) of reclosure, as well as utility of antibiotics. **Compared with reclosure using sutures, reclosure using permeable, adhesive tape** (Cover-Roll; Biersdorf, Inc., Norwalk, CT) is associated with a faster procedure, less pain scores, and similar healing times in a small RCT [333]. **In summary, the disrupted laparotomy wound, if and when not infected, should be closed surgically or with an adhesive tape**.

Enhanced recovery after surgery

Starting in 2018, a three-part series identifying the most evidence-based steps to reduce maternal and neonatal morbidity, as well as allowing patients to be discharged home 0.5–1.5 days early [334–336], was released. Various interventions described in this chapter have been researched and utilized in an attempt to reduce the risk of SSI [337]. A large RCT showed an overall risk reduction of 71% (16.1% versus 27.5%, RR 1.71, 95% CI 1.18, 11.92) through the use of evidence-based bundles [338]. An earlier meta-analysis showed that evidence-based bundles are associated with significant reduction in SSI after CD (2.0% versus 6.2%, RR 0.33, 95% CI 0.25, 0.43) [339]. Two recent RCTs compared ERAS to standard management and found reduced length of stay (–18.5 hours, p <0.01, 95% CI –23.67, –13.34) and lower incidence of severe pain and headache [340], as well as improved patient satisfaction and increased breastfeeding rates [330]. **In summary, these evidence-based bundles should be applied to improve outcomes post-CD.**

Postoperative counseling

Interval until next pregnancy after a CD should be about 18–23 months, as shorter intervals have been associated with increased risk of uterine rupture [341, 342]. See also Chap. 14.

Short- and long-term outcomes for the baby

Scheduled CD compared with vaginal delivery (but not compared with unscheduled CD) has been associated with a small absolute increased risk of childhood asthma requiring hospital admission, salbutamol inhaler prescription at age 5 years, and all-cause death by age 21 years (0.40% versus 0.32%; difference, 0.08% [95% CI, 0.02%–1.00%]; adjusted hazard ratio [HR], 1.41 [95% CI, 1.05–1.90]) [343].

Short- and long-term outcomes for the mother

The dominant maternal risk in subsequent pregnancies is placenta accreta and its associated complications (Chap. 29). Pregnancies following CD also have increased risks for other types of abnormal placentation, reduced fetal growth, and preterm birth. Chronic maternal morbidities associated with CD include pelvic pain and adhesions. Adverse reproductive effects may include decreased fertility and increased risk of spontaneous abortion and ectopic pregnancy [344].

For future research

In order to make comparisons of CD rates over time, it is important that everyone use a similar classification scheme. Robson proposed a scheme that is mutually exclusive and totally inclusive and takes into consideration category of pregnancy (singleton cephalic/breech/other lie, multiples), prior obstetric record (nulliparous, multiparous, with or without uterine scar), course of labor (spontaneous, induced, CD before labor), and gestational age (based on completed weeks at time of delivery) [345], and its use is increasing worldwide [346].

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15

TRIAL OF LABOR AFTER CESAREAN

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Key points

- **A woman with a prior cesarean delivery (CD) has two options for mode of delivery in the subsequent pregnancy: A planned repeat cesarean delivery (PRCD) or a trial of labor after cesarean (TOLAC) to try to achieve a vaginal birth after cesarean (VBAC).**
- **There is insufficient evidence (no large randomized controlled trial) to compare the safety, complications, and maternal and fetal/neonatal morbidity and mortality between these two options.**
- **TOLAC is a reasonable option for most women with a single prior low transverse CD with no other contraindications to a vaginal birth (Table 15.1).**
- **Absolute contraindications to TOLAC are as follows:**
  - Medical or obstetric complications that preclude vaginal delivery
  - Inability to perform emergency CD
  - Vertical (classical) uterine scar or fundal or perifundal complete (from endometrium to serosa) uterine scar from other surgery (e.g. myomectomy)
  - Prior uterine rupture
- **Successful VBAC rates in the general population of women with previous low transverse uterine incisions vary from about 40% to 80%.**
- **Screening tools to estimate the likelihood of successful TOLAC can be used selectively and are best used to confirm high rates of success but are less predictive at low rates**. One available for clinical use is at https://mfmunetwork.bsc.gwu.edu/web/mfmunetwork/vaginal-birth-after-cesarean-calculator.
- Rates of **maternal and perinatal complications** are in general similar and low with both TOLAC and PRCD, except for the **risk of uterine rupture (associated with TOLAC), which confers both maternal and perinatal risks.**
- **Uterine rupture** is the **main complication** associated **with TOLAC**. Most maternal and perinatal morbidity results from repeat CD after TOLAC (Table 15.2).
- **The overall risk of uterine rupture during a TOLAC at term is 0.7% after one prior low transverse CD, versus 0.26% after PRCD. The risk is increased with >1 prior CD, prior vertical scar, prior rupture, and induction of labor with no prior vaginal deliveries.**
- **With term uterine rupture, the risks of fetal/neonatal morbidity/mortality are** about 33%, the risk of **pH <7.00** 40%, **admission to neonatal intensive care unit (NICU):** 6% risk of **hypoxic-ischemic encephalopathy (HIE),** and 1.8% risk of **neonatal death (rupture-related risk of neonatal death: 1/10,000 TOLAC)** in equipped academic centers.
- **Compared with PRCD, TOLAC is associated with slightly higher rates of adverse perinatal outcome**: Cord pH <7.00 (1.5/1000 TOLAC), HIE (5–8/10,000 TOLAC), and perinatal death (13/10,000 with TOLAC vs. 1/10,000 for PRCD) (Table 15.3). The overall risk of adverse perinatal outcome is 1/2000 with TOLAC, slightly higher than with PRCD.
- When compared with women without a previous CD (instead of with those having a planned primary CD), the perinatal mortality for TOLAC is higher than PRCD (10/10,000 vs. 0.4/10,000 births), but this rate is twice as high as that of a non-VBAC multipara in labor and the same as that of a nullipara in labor.
- **Appropriate counseling including risks as described** should be provided to the woman with a prior CD deciding on subsequent mode of delivery. **The ultimate decision regarding TOLAC or PRCD is up to the patient.**
- **To minimize risks, an experienced obstetrician in addition to anesthesia, nursing, and operating room personnel in a facility equipped to perform emergency CD must be immediately available throughout the TOLAC.**

Historical perspective

Each year almost 1.5 million childbearing U.S. women have cesarean deliveries (CDs). Most of these are primary CDs, but the largest single indication for CD is prior CD, accounting for over half a million CDs each year [1]. In order to reduce this trend, there is a need to both prevent the first CD and increase the rate of trial of labor after cesarean (TOLAC) in appropriate candidates.

TABLE 15.1: Candidates and Absolute and Relative Contraindications for Trial of Labor after Cesarean

- Singleton gestation
- Clinically adequate pelvis
- One (or two) prior low transverse cesarean delivery(ies)
- No other uterine scars or previous rupture

Limited Evidence

- A twin pregnancy who is a candidate for VBAC
- Unknown uterine scar (low clinical suspicion of prior classical uterine incision)

Absolute Contraindications

- Medical or obstetrical complications that preclude vaginal delivery
- Inability to perform emergency CD
- Vertical (classical) uterine scar
- Fundal or perifundal complete (from endometrium to serosa) uterine scar from other surgery (e.g. myomectomy)
- Prior uterine rupture

Relative Contraindications

- Multiple uterine scars (e.g. ≥3 prior CDs)
- Any other factor associated with a risk of rupture of >1% (see text)

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TABLE 15.2: Factors Associated with Success and Risk of Uterine Rupture Associated with TOLAC

Factor	Effect on Success Rates[a]	Effect on Risk of Uterine Rupture with TOLAC (% Risk)	Comment (References)
Maternal Demographics			
Older age	↓	↑	
Obesity	↓↓	NA	
Obstetric History			
Prior vaginal delivery	↑↑	↓↓ (0.2%)	Especially prior VBAC. **Recommend TOLAC** [4, 17, 41]
No prior uterine scars	NA	NA (<0.01%)	
Prior nonrecurring indication for CD	↑		For example, prior CD for Malpresentation
Labor before primary CD		↓	[51]
More than 1 prior CDs	↓	↑ (see later)	10%–15% lower success rate per CD
One prior LT CD (no prior VBAC)		(0.7%, range 0.5–1.0)[b]	[4, 5]
One prior LT CD (prior VBAC)		↓ (<0.5%)	[15, 45, 46]
Two prior LT CDs (no prior VBAC)		↑ (1.8%, 1%–3.7%)	[12, 45, 46]
Two prior LT CDs (prior VBAC)		↓ (0.5%)	[45]
Prior vertical (classical) CD		↑↑ (4%–10%)	**Avoid TOLAC** [5]
Prior low-vertical CD		↑ (1%–2%)	[4, 8]
Prior "unknown uterine scar" CD		(0.5%–2%)	[4]
One-layer uterine closure		↑ (1%–2%)	[8, 47, 48][c]
Fever at prior CD		↑	If both intrapartum and postpartum fever
Prior preterm CD		↑ (1%)	
Prior uterine rupture		↑↑ (6% if lower segment rupture; 32% if upper segment rupture)	**Avoid TOLAC** [5]
Short interpregnancy interval		↑↑ (2%–5%)	<18 months; avoid TOLAC [58, 59]
Current Labor Factors			
PRCD	NA	(0%–0.15% in labor) (0.5 risk of dehiscence)	[4, 67]
Favorable cervical status	↑↑	↓↓	Bishop score >8 or CL <15 mm
Postdates	↓	–	Uterine rupture rate increased if induced/augmented
Fetal macrosomia (e.g., BW >4000–4500 g)	↓	↑	Uterine rupture rate increased by relative risk 2.3 [20]
Induction/augmentation of labor	↓	↑ (mostly 1%–2%)	Avoid misoprostol; avoid PGE2 followed by oxytocin; avoid oxytocin >20 mU/minute; see later [4, 50–53]
Misoprostol induction		↑↑ (>5%)	**Avoid**
PGE2-only induction		↑ (1%)	Cannot predict if PGE2 will be sufficient
PGE2 then oxytocin induction		↑ (1%–3%)	Probably avoid
Foley induction		–	Probably safe
Oxytocin-only induction		↑ (1.1%)	
Oxytocin augmentation		↑ (0.9%)	

[a] Chance of achieving vaginal birth after CD.

[b] Used as reference.

[c] See Chap. 13.

Abbreviations: CD, cesarean delivery; PRCD, planned repeat CD; TOLAC, trial of labor after CD; NA, not applicable; BW, birth weight.

Until the late 1970s, "Once a cesarean always a cesarean" was the general rule among most obstetricians. This phrase did not derive from formal studies and was clearly not evidence based. A classical uterine incision was used until the1920s, when the low transverse incision was first introduced. The low transverse incision was associated with a tenfold decreased rate of uterine rupture in labor than the classical incision. On the basis of studies in the 1970s, when the vaginal birth after cesarean (VBAC) rate was very low, the National Institutes of Health (NIH) in 1980 and then the American College of Obstetricians and Gynecologists (ACOG) from 1988 to 2019 stated that **a trial of labor (TOL) after a previous low transverse CD is a reasonable option for most women with a prior low transverse CD** [2, 3]. In response to these recommendations, the **VBAC rate**

TABLE 15.3: Maternal and Perinatal Risks of TOLAC versus PRCD

			TOLAC	
	Favors	PRCD	1 Prior CD	≥2 Prior CDs
Maternal Complications				
Uterine rupture	PRCD	1/200–250	1/111–140	1/55–140
Operative injury	PRCD	1/166–200	1/250	1/250
Hysterectomy	–	0–1/250	1/200–500	1/166
Transfusion	–	1/71–100	1/58–140	1/31
VTE	–	1/1000	4/10,000	NA
Endometritis	–	1/47–66	1/34	1/32
Hospitalization	TOLAC			
Death	–	1/2500–5000	1/5000	NA
Satisfaction	–			
Long-term risks	[a]			
Perinatal Complications				
Stillbirth	PRCD	1/1000	2–4/1000	NA
Low cord pH	NA	NA	1.5/1000	NA
Neonatal death	–	5/10,000	8/10,000	NA
Perinatal death	PRCD	1/10,000	13/10,000	NA
Respiratory	TOLAC	1–5/100	0.1–1.8/100	NA
Hyperbilirubinemia	TOLAC	5.8/100	2.2/100	NA
HIE	PRCD	1/10,000	5–8/10,000	NA

Source: From Refs. [2, 9, 27, 41].

Note: Please notice that some numbers may contradict each other, as they are from different sources.

[a] See text.

Abbreviations: CD, cesarean delivery; TOLAC, trial of labor after CD; PRCD, planned repeat CD; NA, not available; HIE, hypoxic-ischemic encephalopathy.

in the United States increased from 3.5% in 1980 to a high of **28.3% in 1996** (Figure 15.1).

As more VBACs were attempted in the 1980s and 1990s, more ruptures were seen and litigation for complications of a TOL also increased. In 1999, ACOG addressed these risks and added the requirements of a "readily available" physician "throughout labor" and "availability of anesthesia and personnel for emergency CD." Since that time, after declining until about 1997, CDs have increased globally, 32% in the United States in 2018 and 28% in England in 2018 [4–6].

At the same time, U.S. **VBAC rates decreased to just 9% in 2011 and rose** from 2016 to 2018, reaching 13.3% in 2018 (Figure 15.2) [4, 5], although they have remained relatively high in the United Kingdom at 33% (range 6%–64%) [5]. The ACOG **requirement for "immediately available" personnel for women undergoing a TOLAC, but not for other laboring women, eliminated the option of TOLAC/VBAC in many community hospitals**. Since 1996, **about one-third of hospitals and one-half of physicians have stopped offering TOLAC/VBAC in the United States** [7].

Definitions

TOLAC: Trial of labor after cesarean.
VBAC: Vaginal birth after cesarean.
PRCD: Planned repeat cesarean delivery (before labor).
VBAC rate: Number of vaginal births after previous CD per 100 live births to all women with a previous CD (same denominator as the CD rate).
TOLAC rate: If the average success rate of a TOLAC is about 70%, then the TOLAC rate is the VBAC rate/0.7.
Adjusted VBAC rate: Number of women with prior CD **and no contraindications to TOL** who had a VBAC per 100 live births to all women with a previous CD.
Successful VBAC rate: Percentage of women with prior CD who attempted a TOLAC achieving VBAC.
Successful adjusted VBAC rate: Percentage of women with prior CD **and no contraindications to TOLAC** achieving a VBAC.
Failed TOLAC (failed VBAC): TOLAC that results in a repeat CD.
Uterine dehiscence: Disruption of the uterine muscle **with intact serosa** [7]. It can include asymptomatic opening if the uterine scar is from a prior surgery, without protrusion of fetus/fetal organs outside the uterus.
Uterine rupture: Disruption or tear of the uterine muscle and visceral peritoneum, or separation of the uterine muscle with **extension to the bladder or broad ligament** [7]. It includes symptomatic gross rupture of the uterine scar from a prior surgery, with or without protrusion of fetus/fetal parts outside the uterus.

General considerations

A woman with a prior CD has two options for mode of delivery in a subsequent pregnancy: A **PRCD or a TOLAC** to try to achieve a VBAC.

There are two randomized controlled trials (RCTs) examining outcomes for women who underwent PRCD vs. TOLAC [8, 9]. Only one of these studies reported clinical outcomes and was quite small, with a sample size of 22 [9]. The other, while larger, looked at maternal psychometric outcomes [8]. There is also a small prospective cohort study to compare these two options, which also focuses on psychological outcomes, not maternal and fetal safety and complications [10]. Virtually all studies on VBAC, with a few exceptions [11], are retrospective and often use differing criteria for patient selection and differ in their ability to correctly ascertain (make sure all cases are included) and define uterine rupture. Most studies also include women at various gestational ages and may therefore not specifically apply to women at term considering their options of delivery after a prior CD. Studies with <1000 TOLACs cannot adequately assess maternal and fetal/neonatal morbidity and mortality, as these complications are rare, and meta-analyses [12, 13] might compound errors from different retrospective studies. Many studies do not differentiate between asymptomatic uterine dehiscence and true acute symptomatic uterine rupture.

The **main issues** regarding TOLAC are the following:

1. Which women are **candidates** for TOLAC and which should instead be recommended a PRCD?
2. Among women who attempt a TOLAC, what is the **VBAC rate** (successful TOLAC) and which factors influence it?
3. What are the short- and long-term **maternal and perinatal benefits and harms** of attempting TOLAC versus PRCD, and what factors influence benefits and harms?

Complications and safety are especially related to the risk of **uterine rupture**.

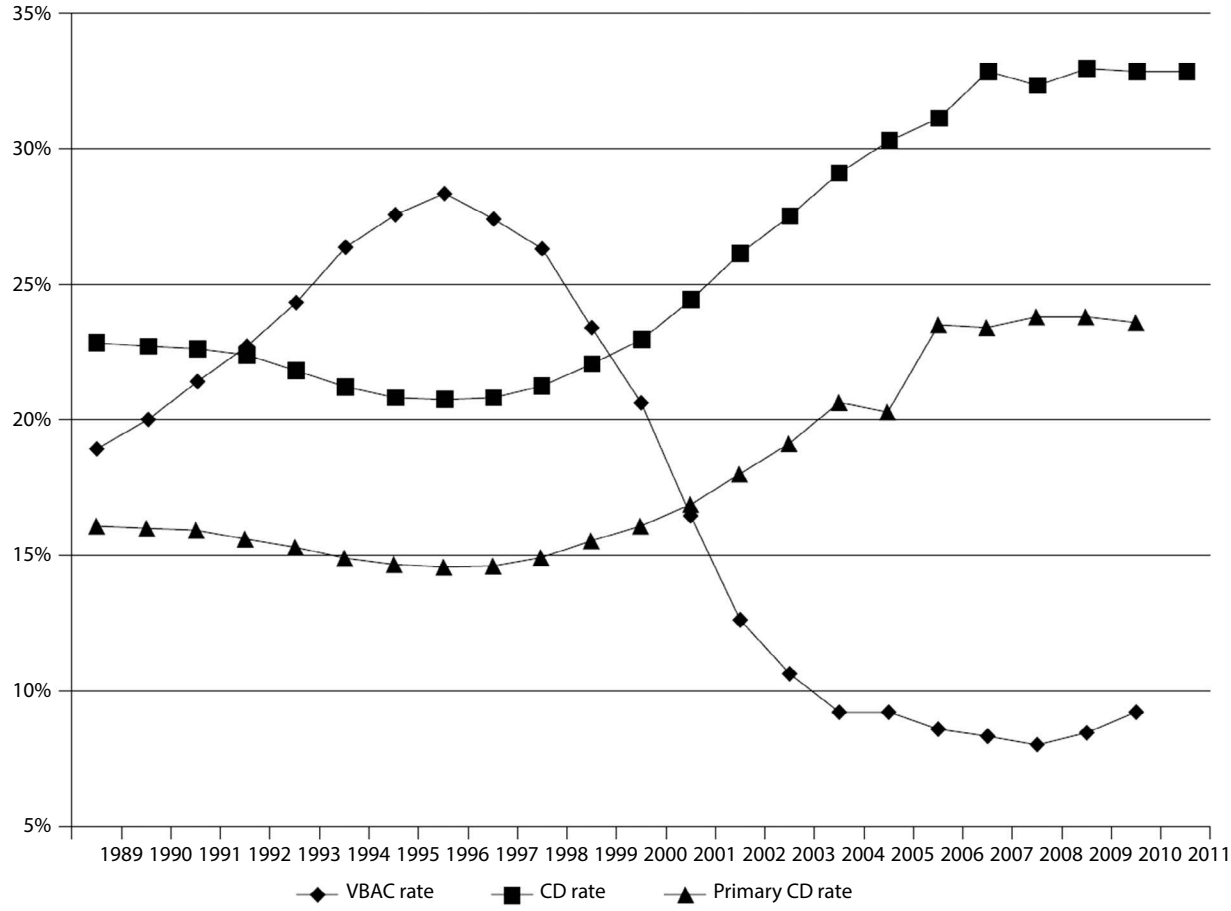


FIGURE 15.1 Rates of vaginal birth after Cesarean (VBAC rate), total cesarean delivery (CD rate), primary Cesarean deliveries (primary CD), and repeat cesarean delivery (RCD). (From Caughey et al., AJOG 2014, 210(3):179–193, with permission.)

These issues are important in order to **properly counsel** women who are considering a TOLAC [7]. This information should be shared with the woman in a way best suited to her understanding. When a TOLAC and a PRCD are medically equivalent options, the woman's preference should be honored if possible [1].

Candidates for TOLAC

The choice of candidates for TOLAC should be based on an acceptable balance between the chance of achieving a VBAC and fetal and maternal risks. The ACOG and the 2010 NIH consensus

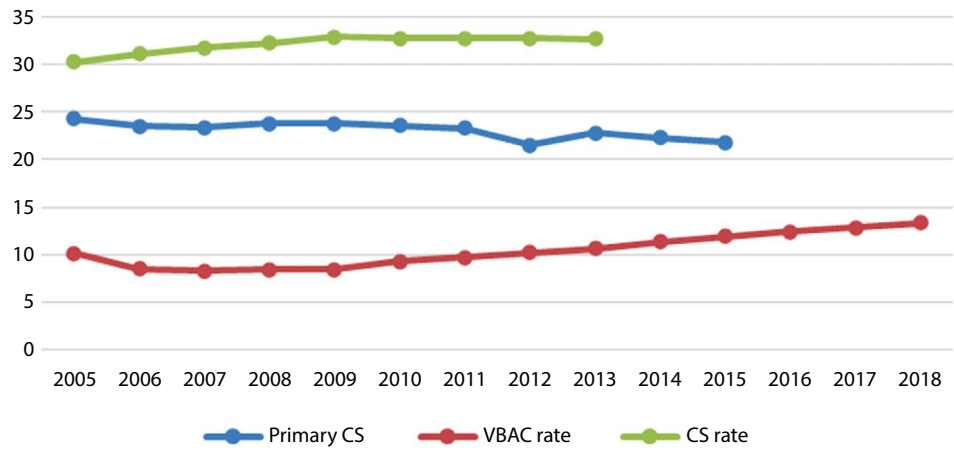


FIGURE 15.2 Rate of VBAC and cesarean delivery since 2005.

statement acknowledged that **TOLAC is a reasonable option for most women with a single prior low transverse CD with no other contraindications to a vaginal birth** [2, 3, 7]. Criteria to be a candidate and absolute and relative **contraindications** for TOLAC are shown in Table 15.1.

Factors affecting a successful TOLAC

Vaginal delivery rates for TOLAC in the general population of women with previous low transverse uterine incisions vary from 60% to 80% [11, 13–15]. In tertiary care centers the rates may be higher, about 73%–76% [11, 16]. The rate is highly dependent on demographic and obstetric factors (Table 15.2). Based on these factors, **women with a probability for VBAC of at least 60%–70% have similar or less maternal and perinatal morbidity with a TOLAC than a PRCD** [17, 18]. Conversely, women with less than a 60% probability of VBAC have a greater likelihood of morbidity with TOLAC than if they had a PRCD. One study demonstrated that composite neonatal morbidity is similar between TOLAC and PRCD for the women with the greatest probability of achieving VBAC [17]. Factors that influence the likelihood of VBAC after TOLAC and their effect on success rates are shown in Table 15.2 and described later in this chapter.

Maternal demographics

Age

There is inconsistent evidence regarding the effect of age on VBAC after a TOLAC. Prospective studies did not show any relationship, although overall there appears to be a small inverse association between maternal age and the likelihood of vaginal delivery [1].

Race/Ethnicity

Race and ethnicity have been one of the strongest demographic predictors of VBAC. **Hispanic and African American women have lower rates of VBAC** than non-Hispanic white women, but there are concerns that these data are related to other factors in care rather than race itself. Other factors such as marital status and insurance type were also identified as risk factors but not included in the final predictive model [19].

Obesity

Obese women attempting a VBAC have **lower vaginal delivery rates**. This appears to be true whether measured at first prenatal visit (per body mass index [BMI] unit) or at delivery (BMI >30) (adjusted ORs [aORs] 0.94, 95% confidence interval [CI] 0.93–0.95 and 0.55, 95% CI 0.51–0.60, respectively [20, 21]). **Obese women, weighing ≥300 lb, had rates of VBAC of only 15%,** while women weighing 200–300 lb had rates of 56% [19, 22]. **Greater maternal height and BMI <30 kg/m² are associated with an increased likelihood of VBAC**.

Obstetric history

Prior vaginal delivery

A prior vaginal delivery, either before or after a prior CD, is the strongest predictor of a VBAC after a TOLAC. A previous successful VBAC is the most predictive [23]. **The VBAC rate is >85% for women with a prior VBAC**, compared with 65% for women without a prior vaginal delivery [24, 25]. The rate of VBAC increases with each prior VBAC. Women with zero, one, two, three, and four or more prior VBACs have likelihoods of VBAC of 63%, 88%, 91%, 91%, and 91% (p <0.001), respectively [26].

Prior indication for cesarean

Breech presentation or other **nonrecurring indication** (e.g. nonreassuring fetal monitoring) for the prior CD significantly increases the chances for a vaginal delivery (85%) compared with CD done for a recurring indication such as dystocia or failure to progress. These rates are similar to vaginal delivery rates in nulliparous women. Nevertheless, about 60%–70% of women undergoing a TOLAC for **dystocia** (failure to progress) deliver vaginally [1]. In addition, most studies show no reduction in the rates for a successful TOLAC after a **prior CD done for failure to progress in the second stage of labor** (75%–80%), with no increased risk of operative vaginal delivery [1, 27–29].

This is confirmed in later retrospective studies showing the success of TOLAC was 75.6% for women with prior arrest in the first stage of labor, 73.1% for women with a prior second-stage arrest, and 59.0% with prior failed induction [30]. For women attempting TOLAC with prior cesarean for arrest of descent, the TOLAC success rate was 84% [31], and for those attempting TOLAC with prior cesarean for failed vacuum, the TOLAC success rate was 67% [32].

Uterine scar type

Vaginal delivery rates appear to be **similar** for low transverse, low vertical, and unknown incision types [21, 33]. Most women with unknown scar types have had low transverse incisions.

Number of prior cesarean deliveries

Previous studies had reported that 75%–80% of women attempting a VBAC with a single prior cesarean will deliver vaginally versus about **60%–70% with more than one prior cesarean**. Later studies have shown that **the greater the number of prior CDs, the lower the chances for a vaginal delivery (about 10%–15% lower per CD)** [33]. But a large retrospective multicenter study found similar rates of vaginal delivery after TOL in women with two versus one prior CD (75%) [34], while a meta-analysis of six studies that compared outcomes between women having a TOL after one or two CDs found similar vaginal delivery rates of 77% and 72%, respectively [35]. Likewise, another study showed that the vaginal birth rates were similar (65% vs. 69%) in women undergoing induction with one or two prior CDs [36]. However, a recent large retrospective study of over 42,000 women revealed a much lower rate of successful VBAC in women with two prior CDs—only 2.9% of these women attempted a TOL, and of these, only 39.4% had a successful VBAC [37].

ACOG considers it **reasonable to offer TOLAC to those women with two prior low transverse CDs who also have a good probability of successful VBAC** (ACOG). See "Prediction Tools for Vaginal Delivery" later.

Interdelivery interval

An interdelivery interval of <18 months may be associated with similar success rates of TOL after CD compared to longer intervals [33], but in one study, rates were lower with induction [38].

Current labor factors

Cervical status

Labor factors associated with a higher VBAC rate include greater cervical dilation at admission or at rupture of membranes. The more **favorable** the **cervix**, the greater the odds for a vaginal delivery. Fetal head engagement and a lower station also increase the likelihood of VBAC [1]. Prelabor rupture of membranes is associated with a decreased likelihood of VBAC (odds

ratio [OR] 4.47, 95% CI 2.07–9.63) [39]. Shorter cervical lengths at mid-trimester ultrasound are associated with an increased likelihood of VBAC but do not improve the VBAC prediction model of Grobman [20, 36].

Gestational age

Preterm patients with a prior CD have a slightly higher VBAC success rate than term patients (82% vs. 74%) [40]. **Gestational age greater than 40 weeks** is associated with a decreased rate of VBAC. There are conflicting data regarding the chance of VBAC after TOLAC in **postterm** pregnancy. Successful VBAC rates of 65%–82% have been reported for women past 40 weeks, with the higher rates in women with prior vaginal deliveries [1]. In the Maternal-Fetal Medicine Unit (MFMU) cohort, women >41 weeks had a lower chance for vaginal delivery than women <41 weeks (aOR 0.61, 95% CI 0.55–0.68) [21]. **If VBAC is still desired after 40 weeks, awaiting the onset of spontaneous labor may be a better option than induction before 40 weeks for women planning a VBAC, given the lower success rates with induction in this population, particularly for women with an unfavorable cervix** [21, 41].

Induction/Augmentation of labor

The overall estimated rate of vaginal birth with a TOLAC after any method of labor induction is 63% [1]. **Women with a prior CD who are induced have lower rates of successful TOLAC (about 10%) than those who labor spontaneously** [12, 33, 42]. Studies demonstrate that the rate of VBAC ranges from 54% for induction of labor with mechanical methods (transcervical balloon catheter) to 69% for induction with pharmacologic methods. One RCT showed that for patients with a Bishop score less than or equal to 4, beginning induction with a cervical balloon was associated with a higher rate of successful VBAC (50%) compared to starting the induction with oxytocin alone (37%) [43].

Fetal macrosomia

The most consistent infant factor associated with an increased likelihood of VBAC is birth weight <4000 g. As expected, large for gestational age/macrosomia, especially birth weight >4000 g, decreases the odds of a VBAC after TOLAC [44]. The success rates for VBAC in women with a previous CD and no other births is about **60% in the >4000 g group** and **71% in the ≤4000 g group** [45]. There is a progressive reduction in VBAC success rates as birth weight increases. **With a prior VBAC or a vaginal delivery**, there is **no success rate below 63% for any of the birth weight strata**. But **with no previous vaginal delivery, VBAC success rates can drop below 50% as neonatal weight exceeds 4000** g [24, 44]. This success rate can decrease further if the indication for the previous CD is cephalopelvic disproportion or failure to progress. **There are limited data regarding prenatal estimated fetal birth weight and VBAC success**. Even so, VBAC rates after TOL were noted to be 60%–70% in fetuses suspected to be macrosomic [24]. This is likely due to the limitations of estimating birth weight by ultrasound. Thus, suspected macrosomia alone should not rule out a TOLAC [3].

Multiple gestations

Vaginal delivery rates of both twins after a prior CD generally range from 65% to 84% [33, 46, 47]. In most series, rates do not seem to differ from success rates in singletons, without increased risk for maternal morbidity or uterine rupture [46, 47].

Prediction tools for vaginal delivery

Given the associations noted earlier, several different scoring systems have been proposed to predict the likelihood of vaginal delivery or cesarean in women undergoing a TOLAC [1, 20, 24, 40, 48, 49]. The best studies used scoring systems that were validated in separate data sets and in external studies [1]. These scoring systems performed as well in the validation testing as they did in the original data set. Unfortunately, although these models are accurate at predicting which women will have a VBAC, they are limited in their ability to predict who will have a repeat cesarean following a TOLAC [50, 51]. Half of women with unfavorable risk factors had a vaginal delivery.

One available tool developed by Grobman et al. for the MFMU Network can be found at http://www.bsc.gwu.edu/mfmu/vagbirth.html, but this tool only includes factors known at the beginning of pregnancy [20]. Grobman also proposed a second nomogram with improved performance that also utilized information obtained at the time of admission (Figure 15.3) [52]. Metz et al. proposed another simple validated tool to be used at the time of admission (Figures 15.4 and 15.5) [50] and validated the original Grobman model in a population of women with two prior CDs [53].

One study compared the actual outcomes of 568 ethnically diverse U.S. populations of women attempting VBAC to the success rate calculated by the MFMU Network calculator. For women with high predicted success rates, there was good correlation with actual outcomes, but for those with a low predicted rate (29%), the actual VBAC success rate was 57% [54]. The authors of the NIH-sponsored review of prediction tools recommend clinicians use a sequential approach to screening [51]. Initially, prenatal predictors such as previous vaginal delivery and previous indication for CD, and possibly patient demographics and fetal estimated weight, should be considered. This can then be modified by intrapartum predictors such as onset of spontaneous labor or the need for induction, and cervical status can be used to reevaluate the likelihood of vaginal delivery [20, 50].

It should be noted that the inclusion of race-based correction factors may not be valid and may perpetuate health care bias, as the data on which they are based may reflect social disadvantage similar to insurance type and marital status, which were not included in the final algorithm. In addition, the models function equally well without the inclusion of race [19].

A recent comparison of three of these models, including the two by Grobman and the one by Metz [20, 50, 52], also showed that two [20, 52] were very **accurate when the probability of success was >60% but not accurate when <60%. Calculators may be most useful in counseling women who are not planning VBAC yet have a high probability of success. They are less helpful for discouraging women based on low probabilities of success** [55]. They are probably unnecessary for women with >80% rate of success who are planning a VBAC.

Uterine rupture

Complications and safety of TOLAC are especially related to the risk of **uterine rupture**. Uterine rupture is the most serious complication associated with TOLAC. It is defined as a complete separation through the entire thickness of the uterine wall (including serosa). At all gestational ages, pooled data from one review indicate that uterine rupture occurs in approximately 470/100,000 (0.47%, 95% CI 0.28–0.47) of women undergoing TOLAC and in 26/100,000 (0.026%, 95% CI 0.009–0.082) of women undergoing a PRCD (relative risk [RR] 20.74, 95% CI 9.77–44.02; $p < 0.0010$) [1].

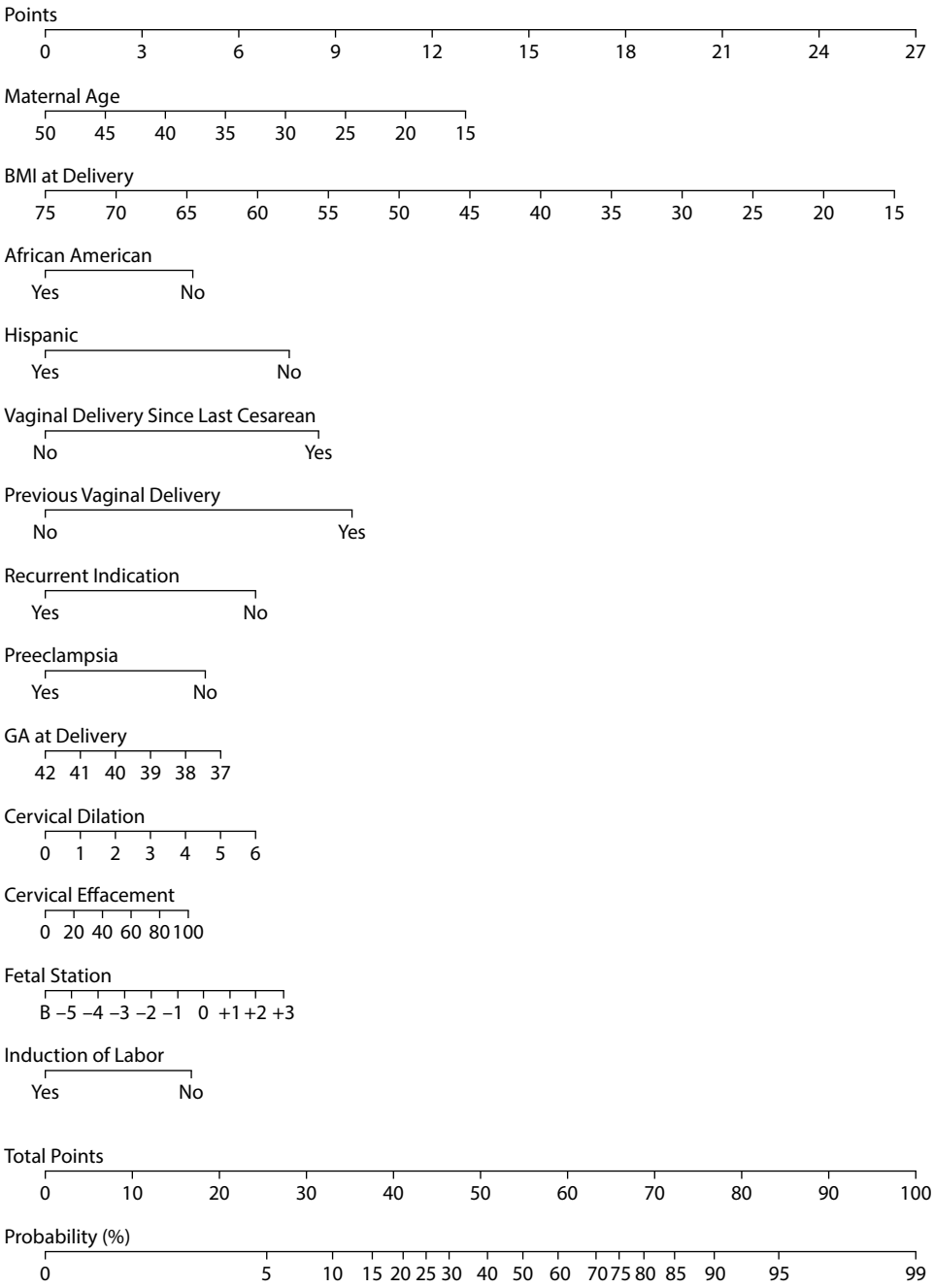


FIGURE 15.3 Predictive graphical nomogram, incorporating information available up until the time of admission for delivery, for probability of VBAC success resulting from a trial of labor. (From Grobman W, Lai Y, Landon M, et. al. Does information available at admission for delivery improve prediction of vaginal birth after cesarean? *Am J Perinatol*. 2009;26(10):693–701. [II-2]. Ref. [52], with permission.)

At term, the overall risk for rupture is 778/100,000 (0.78%, 95% CI 0.62–0.96). This means that overall there are about 5 to 6 additional ruptures per 1000 in women undergoing a TOLAC [1]. No maternal deaths due to uterine rupture have been reported [1, 56]. **Perinatal death occurs in about 6% of women with uterine rupture, which translates to an overall risk of intrapartum fetal death of about 20/100,000** and a risk of perinatal death at term of about 0%–2.8% in women undergoing a TOLAC [1].

Factors affecting the risk for uterine rupture

The risk for rupture is modified by a number of important factors [57] listed in Figure 15.6 and described next. Prior vaginal delivery and prior VBAC reduce the risk of uterine rupture, while number of prior CDs, vertical scars, single-layer closure, induction or augmentation, greater maternal age, fever, prior preterm CD, and TOLAC at ≥40 weeks are associated with higher rupture rates.

Calculation of Integer Vaginal Birth after Cesarean Score
Calculate the Bishop score using the cervical examination at the time of admission
Add 4 points for history of vaginal delivery
Add 2 points if pre-pregnancy body mass index is less than 30
Add 3 points if primary cesarean delivery was not because of a recurring indication
Add 2 points if maternal age at the time of delivery is younger than 35 years
Sum total score in figure 15.5

FIGURE 15.4 Calculation of integer vaginal birth after Cesarean score. (From Metz, T.D., et al., Simple, validated vaginal birth after cesarean delivery prediction model for use at the time of admission. *Obstet Gynecol*, 2013;122(3): p. 571–578. [II-2]. Ref. [50], with permission.)

Increase risk

Maternal age

Maternal age (>30 years old) is associated with an increased risk (1%–1.4%) of uterine rupture [58, 59].

Number of prior cesareans

Women with two or more prior low transverse CDs may be at increased risk of uterine rupture compared with women with one prior CD, but the absolute risk is small (1.36%), while the success rate is high (71%) [35]. **Current ACOG recommendations allow this option regardless of whether there is a prior vaginal delivery** [3]. **Most ruptures occur in women undergoing induction or augmentation and in those without a prior vaginal delivery** [34]. Earlier data had indicated an overall relative increased risk of rupture (about twofold to threefold) in women having a TOL after two low transverse CDs compared with one [56, 60–62]. A meta-analysis confirmed these findings **(0.9% for one prior CD vs. 1.8% for two prior CDs)** [34]. A follow-up case-control analysis of the study by Macones et al. showed no increased risk (OR 1.46, 95% CI 0.87–2.44), and in the MFMU cohort [60], there was no difference in the incidence of rupture after two CDs compared with one (0.9% vs. 0.7%). Furthermore, the rupture rate in women with a prior vaginal delivery and two prior CDs is only 0.5%, no greater than a VBAC with only one prior CD [60].

Prior CD characteristics

Direction of scar

Classical and low vertical uterine scars have higher rates of rupture compared with low transverse uterine incisions (4%–10%, and 1–2%, respectively) [3]. **Records regarding the prior CD(s) should be obtained, with special care in documentation of direction of scar. If a woman has had a prior vertical (classical) CD, PRCD at 36–37 weeks is recommended** [3, 63].

Layers of closure

There is insufficient evidence to assess if the numbers of layers performed at prior uterine closure affect the outcomes, specifically the rate of uterine rupture, for future pregnancies. Randomized trials have insufficient follow-up numbers (see Chap. 13). Compared with women who had a double-layer closure, women with a single-layer closure have been reported to have anywhere from a similar to a fourfold increased risk of uterine rupture compared with those with a double-layer closure [64–66]. One large multicenter case-controlled study that examined operative reports found a fourfold increase in uterine rupture for women with a single-layer uterine closure compared to those with a double-layer uterine closure (OR 3.95; 95% CI 1.35–11.49) [64]. However, a later study showed no difference in uterine rupture by layers of closure (OR 1.17; 95% CI 0.78–1.76) [53].

Calculated VBAC Score	No. of Study Participants	Chance of Successful VBAC	Actual VBAC Success Rate
4	2 (0.17)	11.7 (6.4–20.5)	0.0
5	3 (0.26)	14.7 (8.5–24.3)	33.3
6	5 (0.43)	19.0 (11.8–29.1)	20.0
7	5 (0.43)	24.7 (16.7–35.0)	40.0
8	7 (0.60)	31.9 (23.3–41.9)	42.9
9	16 (1.37)	40.2 (31.8–49.2)	25.0
10	23 (1.97)	49.1 (41.6–56.6)	60.9
11	46 (3.93)	57.7 (51.6–63.6)	58.7
12	58 (4.96)	65.6 (61.0–69.9)	65.5
13	95 (8.12)	72.2 (68.7–75.4)	73.7
14	102 (8.72)	77.5 (74.7–80.1)	71.3
15	150 (12.82)	81.6 (79.1–83.8)	80.7
16	134 (11.45)	84.7 (82.3–86.8)	84.2
17	144 (12.31)	87.0 (84.6–89.0)	86.1
18	139 (11.88)	88.6 (86.3–90.6)	92.1
19	94 (8.03)	89.8 (87.6–91.8)	90.4
20	62 (5.30)	90.7 (88.5–92.6)	91.9
21	48 (4.10)	91.4 (89.1–93.2)	91.7
22	25 (2.14)	91.9 (89.6–93.7)	96.0
23	12 (1.03)	92.3 (90.1–94.0)	91.7

FIGURE 15.5 Chance of successful vaginal birth after Cesarean delivery based on calculated vaginal birth Cesarean delivery score. (From Metz, T.D., et al., Simple, validated vaginal birth after cesarean delivery prediction model for use at the time of admission. *Obstet Gynecol*, 2013;122(3): p. 571–578. [II-2]. Ref. [50], with permission.) *Abbreviations*: VBAC, vaginal birth after cesarean; CI, confidence interval. Data are n(%), %, (95% CI) or %.

Fever

The presence of both intrapartum and postpartum fever at CD, but not either alone, may increase the risk of uterine rupture in a subsequent pregnancy [67].

Previous preterm CD

The MFMU Network data showed a **higher risk of rupture** in women with a prior preterm CD compared with those with a prior term CD (1% vs. 0.68%; aOR 1.6, 95% CI 1.01–2.50) [68]. No difference in rupture rates were found in a secondary analysis of the retrospective, multicenter cohort study comparing prior CD before and after 34 weeks (aOR 1.5, 95% CI 0.7–3.5) [62].

Prior uterine rupture

As prior uterine rupture is associated with **high rates (6%–32%) of recurrent rupture** with TOLAC, these pregnancies should have a **PRCD before labor**, possibly around 36–37 weeks [63].

Interval between deliveries

Interval between deliveries **of <18 months** are associated with an **increased risk of uterine rupture** (2.3%–4.8%) compared with longer intervals (1.1%–1.3%) in a number of studies [58, 59, 69, 70].

Post dates

The risk of uterine rupture does not increase substantially after 40 weeks, but is increased with induction of labor regardless of gestational age [71, 72].

Macrosomia >4000 g

Macrosomia >4000 g is associated with a slightly increased risk of rupture. A multicenter case-control study showed that birth weight >3500 g had twice the risk for rupture (OR 2.03, 95% CI 1.21–3.38) [44].

Induction/Augmentation

The rate of uterine rupture in women with one prior low transverse CD undergoing TOLAC with spontaneous labor is about 0.4%. Almost all studies compare women undergoing induction with those in spontaneous labor instead of expectant management. These studies (including the large prospective MFMU observational trial) reported **higher rates of uterine rupture (up to 1%–2%) with induction** at any gestational age and of any kind [11, 73, 74]. There are no RCTs comparing these two groups, but a meta-analysis of eight studies comparing women with prior CD undergoing induction to those in spontaneous labor showed lower rates of vaginal delivery and higher rates of rupture among women undergoing induction, but no differences in overall maternal or neonatal morbidity [75].

At term, the risk of rupture is not statistically significantly greater than women with spontaneous labor (OR 1.42, 95% CI 0.57–3.52). But women induced at >40 weeks have a higher risk of rupture than those induced between 37 and 40 weeks (3.2% vs. 1.5%) [1].

In the MFMU cohort, induction increased the risk of rupture **only in women without a prior vaginal delivery** (induced 1.5% vs. spontaneous 0.8%). In women with a prior vaginal delivery, the incidence of rupture was similar (0.6% vs. 0.4%) [41]. A case-control study including 111 cases of uterine rupture did not find an increase in rupture compared to spontaneous labor even after controlling for labor duration. But the risk was slightly higher with an unfavorable cervix (<4 cm) [76].

Two studies compared induction to expectant management instead of spontaneous labor, a more clinically appropriate comparison. One was a secondary analysis of the MFMU data and showed that induction had higher rates of vaginal delivery (73.8% vs. 61.3%) but also had higher rates of rupture (1.4% vs. 0.5%) [77]. The other was a secondary analysis of the Consortium on Safe Labor and found lower rates of vaginal delivery at 37–39 weeks but not at 40 weeks and no difference in uterine rupture [42].

Type of induction

The risks of uterine rupture with induction in women who had one prior CD may also depend on the **type of induction**. Risk of rupture may be as high as **1.4%–2.5% with induction with prostaglandin** (with or without oxytocin) [9, 67] and about **1.1% with oxytocin alone** [78]. In one large population-based study, sequential use of prostaglandin and oxytocin was the strongest risk factor for rupture (OR 48, 95% CI 20.5–112.3) [58]. The MFMU data, which included all prostaglandins, and the Grobman et al. study, which excluded misoprostol, did not find an increased risk for rupture when prostaglandins were used alone, but they did note a **threefold increased risk with sequential use of prostaglandins and oxytocin versus spontaneous labor** [41]. The Cochrane review concluded that there is insufficient evidence from RCTs regarding the method of induction (only two small RCTs comparing two different types of prostaglandins to oxytocin). One study was stopped due to two ruptures in the misoprostol group (2/17) [79]. ACOG therefore advises that induction with **sequential use of prostaglandins and oxytocin be avoided** [3]. ACOG considers the **use of a Foley bulb for cervical ripening an acceptable method of labor induction**, as limited data appear to show no increased rates for rupture [3]. AN RCT showed significantly higher VBAC success rates if a Foley bulb is used for ripening (compared to low-dose oxytocin) in women with a low Bishop score [43]. There are no randomized trials comparing induction to elective repeat cesarean delivery (ERCD).

Augmentation of labor

Augmentation may be associated with an increased risk of rupture, up to about 1%, but the risk is mainly related to higher doses of oxytocin [11, 80, 81]. A secondary analysis of a large retrospective cohort and a follow-up nested case-control study reported a dose–response relationship between the maximum oxytocin dose and increased risk for uterine rupture (fourfold increased risk with 21–30 mU/minute vs. no oxytocin; attributable risk of 2.9%–3.6%) [81, 82]. **Oxytocin should be used judiciously in women undergoing TOLAC, with a possible maximum dose of 20 mU/minute**.

Length of second stage

The length of the second stage has been associated with an increasing risk for uterine rupture in a secondary analysis of the MFMU Cesarean Registry. The risk of uterine rupture or dehiscence increased with second-stage length from less than 1 hour (0.7%), 1 to less than 2 hours (1.4%), 2 to less than 3 hours (1.5%), to 3 hours or greater (3.1%) (p <0.001) [83].

Second-trimester induction of labor

Induction of labor in the second trimester with misoprostol is associated with a **0.4% risk of uterine rupture** (with 0% risk of hysterectomy and 0.2% risk of transfusion) **after one prior low transverse CD** and about 50% risk with a prior classical CD [81]. There is insufficient evidence to assess the safety of mifepristone induction in women with a prior CD.

No change or decreased risk

Prior vaginal delivery

Prior vaginal delivery significantly **reduces the risk for rupture during TOLAC from 1.1%, in women with no prior vaginal deliveries, to 0.2%**. After controlling for maternal demographics and labor characteristics, prior vaginal delivery reduced the risk for rupture fivefold (OR 0.2, 95% CI 0.04–0.08) [84]. This protective effect was also confirmed by large retrospective (OR 0.30, 95% CI 0.23–0.62) [85] and prospective (OR 0.66, 95% CI 0.45–0.95) studies [11].

Labor before primary CD

Labor before the primary CD has been associated with a lower risk of uterine rupture in a future TOLAC compared with no labor before the primary CD [86].

Twins

The risk of rupture or maternal mortality is not increased with prior CD and subsequent TOL with twins, with uncommon perinatal morbidity at ≥34 weeks [46, 87].

Prior CD for twins
Compared with women with prior CD for singletons, women with prior CD for twins have similar risk of uterine rupture and TOLAC success [88].

Preterm
In one study there was a trend toward a lower uterine rupture rate in preterm patients who attempted a VBAC [40]. In the large MFMU cohort, the rates of uterine rupture and dehiscence were lower in preterm TOL versus term; 0.34% vs. 0.74%, $p = 0.03$ and 0.26% vs. 0.67%, $p = 0.02$, respectively [89]. On the other hand, women with a very preterm delivery (<26 weeks) with a prior low transverse CD may have an increased rate of rupture with subsequent TOL compared to women with a prior term low transverse CD, 1.8% vs. 0.4%, respectively [73].

Benefits and harms associated with TOLAC (aside from rupture)

Most of the benefits and the least morbidity of a TOLAC are dependent on having a VBAC, while the potential harms of a TOLAC are associated with an unsuccessful TOLAC resulting in CD. Studies comparing TOLAC to PRCD usually include both VBAC and TOLAC ending in CD. Thus, the outcomes for women who have a TOLAC reflect both possibilities. These data are therefore appropriate for women with a previous CD who are deciding on the mode of delivery for the current pregnancy. Most studies show that rates of all maternal and perinatal complications except rupture are infrequent and similar with both TOL and PRCD, but these are small studies with few events [15, 16, 90].

One study of 2345 women with one prior CD compared outcomes among those with a planned ERCD and planned TOL and noted lower rates of serious perinatal complications (0.9% vs. 2.4%) and major maternal hemorrhage (0.8% vs. 2.3%) in the ERCD group. The vaginal delivery rate was 56.8% in the TOL group, with similar rates of uterine rupture in both groups (0.1 vs. 0.2%) [9].

Maternal (Table 15.3)
Surgical complications
Overall rates of surgical injury are low but may be **slightly higher with TOLAC** compared with PRCD. This is primarily due to those women who have a TOLAC but deliver with a repeat CD in labor [9–11, 17, 91, 92]. There are no studies that specifically evaluated the risks of complications due to subsequent surgery after a TOLAC or PRCD. Nevertheless, an increasing number of abdominal surgeries is commonly associated with increased risks of adhesions, injury to bowel and bladder, and other complications at the time of subsequent CD or nonpregnancy-related hysterectomy.

Hysterectomy
The risk of hysterectomy is about 1–2/1000 TOLACs and similar to PRCD [10, 11, 13, 16, 90, 93, 94]

Transfusion
The risk of transfusion is very low, and in most studies not significantly different for TOLAC or PRCD (0.9% vs. 1.2%) [1, 11]. It has been estimated at about 2 units packed red blood cells (pRBC)/1000 TOLAC [13]. The risk is higher when labor is induced with no prior vaginal deliveries, and it is related to the need for CD following a TOLAC [11].

Venous thromboembolism
The risk is about 4/10,000 with TOLAC, similar to PRCD (1/1000) [11].

Endometritis
The risk is very similar for TOLAC or PRCD, with a 6% vs. 7–8% rate of fever [12], or 3% vs. 2% in academic centers [11]. The overall absolute risk for any fever with TOLAC is 6.5% [1]. Morbid obesity, cesarean after TOLAC, and increased number of CDs increase infection rates.

Hospitalization
Overall, because most women deliver vaginally, a TOLAC results in a shorter **hospitalization** compared with PRCD. This benefit does not apply to morbidly obese women.

Maternal mortality
The risk of **maternal mortality is lower overall for women having a TOLAC** (3–4/100,000) compared with PRCD (13.4/100,000). This compares to the overall U.S. maternal mortality rate of 11–15/100,000. At term, maternal mortality is lower: 1.9 for TOLAC versus 9.6 PRCD per 100,000 live births [1]. Based on limited evidence, mortality is lower for TOLAC in high-volume hospitals (more than 500 deliveries per year) [8].

Short-term satisfaction
Anxiety, depression, psychological well-being, and satisfaction scores are similar between women who choose TOLAC versus those who elect for PRCD [10].

Long-term maternal risks
There is a clear association between the number of CDs and abnormal placentation, as well as other surgical complications [92]. This complication is an important consideration for the 28% of women who have more than two births. For each CD, the risk for placenta previa significantly increases, occurring in 900, 1700, and 3000 per 100,000 women who have one, two, and three or more prior CDs, respectively. The overall risk for placenta accreta also increases (0.2% in the first CD to 0.3%, 0.6%, 2.1%, 2.3%, and 6.7% for second, third, fourth, fifth, and sixth and up CD, respectively). In the presence of placenta previa, the risk for abnormal placentation is markedly increased for each additional CD (3.3%, 11%, 40%, and >60% for the first, second, third, and fourth or more CDs, respectively).

Even without a placenta previa, the incidence of abnormal placentation, although much lower, increases with the number of CDs (see Chap. 25). **The major benefit of TOLAC is about a >70% chance of a VBAC and avoidance of multiple CDs**.

In addition, as noted earlier, women who undergo multiple CDs are at increased risk for many complications unrelated to placentation, including hysterectomy, adhesions, injury to bowel and bladder, transfusions >4 units of pRBCs, need for postoperative ventilation, ICU admission, and increased operative time and hospital stay [95]. There is insufficient evidence regarding long-term pelvic floor function comparing TOLAC with PRCD. PRCD should not be used as a way to prevent pelvic floor disorders [1].

A decision analysis evaluating both the immediate and subsequent risks of the delivery decision for women with a prior CD suggested that **for women planning only one additional pregnancy, PRCD results in fewer hysterectomies than TOLAC**, while for women planning two or more additional pregnancies, a TOL provides the lowest risk [96, 97]. Therefore, when

counseling women about risks and benefits of a TOLAC compared with PRCD, the discussion should address her plans for future pregnancies.

Fetal/Neonatal

The overall risk of serious **perinatal complications** is about 1 in 2000 **TOLAC**, which is **slightly greater** than that of PRCD [11]. Combining all poor perinatal outcomes, **more than 600 PRCDs would need to be performed to prevent one poor perinatal outcome**. Although a woman with a TOLAC is at higher risk of uterine rupture than any other group, the risk of perinatal death is similar to that of any nulliparous woman in labor [16]. **The most serious fetal risk in women with prior CD is from uterine rupture during TOLAC**. Risks of fetal/neonatal morbidity/mortality with term uterine rupture are **33% risk of pH <7.00, 40% risk of admission to the NICU, 6% risk of hypoxic-ischemic encephalopathy (HIE), and 1.8% risk of neonatal death. The rupture-related risk of neonatal death is 1/10,000 in equipped academic centers** [11]. **In other centers, these risks are higher, including the risk of neonatal death from rupture up to 10%–25%**. The large population-based Norway study showed that normal prenatal outcomes occurred in about 44.7% with complete rupture (Figure 15.6) [76].

Stillbirth

The rates of stillbirths are **2–6/1000 for TOLAC versus 1–2/1000 for PRCD**. At 39 weeks or more, the rate of antepartum stillbirth in the MFMU cohort was 1/1000 with TOLAC and 3/10,000 with PRCD [9, 72]. This difference might be due to stillbirths occurring at ≥39 weeks with TOLAC and/or to encouragement for TOLAC with diagnosis of stillbirth [11].

Low cord pH

The risk of cord pH <7.00 is about 1.5/1000 TOLAC [13].

Neonatal death

Neonatal death rates are similar between TOLAC versus PRCD (0.08% vs. 0.05%, respectively) in academic centers, with the neonatal death rate associated with a rupture at term of about 1.8% [11].

Perinatal death

Perinatal death rates at term (excluding malformations) are **1.3/1000 with TOLAC versus 0.5/1000 for PRCD** [10]. **Overall risk of adverse perinatal outcome is 1/2000 with TOLAC, slightly higher than with PRCD** [11]. In one study of women at term with vertex presentations, the risk of delivery-related perinatal mortality with a TOLAC was 11 times that of PRCD (OR 11.6, 95% CI 1.6–86.7). When compared with women **without a previous CD** (instead of to those having a PRCD), the **perinatal mortality for TOLAC was the same as that of a nullipara in labor**, but about twice as high as that of a non-TOLAC multipara in labor [16].

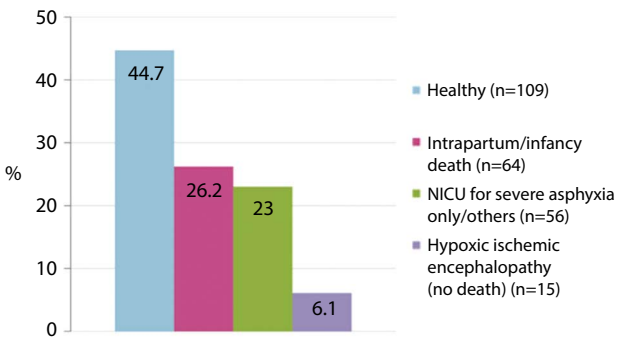


FIGURE 15.6 Infant outcome after complete uterine rupture (n = 244 births). (From Al-Zirqi I, Daltveit AK, Vangen S. Infant outcome after complete uterine rupture. *Am J Obstet Gynecol.* 2018;219:109.e1. [II-2, population based with medical record review, n = 244 ruptures]. Ref. [109], with permission.)

Respiratory complications

Rates of **respiratory complications**, transient tachypnea of the newborn, and need for oxygen and ventilator support may be **slightly higher in infants delivered by PRCD** versus those delivered by VBAC [1, 98]. It is unclear if there is a difference in respiratory outcomes in infants born by PRCD versus those born by repeat CD after a TOLAC.

Hypoxic-ischemic encephalopathy

Aside from perinatal death, HIE is the most serious adverse outcome of uterine rupture and is one of the primary concerns regarding the decision to have a TOLAC. The incidence is **46/100,000 live births for TOLAC**, versus none in the PRCD [11]. The overall risk of rupture-related HIE is 1 in 2500 TOLAC. In term infants, the overall incidence for HIE is 100/100,000 live births.

Management

Patients with contraindications (Table 15.1) **to TOLAC should receive a PRCD at 39 weeks, or earlier if labor starts, or in certain cases (e.g. prior early uterine rupture). TOLAC can be offered if the risk of uterine rupture is estimated to be <2%, possibly <1%** (Table 15.2), **and if spontaneous labor starts by 40 weeks. If the patient reaches her estimated due date (EDC) with no labor and an unfavorable cervix, a PRCD may be appropriate, but induction with mechanical ripening in women with at least a 60% chance of success is also a reasonable option. A VBAC calculator may be helpful in this situation.**

Counseling for TOLAC

TOLAC can be offered to most women with a single or even two prior low transverse CDs, but several safety and success factors should be considered and discussed with the woman (Tables 15.1–15.3).

The composite of **maternal complications** is slightly **higher with TOLAC** compared with the PRCD group **primarily due to the risk of rupture and the increased risks of a CD in labor**. These estimates do not consider the long-term increased risks of repetitive CD and the associated risks of placenta previa and accreta. **Counseling should take into account how many future pregnancies are planned**.

The overall risk of serious **perinatal complications** is about 1 in 2000 **TOLACs**, which is **slightly greater** than that of PRCD [11]. Combining all poor perinatal outcomes, **more than 600 PRCDs would need to be performed to prevent one poor perinatal outcome**. Although a woman with a TOLAC is at higher risk of uterine rupture than any other group, the risk of perinatal death is similar to that of any nulliparous woman in labor [16].

For the approximately 60%–80% of women having TOLAC **who will deliver vaginally**, the maternal and perinatal morbidity and mortality are lower than with PRCD.

For women in whom the chance of having a vaginal delivery with a TOLAC is over 60%, the maternal and perinatal morbidity and mortality are lower than with PRCD. **About 50% of women with a prior CD have a 70% or higher chance of a successful VBAC, and they have no higher risk of maternal or perinatal morbidity and mortality compared** with **those who have PRCD** [15].

Although the overall risks of TOLAC for all women are higher than PRCD, the absolute risks are small and comparable to other potential complications of labor. Efforts to reduce the frequency of the first CD reduce the need for a TOLAC or repeat CD.

TOLAC should be approached with caution in those with the lowest chance of vaginal delivery and highest risk of rupture: For example, induction of labor in obese women over age 40 with an unfavorable cervix and no prior vaginal deliveries.

The ultimate decision regarding whether to have a TOLAC or PRCD should be based on the patient choice, after appropriate counseling and the availability of adequate resources and personnel to respond to obstetric emergencies. Most women should begin the decision process before term, and their decision should be documented in the medical record. The decision can then be modified at term in women to assess if spontaneous labor and/or favorable cervix make their chances of complications lower and of success higher. There is no evidence that examining the adequacy of the pelvis benefits outcomes.

Prenatal education

Women who have had a prior CD need information and guidance to help them decide whether to have a TOL or an ERCD. Individualized prenatal education directed toward avoidance of a PRCD does not increase the rate of VBAC [99].

The Cochrane review evaluated three RCTs of decision support tools to help assist women in choosing ERCD or TOLAC and found no differences in the planned mode of birth or the percentage of women who remained unsure about their final decision [100]. A subsequent RCT showed that interactive or written evidence-based decision tools helped reduce conflict around the birth decision compared to baseline [101]. A survey of a **woman's level of knowledge** prior to TOLAC or ERCD showed most women had a poor understanding of the risks, benefits, and likelihood of success of either option; they also were most likely to choose the mode of delivery favored by their provider [102].

Consent

Specific consent for TOL after CD or PRCD should be signed by the woman after appropriate counseling.

Nonvertex presentation

External cephalic version (ECV) can safely be performed in women with a prior CD. The success rate for ECV is similar or higher in women with a prior CD compared to controls without a prior CD (82% vs. 61%) [103]. Women with a successful version have successful VBAC rates of 65%–76% [103, 104].

Ultrasound of the lower uterine segment

The data supporting the use of ultrasound to predict uterine rupture are limited, and so **currently measurement of lower uterine segment (LUS) thickness is not routinely recommended for clinical management**. Studies of the prior uterine scar have used varying terminology and methods and a wide range of results, yet there is still no consensus regarding the prevalence, clinical significance, best cutoffs, and appropriate management of ultrasound findings. In one small study a cutoff of <2.3 mm for the LUS thickness (from the bladder urine interface to the decidua amniotic fluid or fetal scalp interface) was associated with rupture [78]. A subsequent meta-analysis of 21 studies looking at data for 2776 women provided support for using ultrasound measurement of the LUS in assessing for the presence of a uterine defect but recommended prospective validation before it can be used in routine clinical practice [105]. In a multicenter study of 1849 women where LUS thickness was used in counseling, of 984 trials of labor, there were no symptomatic uterine ruptures. Over 90% of women with a LUS thickness <2.0 mm had an ERCD [106]. A systematic review of 12 studies, including 1834 women and with a 6.6% rate of uterine scar defects, confirmed the strong association between the degree of LUS thinning measured in the third trimester of pregnancy and the risk of uterine scar rupture/dehiscence at delivery. The cutoff value proposed for predicting these complications varied between 2.0 and 3.5 mm. Due to the heterogeneity of the studies, no precise cutoff value could be recommended [107].

Requirements to minimize risks during a TOLAC [1]

To minimize risks, the following must be immediately available throughout the TOLAC:

- **Experienced obstetrician**
- **Anesthesia**
- **Nursing and operating room personnel**
- **Ability to perform emergency CD**

Labor and delivery units with >500/1000 births per year have lower risks of uterine rupture and complications compared with units with less volume [10, 101]. If centers cannot provide the resources noted, this does not mean TOLAC should not be offered. Referral should be made to adequate facilities early during prenatal care so that TOLAC is safely available.

Detecting and managing rupture intrapartum

Fetal heart rate (FHR) disturbances are the most common (but not universal) sign of uterine rupture (55%–85%). The most commonly reported FHR disturbance is repetitive, progressively severe variable decelerations and prolonged bradycardia, although in most cases these are not caused by rupture [108]. Nevertheless, **in women with a prior CD, in the presence of such FHR disturbances, uterine rupture must be considered**. **Immediate delivery is indicated**, as one large population-based study from Norway showed a time to delivery <20 minutes limited the incidence of intrapartum/infant deaths [109].

Abdominal pain over the area of the prior uterine scar is a poor predictor of uterine rupture. Epidural usually does not mask rupture. Epidural should not be withheld in women attempting TOL after prior CD. Intrauterine pressure catheter (IUPC) monitoring has not been shown to be helpful [110]. Significant loss of fetal station, especially in the second stage, may occur with rupture, but is of limited predictive value. There are insufficient data to assess the utility of uterine exploration after a successful VBAC.

Neonates delivered within 18 minutes after a suspected uterine rupture have the best outcome, with all normal umbilical pH levels and 5-minute Apgar scores in one series, while those with a decision-to-delivery time >30 minutes have poor outcomes [1, 111].

Cost-effectiveness

Multiple cost-effectiveness analyses have been performed to examine the relative cost of TOLAC vs. PRCD. For women with at least a 47% likelihood of successful vaginal delivery, TOLAC appears to be more cost-effective than ERCD [112, 113]. In one analysis, TOLAC has similar cost-effectiveness for the first TOL but becomes less costly and more effective with subsequent deliveries [114].

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16

EARLY PREGNANCY LOSS

Lisa K. Perriera, Beatrice A. Chen, and Aileen M. Gariepy

Key points

- The diagnosis of early (e.g. first trimester, <14 weeks) pregnancy loss may be suspected based on symptoms, but is usually made by **transvaginal ultrasound** and/or serial beta-human chorionic gonadotrophin (BHCG) levels.
- **Early pregnancy loss (EPL)** is an inclusive term that comprises the following: Incomplete, inevitable, or complete spontaneous abortion (SAB); anembryonic pregnancy ("blighted ovum"); and embryonic/fetal demise ("missed abortion"). Early pregnancy failure (EPF) is a term that should be avoided, as it contributes to internalization of blame for patients.
- There are **three options** for the management of EPL: **Expectant, medical, and surgical management**. Choice of management for EPL **does not affect future fertility**.
- **Patient preference should guide treatment choice**.
- **Successful management** of EPL consists of complete evacuation of the uterus. The success of each management option depends on several factors, for example, whether or not patients are experiencing symptoms.
- Threatened pregnancy loss can be defined as vaginal bleeding in pregnancy before 20 weeks of gestation. Progesterone supplementation may reduce miscarriage rates in women with threatened miscarriage.
- While progesterone supplementation cannot be recommended for prevention of EPL in general, there may be benefit in women with a history of recurrent miscarriage. Progesterone treatment for these women may be warranted (see Chap. 17)

Medical management

- **Medical management** is a **safe and effective** alternative to expectant management or surgical curettage for early pregnancy loss (EPL).
- Medical management of EPL is more effective than expectant management.
- **Due to its efficacy, mifepristone followed by misoprostol is the preferred medical treatment for early pregnancy loss less than 13 weeks gestation**.
- **Mifepristone 200 mg orally followed by misoprostol 800 µg vaginally 24 hours later for the treatment of anembryonic pregnancy or embryonic demise less than 13 weeks' gestation has a success rate of 83% at initial follow-up at 1–4 days and an overall success rate of 91% at 30 days after treatment if a second dose of misoprostol is offered**.
- **When mifepristone is unavailable, misoprostol 800 µg vaginally, with a repeat dose on day 3 if complete evacuation is not confirmed by ultrasound**, has a success rate of **93% with incomplete or inevitable abortion, 88% with embryonic or fetal death, and 81% with anembryonic pregnancy** in patients at **<13 weeks** of gestation.
- Patients choosing medical management of EPL report an **average of 12 days of bleeding**. Hemorrhage after medical management of EPL is rare.
- **Follow-up:** Absence of a gestational sac using **transvaginal ultrasound** after medical management of EPL confirms **successful expulsion of the gestational sac**. **Measurement of endometrial thickness is not predictive of, and should not be used to determine, success**.
- **Advantages of medical management** of EPL: Avoidance of surgery and anesthesia, perception of more natural treatment, increased privacy, and increased control.

Surgical management

- Surgical management has a high (>97%) success rate.
- Endometritis or hemorrhage rates are less than 1%.
- Maternal safety is highest with vacuum aspiration under local anesthetic, avoiding regional or general anesthesia. Some recommend continuous ultrasound guidance, if available.

Definitions

- **Pregnancy loss (PL):** Spontaneous loss of pregnancy from conception to <20 weeks.
- **Miscarriage:** Lay term signifying PL.
- **Threatened PL:** Vaginal bleeding in pregnancy before 20 weeks' gestation.
- **Early PL:** Inclusive medical term describing inevitable abortion, incomplete abortion, anembryonic pregnancy, and embryonic/fetal demise at **<14 weeks** [1]. It is also called "first-trimester" PL. Early first-trimester PL is a loss of pregnancy between conception and $9^{6/7}$ weeks. Late first-trimester PL is a loss of pregnancy between 10 and $13^{6/7}$ weeks. The terms early pregnancy loss, miscarriage, and spontaneous abortion are often used interchangeably in the first trimester [2].
  - **Spontaneous abortion** (aka loss): The term **spontaneous abortion** is often used as an equivalent term for EPL but should be avoided, since women may associate negative feelings with this term. This guideline does not discuss voluntary (elective) termination (induced abortion).
  - **Complete abortion:** Clinical definition describing an EPL that is characterized by a history of a positive pregnancy test and ultrasound showing intrauterine pregnancy, vaginal bleeding with passage of tissue, and a closed cervical os at the time of diagnosis. Transvaginal ultrasound exam shows absence of a gestational sac.
  - **Incomplete abortion:** Clinical definition describing a history of positive pregnancy test and ultrasound showing intrauterine pregnancy, vaginal bleeding, and a cervical os that is open. Transvaginal ultrasound exam shows heterogeneous tissue distorting the endometrial canal with or without a gestational sac. There is no agreement

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TABLE 16.1: Diagnostic Criteria for Early Pregnancy Loss

Diagnosis	Ultrasound Findings
Anembryonic pregnancy (any of the three)	• A gestational sac ≥25 mm MSD without an embryo • Absence of an embryo with cardiac activity ≥11 days after an ultrasound showed a gestational sac with a yolk sac • Absence of an embryo with cardiac activity ≥2 weeks after an ultrasound showing a gestational sac without a yolk sac
Embryonic/Fetal demise	• Absence of cardiac motion in an embryo measuring ≥7 mm

Source: Adapted from Ref. [4].
Abbreviation: MSD, mean sac diameter.

on a measurement of endometrial thickness that can distinguish incomplete from complete abortion [3].

- **Inevitable abortion:** Clinical definition describing an EPL that is characterized by a history of a positive pregnancy test, vaginal bleeding without passage of tissue, gestational sac in the uterus, and an open cervical os.
- **Anembryonic pregnancy:** Previously described as "blighted ovum." This is a gestational sac without a visible yolk sac and/or embryo (with no heart motion) in relationship to the mean sac diameter (MSD) size (Table 16.1). It occurs when the embryonic disk has failed to develop or has already been resorbed [4].
- **Embryonic/fetal demise:** Previously described as "missed abortion." It is defined by the failure of a previously identified embryo to grow and/or retain cardiac activity over time (Table 16.1).

- **Expectant management:** No intervention. Awaiting natural passage of tissue.
- **Medical management:** The use of medications to expel the products of conception.
- **Surgical management:** The mechanical removal of the products of conception.

Diagnosis

Transvaginal ultrasound

To ensure 100% specificity to confirm early pregnancy loss, the diagnostic criteria shown in Table 16.1 were adopted by the Society of Radiologists in Ultrasound Multispecialty Panel on Early First Trimester Diagnosis of Miscarriage and Exclusion of a Viable Intrauterine Pregnancy [5].

It is important to recognize that not all patients may desire 100% certainty of pregnancy loss [2], and the wishes of the patient must be considered when determining the level of diagnostic certainty that will be used. Table 16.2 lists the sensitivity and specificity of different diagnostic cutoffs that can be used to counsel patients [5, 6].

Beta-human chorionic gonadotropin

In a clinically stable patient with a highly desired pregnancy, a single beta-human chorionic gonadotropin (BHCG) level ≤3000 mIU/mL cannot differentiate between an ectopic pregnancy or EPL if a gestational sac is not visualized in the uterus [5]. If the pregnancy is desired, ectopic precautions should be given and intervention should be avoided until additional testing is performed.

Symptoms

Symptoms of EPL include vaginal bleeding, lower abdominal cramping, and dilation of the cervix. Women with EPL may also be asymptomatic.

Epidemiology/Incidence

Fifteen to twenty percent of clinically recognized pregnancies end in EPL [7]. It is **estimated that up to 60% of conceptions become an EPL, and most are not clinically recognized** (e.g. "late cycle"). Human reproduction is relatively inefficient. Only 30% of fertilized eggs result in a viable pregnancy. Sporadic EPL is very common in humans. At least 15%–20% of clinically identified pregnancies (implanted) physiologically end with early PL, and only 50%–60% of all conceptions advance to >20 weeks [8]. Most PLs represent failure of implantation and are difficult to recognize clinically. Oocyte quality and normal karyotype are most important for normal implantation, more so than uterine factors. **The prognosis after one uncomplicated EPL in a healthy young woman is for >70%–80% chance of a viable pregnancy in the next pregnancy. Therefore, no workup or therapy is usually indicated after one PL.** For women with two or more EPLs, see Chap. 17.

Etiology

Chromosomal abnormalities are responsible for >50% of all spontaneous EPLs, most commonly aneuploidy. When tissue from EPLs <13 weeks (81% <9 weeks) obtained by chorionic villus

TABLE 16.2: Sensitivity, Specificity, and False-Positive Rates When Diagnosing Early Pregnancy Loss

	Sensitivity (95% CI)	Specificity (95% CI)	FPR (%)
CRL >5 mm without cardiac activity	0.50 (0.12–0.88)	1.00 (0.90–1.00)	0
CRL >6 mm without cardiac activity	0.50 (0.07–0.93)	1.00 (0.87–1.00)	0
CRL >7 mm without cardiac activity	NA	1.00 (NA)	NA
MSD >13 mm without yolk sac	0.96 (0.92–0.99)	1.00 (0.69–1.00)	0
MSD >16 mm without yolk sac	0.50 (NA)	1.00 (0.88–1.00)	NA
MSD >20 mm without yolk sac	0.41 (0.30–0.52)	1.00 (0.96–1.00)	0
MSD >25 mm without yolk sac	NA	1.00 (NA)	NA

Source: Modified from Refs. [5, 6].
Abbreviations: CRL, crown–rump length; MSD, mean sac diameter; CI, confidence intervals; FPR, false-positive rate; NA, not available.

sampling (CVS) and manual vacuum aspiration (MVA) is analyzed, about **72% of cases revealed aneuploidy, with trisomy being the most common** [9]. Many spontaneous losses may be secondary to other genetic defects that are impossible to discern by simple karyotype. Many other factors are also associated with spontaneous losses (see Chap. 17).

Risk factors

The risk of EPL increases with maternal age, ranging from 9% at 22 years old to 84% at 48 years old [10]. Other risk factors include smoking, alcohol, excessive caffeine intake, African racial origin, previous EPL, previous stillbirth, medical complications such as diabetes, assisted reproductive technology, and vaginal bleeding [11]. A recent meta-analysis showed that caffeine and coffee consumption, especially more than three servings per day, during pregnancy are significantly associated with pregnancy loss [12].

Threatened pregnancy loss

Threatened PL can be defined as vaginal bleeding in pregnancy before 20 weeks of gestation. Several **interventions** have been studied, but **none has been confirmed to be beneficial**.

Complications

- **Vaginal bleeding in the first trimester** has been associated with several complications in pregnancy, including antepartum hemorrhage (odds ratio [OR] 2.47), preterm prelabor rupture of membranes (PPROM) (OR 1.78), preterm birth (PTB) (OR 2.05), fetal growth restriction (FGR) (OR 1.54), low birth weight (LBW) (OR 1.83), and perinatal mortality (OR 2.15) [13].
- The presence of a **subchorionic hematoma** detected on ultrasound (usually between 5 and 20 weeks) is associated with increased risks of spontaneous abortion (SAB) (OR 2.18), abruption (OR 5.71), intrauterine fetal demise (IUFD) (OR 2.09), PPROM (OR 1.64), and PTB (OR 1.40) [14].

Prevention

- *Lifestyle modifications*
  - Epidemiologic studies suggest that lifestyle modifications can increase fertility potential, although these have not been definitively tested in randomized controlled trials. These modifications include eliminating the use of tobacco products, alcohol, and caffeine and reduction in body mass index (BMI) [15].
- *Multivitamins*
  - In non–high-risk women, vitamin C, vitamin A, and folic acid supplementation before 20 weeks are associated with similar total fetal loss (early/late miscarriage and stillbirth), early or late miscarriage or stillbirth, and most other outcomes compared with controls [16]. Multivitamin supplementation with iron and folic acid may be associated with a decreased risk of stillbirth as compared to iron and folate only (relative risk [RR] 0.92, 95% confidence interval [CI] 0.85–0.99) but is not associated with a difference in the risk of early or late miscarriage. Therefore, **vitamin supplementation cannot be recommended for prevention of EPL**.
- *Progesterone*
  - There is **no evidence to support the routine use of progesterone (synthetic or natural) to prevent EPL in all women**. A meta-analysis of all women, regardless of gravidity and number of previous miscarriages, showed no statistically significant difference in the risk of miscarriage between progesterone and placebo or no treatment groups (OR 0.99; 95% CI 0.78–1.24) and no statistically significant difference in the incidence of adverse effects in either mother or baby [17].
  - However, in a subgroup analysis of four trials involving **women who had recurrent miscarriages (3 + consecutive miscarriages**; four trials, 225 women), **progesterone treatment showed a statistically significant decrease in the miscarriage rate** compared to placebo or no treatment (OR 0.39; 95% CI 0.21–0.72), though these studies were of poorer quality.
  - **While progesterone supplementation cannot be recommended for prevention of EPL, there may be benefit in women with a history of recurrent miscarriage**. **Treatment for these women may be warranted** (see Chap. 17).

Therapy

- *Bed rest*
  - There is insufficient evidence of high quality that supports a policy of bed rest to prevent miscarriage in women with confirmed fetal viability and vaginal bleeding in the first half of pregnancy. There is no statistically significant difference in the risk of miscarriage in the bed rest group versus the no bed rest group (placebo or other treatment) (RR 1.54, 95% CI 0.92–2.58). Neither bed rest in a hospital nor bed rest at home shows a significant difference in the prevention of miscarriage. There is a higher risk of miscarriage in those women in the bed rest group than in those in the HCG therapy group with no bed rest (RR 2.50, 95% CI 1.22–5.11). The small number of participants included in these studies makes these analyses inconclusive [18].
  - **Bed rest cannot be recommended for prevention of miscarriage**. In fact, it might be harmful, given the higher rates of venous thromboembolism (VTE), muscle atrophy, and other detriments associated with bed rest.
- *Progesterone*
  - **Progesterone supplementation may reduce miscarriage rates in women with threatened miscarriage**. Treatment with oral progestogen compared to no treatment may reduce the miscarriage rate (RR 0.57, 95% CI 0.38–0.85), though there was no evidence of effectiveness with the use of vaginal progesterone compared with placebo in reducing the risk of miscarriage (RR 0.75, 95% CI 0.47–1.21) [19].
- *Human chorionic gonadotropin*
  - The **current evidence does not support the routine use of HCG in the treatment of threatened miscarriage**. There is no statistically significant difference in the incidence of miscarriage between HCG and "no HCG" (placebo or no treatment) groups (RR 0.66, 95% CI 0.42–1.05). There were no reported adverse effects of HCG on the patient or fetus [20].
- *Muscle relaxant*
  - There is **insufficient evidence** to support the use of uterine muscle relaxant drugs for women with threatened miscarriage, and **therefore they should not be used**.

In one poor-quality randomized controlled trial (RCT), compared with placebo, buphenine (a beta-agonist) was associated with a lower risk of intrauterine death (RR 0.25, 95% CI 0.12–0.51). PTB was the only other outcome reported (RR 1.67, 95% CI 0.63–4.38) [21].

Management of EPL

General principles

- There are **three main options** for the woman with EPL (unless the spontaneous loss is complete): **Expectant**, **medical**, and **surgical management**.
- Successful management of EPL entails complete evacuation of the uterus, defined as expulsion of the gestational sac. The success of each management option depends on several factors, for example, whether or not the patient has symptoms.
- Failure of expectant or medical management results in the need for surgical evacuation.

Principles of surgical management

- **Procedure:** Surgical management of EPL is best accomplished with electric or manual **vacuum aspiration compared to sharp curettage**.
- When comparing vacuum aspiration versus sharp curettage, **vacuum aspiration is preferred**, as it is associated with [22]:
  - Less blood loss (mean difference [MD] –17.10 mL, 95% CI –24.05 to –10.15 mL).
  - Less pain during the procedure (RR 0.74, 95% CI 0.61–0.90).
  - Shorter duration of the procedure (MD –1.20 minutes, 95% CI –1.53 to –0.87 minutes).
  - The small sample sizes of the trials were too small to evaluate rare complications such as uterine perforation and other morbidity.
- Vacuum aspiration can be accomplished with **electric vacuum aspiration (EVA) or MVA**. Both EVA and MVA are types of dilation and curettage (D&C).
- **Location:** Vacuum aspiration can be accomplished in the operating room or in the office.
- **MVA is a safe alternative** for gestations 6–12 weeks with EPL and can be performed in the **office under local anesthesia** [23]. This should be strongly preferred at these gestational ages instead of an operating room procedure necessitating general anesthesia [24].
- **There is no significant difference in the success or complication rates for MVA versus EVA** [25].
- **Some experts recommend continuous ultrasound guidance if available**, but this should not be a barrier to access.

Principles of medical management

Medications used:

- **Misoprostol** is a prostaglandin E1 analogue. It is a uterotonic that results in cervical softening and contractions that expel the products of conception. Routes of administration include vaginal, oral, buccal, or sublingual. Side effects vary, based on route of administration [26].
- **Mifepristone** is an antiprogestin that results in weakening of the uterine attachment of a pregnancy. This results in capillary breakdown and synthesis of prostaglandins [27].
- **Methotrexate** (IM or oral) antagonizes folic acid, a cofactor needed for the synthesis of nucleic acids. It is toxic to the rapidly dividing cells of the trophoblast. There is no role for methotrexate in the treatment of EPL [28].
- **Success** of medical management is determined by the absence of significant symptoms, such as heavy vaginal bleeding, and absence of the gestational sac on transvaginal ultrasound. Studies that use an endometrial thickness of >15 mm to define failure of medical management may underestimate success rates of expectant and medical management [4]. Endometrial thickness should not be used to determine success of medical management.
- **Success** of medical management is **higher in patients with symptoms**, such as cramping and bleeding [29].

Contraindications: The contraindications listed in Table 16.3 apply to medical management but some may also apply to expectant management [25, 30, 31].

Complications:

- Complications are rare. The incidence of gynecologic infection after surgical, expectant, or medical management of EPL is low (2%–3%). There is no evidence to show a differential risk of infection by management choice [32].
- In the largest RCT ($n = 652$) comparing medical with surgical management, there was no difference in the following complications [25]:
  - Hemorrhage requiring hospitalization with or without blood transfusion (1%)
  - Hospitalization for endometritis (<1%)
  - Fever (3%–4%)
  - Emergency visit to the hospital within 24 hours of treatment (2%–3%)
  - Unscheduled hospital visits (17%–23%)
  - Decrease in hemoglobin ≥2 g/dL (4%–9%)
  - Decrease in hemoglobin ≥3 g/dL (1%–5%)

Principles of expectant management

Expectant management of EPL is an option for women who would like to avoid surgical or medical treatment of EPL; however, time until resolution of EPL is unpredictable and may take as long as 6 weeks. Success of expectant management can range from 25% to 83%, depending on length of time of follow-up, definition of "failed" expectant management, and inclusion criteria [33–35].

Medical versus surgical management

- **Cochrane** review [36]:
  - Twenty-four RCTs were included in this Cochrane review of **incomplete abortion before 13 weeks** with $n = 5577$.

TABLE 16.3: Contraindications to Medical (or Expectant) Management

- Hemodynamically or medically unstable patients
- Signs of pelvic infection and/or sepsis
- Suspected molar or ectopic pregnancy
- Caution should be used in women with hemoglobin <9.5 g/dL
- History of coagulopathy or current use of anticoagulants
- Contraindication to prostaglandins[a]
- Contraindication to mifepristone (if being used)[a]

Source: Modified from Refs. [25, 31, 40].

[a] Specific to medical management.

- Misoprostol routes varied, including seven studies via oral, six studies via vaginal, two studies via sublingual, and one study via both vaginal and oral.
- There was a slightly lower incidence of complete miscarriage in the misoprostol group (RR 0.96, 95% CI 0.94–0.98), but high success in both groups.
- Women using misoprostol had fewer surgical procedures (RR 0.05, 95% CI 0.02–0.11).
- Risk of unplanned procedure was higher with misoprostol (RR 5.03, 95% CI 2.71–9.35).
- Deaths and "serious complications" with either management are too rare to compare.

- **Largest multicenter RCT** [25]:
  - $n = 652$; 491 participants treated with **800 µg vaginal misoprostol** versus 161 participants treated with vacuum aspiration
  - Participant characteristics:
    - 58% embryonic/fetal demise
    - 36% anembryonic pregnancy
    - 6% incomplete/inevitable abortion
  - **Medical regimen: 800 µg vaginal misoprostol, repeated on day 3 if incomplete expulsion (diagnosed by persistence of gestational sac or endometrial lining greater than 30 mm on transvaginal ultrasound), vacuum aspiration on day 8 if still incomplete**
  - **Success:**
    - 97% success with vacuum aspiration
    - **84% success with misoprostol overall**
    - **71% success with one dose of misoprostol**
    - Success increases to 84% with a second dose of 800 µg vaginal misoprostol if the gestational sac was still present on ultrasound on day 3
  - **Success by type of EPL:**
    - 93% for incomplete/inevitable abortion
    - 88% embryonic/fetal demise
    - 81% anembryonic pregnancy
  - Success did not vary by gestational age
  - Increased rates of nausea, vomiting, and diarrhea and abdominal pain in the misoprostol group
  - No difference in hemorrhage or endometritis between groups (<1%)
  - Success of medical management associated with cramping, vaginal bleeding, and nulliparity [29]

Conclusion: Medical management with misoprostol is an acceptable alternative to surgical evacuation. Patient preference should guide decision-making [36].

Medical versus expectant management

Medical management commonly uses vaginal misoprostol [28]. There are several additional studies looking at mifepristone followed by vaginal or oral misoprostol [37–39].

- **Cochrane review** [28]
  - Forty-three RCTs, $n = 4966$, of embryonic/fetal demise or anembryonic pregnancy.
  - **Vaginal misoprostol** compared with expectant management:
    - Shortens the time to achieve complete uterine evacuation:
      - At less than 24 hours after treatment (RR 4.73, 95% CI 2.70–8.28)
      - At less than 48 hours after treatment (RR 5.74, 95% CI 2.70–12.19)
    - Results in less need for uterine curettage
    - Does not show a significant difference in need for blood transfusion (RR 0.2, 95% CI 0.01–4.0)
    - Does not have a significant increase in nausea (RR 1.38, 95% CI 0.43–4.40) or diarrhea (RR 2.21, 95% CI 0.35–14.06)
  - **Dosage** of vaginal misoprostol: When comparing 400, 600, and 800 µg dosages, higher-dose regimens were not more effective at completing uterine emptying as compared to lower dosages (RR 0.82, 95% CI 0.58–1.14). There was a similar incidence of nausea (RR 0.67, 95% CI 0.31–1.41) between regimens.
  - No advantage of "wet" versus "dry" preparation of vaginal misoprostol or of adding methotrexate.
  - There may be no difference between oral misoprostol and vaginal misoprostol in emptying the uterus, but one of the studies had serious risk of bias (RR 0.68, 95% CI 0.45–1.03).
  - Sublingual misoprostol is equivalent to vaginal misoprostol in inducing complete uterine emptying (RR 0.84, 95% CI 0.61–1.16) but was associated with more frequent diarrhea.
- **Mifepristone:**
  - Efficacy of mifepristone followed by misoprostol for treatment of miscarriage ranges from 65.5% to 91.2% [37–40].
  - In a Cochrane review published in 2019, three trials of mifepristone added to misoprostol did not show increased efficacy with mifepristone [28]. However, this Cochrane review did not include the Schreiber et al. study that was published in 2018.
  - One small RCT ($n = 115$) found that mifepristone in addition to misoprostol did not improve efficacy [39], though one retrospective study did find increased expulsion rates with mifepristone plus misoprostol versus misoprostol alone [41].
  - A definitive multisite RCT ($n = 300$) published in 2018 demonstrated that the success rate for the treatment of embryonic demise or anembryonic pregnancies with one 800 µg dose of misoprostol 24 hours after mifepristone had an initial success rate of 83.8%, a 89.2% success rate at day 8 when an additional dose of misoprostol was offered, and a success rate of 91.2% by day 30 [40]. Those subjects in the misoprostol-only arm had an initial success rate of 67.1% ($p < 0.001$), success at day 8 of 74.5%, and success at day 30 of 75.8%. The number needed to treat in order to achieve an additional outcome of treatment success by the first follow-up was 6.

Conclusion: Medical management with mifepristone 200 mg followed by 800 µg of vaginal misoprostol is significantly more effective than management with misoprostol alone or expectant management. There is now clear evidence that mifepristone combined with misoprostol appears to have higher success rates compared to misoprostol alone. Based on available evidence, adding mifepristone to misoprostol for medical management is recommended, when available.

Expectant versus surgical management

In a Cochrane review of seven RCTs, $n = 1521$ [42]:

- Expectant management has a higher incidence of the following:
  - Incomplete miscarriage by 2 weeks (RR 3.98, 95% CI 2.94–5.38) or by 6–8 weeks (RR 2.56, 95% CI 1.15–5.69).
  - Need for unplanned or additional surgical emptying of the uterus (RR 7.35, 95% CI 5.04–10.72).
  - Surgical management is required in 28% in the expectant group, while only 4% in the surgical group require additional surgery.
  - More days of bleeding (weighted mean difference [WMD] 1.59, 95% CI 0.74–2.45)].
  - Need for blood transfusion (RR 6.45, 95% CI 1.21–34.42).
  - There was no difference in infection risk.
  - Cost was lower in the expectant management group.

Conclusion: Expectant management is associated with more risk than surgical management; however, discussion of risks of all treatment options, shared decision-making, and patient preference should guide decision-making.

Mifepristone: Route, dose, and safety

- **Mifepristone 200 mg orally is the recommended dose and route** [37–40].
- **All studies using mifepristone for medical management have used it in combination with a prostaglandin, typically misoprostol** [37–40].

Misoprostol: Route, dose, and safety

There is published literature on a wide range of therapeutic regimens [4, 31, 40, 43]. Optimal doses and routes of administration of misoprostol have not been determined by randomized trials.

- **Misoprostol 800 µg per vagina** is the most studied regimen for medical management of EPL. Success of medical management of EPL increases with **multiple-dose regimens** [25].
- A single RCT showed that there is equivalent efficacy between a multidose regimen of vaginal misoprostol 400 µg and 800 µg with a lower incidence of fever/rigors and higher satisfaction in the lower dose group [44].
- An international panel of experts recommends a single oral dose of 600 µg misoprostol for medical management of incomplete abortion [30] and a single vaginal dose of 800 µg misoprostol for medical management of anembryonic pregnancy and embryonic/fetal demise [44]. Misoprostol 600 µg sublingual is an alternative regimen [45].
- Overall, misoprostol is safe and well tolerated. Side effects of prostaglandins include diarrhea, nausea, and vomiting. These side effects are increased when misoprostol is given orally. Patients receiving misoprostol vaginally have decreased gastrointestinal side effects and prolonged duration of action when compared with oral administration [26].

Antibiotics

- There is insufficient evidence to recommend or to abandon prophylactic antibiotics for surgical evacuation in women with an incomplete abortion. Clinical judgment is recommended [31, 46].
- There is insufficient evidence to recommend prophylactic antibiotics for women undergoing surgical evacuation of the uterus for embryonic/fetal demise or anembryonic pregnancy, but the risk of infection is thought to be similar to the risk of infection for induced termination of pregnancy.
- One large RCT ($n = 3412$) randomized patients undergoing surgical treatment of pregnancy loss <22 weeks in low-resource countries to antibiotic prophylaxis (400 mg of oral doxycycline and 400 mg of oral metronidazole) to placebo), with a primary outcome of pelvic infection within 14 days after surgery. The risk of pelvic infection for those in the antibiotics and placebo arms were 4.1% and 5.3%, respectively (RR 0.77, 95% CI 0.56–1.04). However, when using strict criteria for the definition of pelvic infection, the risk of pelvic infection was statistically lower in the antibiotic arm (1.5% versus 2.6%, RR 0.60, 95% CI 0.37–0.96).
- The American College of Obstetricians and Gynecologists (ACOG) recommends the use of a single preoperative dose of doxycycline in cases of EPL, but acknowledges the lack of data [2]. Administration of **doxycycline 200 mg within 30 minutes of the procedure** is a low-cost regimen, and the benefits of administration outweigh the risks [47].

Rh negative

Women who are Rh(D) negative and unsensitized should receive Rh(D)-immune globulin within 72 hours of the EPL [2].

Patient counseling

Patients choosing medical management of EPL should have appropriate counseling regarding expected symptoms.

- Bleeding with medical management is heavier and longer in duration than with surgical management and rarely requires intervention [48].
- Women experienced approximately 12 days of bleeding after medical management of EPL [47]. Bleeding will most likely be heavy for about 3–4 days, followed by light bleeding or spotting for several weeks [30].
- Patients should be counseled to contact their physician if they experience heavy vaginal bleeding (soaking through more than two extra-large sanitary pads per hour for 2 consecutive hours) or signs of infection [30].
- Some women experience fever and/or chills during the first 24 hours after misoprostol use. Patients should call their doctor and be evaluated for infection if fever and/or chills persist beyond 24 hours after using misoprostol [30].
- **Nausea and vomiting** may occur with use of misoprostol and will usually resolve 2–6 hours after taking it [30].
- **Pain should be expected with medical or expectant management, and patients should be given prescriptions for pain medications** [2].

Patient acceptability

- In one study, the majority of women would prefer medical management of EPL with misoprostol to surgical management if its efficacy is >65% [49].
- In a large RCT comparing medical versus surgical management of EPL, women receiving medical management had significantly higher reports of treatment-related symptoms

(cramping and bleeding), but overall quality of life and treatment acceptability were similar [50].

- In a large RCT comparing medical versus surgical management of EPL, 83% of women with EPL randomized to medical management with misoprostol would recommend medical management to others, and 78% would probably/absolutely use medical management again [25].

Patient preference

Most women have strong preferences regarding the management of EPL [51]. Preferences are diverse, and different women place different values on the advantages and disadvantages of avoiding the operating room or of miscarrying at home, for example. Patient preference will depend on individual circumstances, expectations, and awareness of the advantages and disadvantages of each management option. Women have greater satisfaction when treated according to their preferences.

Due to the comparable safety and efficacy of all current treatment options for EPL, patient preference should be the guiding force deciding management of EPL.

Cost

Expectant management has a lower cost when compared to surgical management [41]. In a decision analysis comparing surgical and expectant management to an expanded care option (expectant management, surgical management in the office or operating room, and medical management), there was a cost savings of $241.39 per case in the expanded care option [52]. Mifepristone and misoprostol was found to be cost-effective when compared to misoprostol alone [53].

Follow-up

There are no RCTs to assess optimal management of follow-up after EPL. **Transvaginal ultrasound** is the most common follow-up after medical or expectant management of EPL, typically done within 7–14 days [2]. Absence of the gestational sac indicates success [2]. Endometrial thickness after medical or expectant management is not predictive of retained products of conception and/or need for surgical evacuation [54]. For medication abortion we offer BHCG, ultrasound, and telephone combined with high-sensitivity urine pregnancy test in 1 month.

If chorionic villi or a gestational sac is obtained at D&C, there is usually no need for BHCG follow-up. After expectant or medical management of a known intrauterine pregnancy, BHCG levels, in general, do not need to be followed. Ultrasound can be used to confirm expulsion of the gestational sac. BHCG can be used in patients with limited access to ultrasound [2].

Future fertility

There is no need for a workup after one EPL. If more than one EPL has occurred, see Chap. 17. There are insufficient data to suggest an optimal interpregnancy interval between an EPL and the next conception [2]. There seems to be no improvement in outcome associated with waiting 3 months or more, as previously recommended [55]. There are no contraindications to the placement of an intrauterine device immediately after surgical (or other) management of EPL, as long as septic abortion is ruled out [56]. Choice of management for EPL does not affect future fertility. In long-term follow-up of women participating in an RCT of expectant, medical, or surgical management of EPL, there was no significant difference in the live birth rate 5 years after the index miscarriage [57].

- Expectant management: 177/224 (79%, 95% CI 73%–84%)
- Medical management: 181/230 (79%, 95% CI 73%–84%)
- Surgical management: 192/235 (82%, 95% CI 76%–86%)

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17

RECURRENT PREGNANCY LOSS

Reshama S. Navathe and Shabani Ahluwalia

Key points

- The **diagnosis of recurrent pregnancy loss (RPL)** is ≥2 **failed clinical pregnancies**.
- **Workup includes karyotype of products of conception (if available), parental karyotypes, uterine study, and antiphospholipid antibodies (APAs)**.
- Prognosis with negative workup is for a 60%–70% subsequent successful pregnancy in women <35 years old and 40%–50% in women ≥35 years old.
- Women with **RPL who are diagnosed with antiphospholipid syndrome (APS)** should be **treated** with **low-dose aspirin and heparin** in subsequent pregnancies (see Chap. 28 in *Maternal-Fetal Evidence Based Guidelines).* Women with unexplained RPL should not receive anticoagulant therapy.
- Women with **RPL and uterine septum, synechiae, or submucous myomata** can consider **hysteroscopic resection** of these abnormalities.
- Couples with abnormal parental karyotype can be offered genetic counseling, in vitro fertilization (IVF) with preimplantation genetic screening (PGS), prenatal diagnosis, and/or gamete donation.
- Couples should be offered **mental health support**, as RPL can be associated with significant anxiety and depression.
- There is insufficient evidence for universal screening for diabetes mellitus (DM), thyroid disease, progesterone deficiency, infections, thrombophilia, etc., in women with RPL.
- Women with RPL should **not be tested for alloimmunization or receive any of the immune therapies**, as they have thus far not shown benefit in RPL.
- There is increasing evidence that **progesterone supplementation** is beneficial, especially in women with ≥3 RPLs and early pregnancy bleeding.
- There is insufficient evidence to support estrogen, human chorionic gonadotropin (hCG), aspirin alone, and vitamins as interventions.

Diagnosis/Definitions

The definition of recurrent pregnancy loss (RPL) varies in different publications, which makes diagnosing and treating this entity more challenging for physicians and couples. While the majority of RPL comprises early pregnancy loss <14 weeks' gestation, midtrimester losses have been included in some studies, which further complicates accurate diagnosis. We choose to **define RPL as two failed clinical pregnancies <14 weeks** as the most inclusive and currently accepted definition. This includes biochemical pregnancies and those diagnosed by ultrasound or histopathologic findings. This definition includes pregnancy of unknown location, but not confirmed ectopic or molar pregnancies [1]. There are several guiding committees with slightly different variations on this definition (Table 17.1) [2–4]. The European Society of Human Reproduction and Embryology (ESHRE) distinguishes RPL from a similar entity, recurrent miscarriage, which is defined as a loss that has been confirmed as intrauterine [2].

For diagnoses of pregnancy loss, miscarriage, spontaneous and other kinds of abortions, anembryonic pregnancy, embryonic demise, etc., please see Chap. 16.

Classification

Primary RPL: No intervening live births; secondary RPL: Intervening live births. The prognosis is better with secondary RPL [5].

Incidence

Approximately 15% of pregnant women experience loss of a clinically recognized pregnancy. It is estimated that **less than 5% of women experience two consecutive pregnancy losses and only 1% experience three or more** [6].

Etiology

Etiology of RPL is not established in at least 50% of cases after workup. General categories include genetic, anatomic, endocrine, immunologic, thrombophilic, and environmental (Table 17.2) [7].

Risk factors/Associations

Advancing maternal age is associated with a higher rate of RPL. The rate of clinically recognized miscarriage is 20% at age 35, 40% at age 40, and up to 80% at age 45 [8]. Other risk factors include maternal medical diseases, especially poorly controlled, such as hypertension and diabetes (see Chap. 16). **A previous pregnancy loss is a risk factor for recurrence** (Table 17.3) [6, 9]. Women with only an unsuccessful pregnancy history have a greater risk of future miscarriage than primigravidas and women with a history of previous successful pregnancy [10].

Counseling

RPL can be emotionally devastating to couples, and its impact on the mental health of both partners needs to be addressed (Table 17.3) [6, 10, 11]. **Depression** rates are almost fourfold higher than women who do not suffer from RPL [12]. This emphasizes the importance of **mental health evaluation as part of the workup**. Patients could benefit from **intensive supportive care early in pregnancy, focusing on antenatal counseling and psychological support**. Stress has been associated with RPL, but couples should be reassured that stress does not cause RPL [12]. Couples should be provided reassurance after a first early pregnancy loss;

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TABLE 17.1: Definitions of RPL

Committee	Number of Pregnancies	Consecutive?	Specifics
RCOG 2011	3	Yes	Not required to be intrauterine
ASRM 2013	2	No	Clinical pregnancies confirmed by histology or ultrasonography
ESHRE 2018	2	No	Biochemical or intrauterine, can include pregnancy of unknown location

Source: From Refs. [3, 4, and 7].
Abbreviations: RCOG, Royal College of Obstetricians and Gynecologists; ASRM, American Society of Reproductive Medicine; ESHRE, European Society of Human Reproduction and Embryology.

TABLE 17.2: Etiology, Diagnostic Considerations, and Treatment in RPL

Etiology	Percentage	Diagnostic Evaluation	Therapy
Genetic	3%–5%	Karyotype: Parental	Genetic counseling
	Sporadic	Karyotype: POC	Genetic counseling, PGD
Anatomic	10%–20%	3D US	Correction of anatomic defect
		Hysterosalpingogram	
		SIS	
Endocrinology	8%–12%	TSH	Levothyroxine
		Prolactin	Bromocriptine
		Hgb A1c	Diabetic optimization
Immunologic/thrombophilic	5%–15%	APLAS	Aspirin + heparin
Environmental		Tobacco, EtOH	Eliminate exposures
		Exposure	
Unknown	40%–50%		

Source: Adapted from Refs. [7, 21].
Abbreviations: RPL, recurrent pregnancy loss; POC, products of conception; PGD, preimplantation genetic diagnosis; 3D US, three-dimensional ultrasound; SIS, saline infusion sonogram; TSH, thyroid-stimulating hormone; Hgb A1c, hemoglobin A1c; APLAS, antiphospholipid antibody syndrome; EtOH, alcohol.

after subsequent losses, couples should have detailed counseling regarding prognosis (Table 17.3) [6, 9]. It **should be made clear that workup does not always lead to a definitive diagnosis**, and effective treatment may not be available for RPL.

Candidates for evaluation

Workup should in general not be initiated after a first early pregnancy loss, as the prognosis remains at baseline after an initial loss. Workup should be in general be initiated after two failed clinical pregnancies [13].

Workup

Appropriate diagnostic workup of RPL is essential for choosing the proper intervention (Table 17.4) [14]. The initial part of the workup consists of a **detailed history** (medical comorbidities, smoking, alcohol and caffeine use, illicit drug use, environmental exposures, and working conditions, as well as detailed obstetric and gynecologic history) and **physical exam** (weight, blood pressure, pelvic exam). Eliciting the gestational age of miscarriage is important, as often RPL occurs at a similar gestational age in subsequent pregnancies, and the most common cause of RPL varies by gestational age. Sometimes, though, obstetric history is mixed, with early pregnancy loss (PL), second-trimester PL, preterm birth (PTB), and/or fetal death. In these cases, workup may include other tests (see specific chapters, including Chap. 57 in *Maternal-Fetal Evidence Based Guidelines*). **Screening tests (see later)** can be recommended concomitantly, or they can be performed based on clinical scenario and suspected etiology. The latter approach allows for a more cost-effective practice and minimizes unnecessary testing for couples. Appropriate diagnostic workup of RPL is essential for choosing the proper intervention.

TABLE 17.3: Miscarriage Risk after Prior PL

Prior PL (n)	Risk of Miscarriage in Subsequent Pregnancy
0	10%–15%
1	13%–25%
2	17%–35%
3	25%–45%
4	60%–65%

Source: Adapted from Refs. [6, 8].
Abbreviation: PL, pregnancy loss.

Recommended screening tests

Genetic evaluation

POC karyotype/CGH

Management of women with ≥2 RPLs should begin with genetic evaluation of products of conception (POCs) if possible (Figure 17.1) [15]. **About 75% of early pregnancy losses in the first trimester result from random numeric chromosomal errors** [16]. More than 50% of aneuploidies are trisomies; the most common single aneuploidy is 45,XO. Additionally, as maternal age increases, miscarriage associated with aneuploidy increases, accounting for up to 80% in those over 35 years of age [17]. **Aneuploidy is typically considered sufficient explanation for pregnancy loss; this provides the couple with an explanation**

TABLE 17.4: Evaluation of a Woman with Recurrent Miscarriages

Medical History	Comment
Determine pattern and gestational age of preembryonic, embryonic, or fetal death, if such information is available	Preembryonic and embryonic losses before 10 wk of gestation are the most common type of miscarriage, although the onset of symptoms may be later
Evaluate for features suggestive of antiphospholipid syndrome	Features include thrombosis, fetal death, autoimmune disease, and thrombocytopenia
Assess whether patient has a history of uterine malformations (e.g. seen on previous ultrasonographic examination or during intra-abdominal surgery)	Previous obstetric complication such as preterm labor or breech presentation suggests possibility of uterine malformation
Assess whether patient has had another fetus or infant with congenital anomaly	A congenital anomaly suggests the possibility of a parental karyotype abnormality, although these abnormalities may be present in the absence of such a history
Determine whether patient has history of symptoms suggestive of thyroid disease or diabetes	Can aid in direction of diagnostic workup
Physical Examination	
Perform pelvic examination with particular focus on findings compatible with uterine or cervical abnormalities	
Examine patient for other physical findings suggestive of thyroid disease or diabetes	
Recommended Tests[a]	
Lupus anticoagulant, anticardiolipin antibodies, and anti-beta-2-glycoprotein 1 antibodies	Tests for lupus anticoagulant are reported as either positive or negative; levels of anticardiolipin and anti-beta-2-glycoprotein 1 antibodies are clinically significant only in medium-to-high titers as defined by the laboratory; antiphospholipid syndrome is diagnosed when tests are repeatedly positive at least 12 wk apart[b]
Sonohysterography	Sonohysterography and hysterosalpingography are noninvasive screening tests used to evaluate uterine cavity and shape; MRI, hysteroscopy, or both may be more informative but are more expensive and invasive, respectively; all are useful in detecting a uterine abnormality
Chromosome analyses of father and mother	Parental karyotyping is expensive and not always covered by third-party payers; because treatment options are limited and do not surpass results of spontaneous conception, some couples may choose to forgo this testing
Genetic analysis of products of conception	Aneuploid conceptus indicates a more favorable outcome of a subsequent pregnancy and may avert further unnecessary evaluation and treatment. Options include chromosome analysis or (even better) direct array which increases likelihood of results (see text)
Other laboratory tests (e.g. thyrotropin measurement or screening for diabetes), if suggested by history or physical examination	

Source: Adapted from Ref. [6].

[a] Routine testing for thyroid disease, diabetes, polycystic ovary syndrome, heritable thrombophilias, bacteria and viruses, and alloimmune abnormalities is not recommended.

[b] See also Chap. 28 in *Maternal-Fetal Evidence Based Guidelines.*

Abbreviation: MRI, magnetic resonance imaging; wk, weeks.

and has been shown to decrease self-blame [18]. Karyotype can be obtained directly from POCs; however, this test requires growing (dividing) cells to assess DNA in metaphase. Many times cells of abortuses do not grow in culture, especially those with aneuploidy. Potential pitfalls include culturing of maternal cell contaminants, falsely providing a "negative" test result (46,XX). **Array comparative genomic hybridization (aCGH)** does not require dividing cells and therefore **can be useful** in settings of culture failure. As such, aCGH has been suggested for use over karyotype.

Parental karyotype

Three to five percent of couples with RPL have one parent with balanced translocation, mosaicism, or, less commonly, a chromosome inversion. Although these couples experience increased reproductive loss rates, most will have successful pregnancies without intervention [19]. Available intervention includes preimplantation genetic screening (PGS) and donor gametes.

Anatomic evaluation

Ten to twenty percent of women with RPL have uterine anomalies [7]. The most common congenital anomaly associated with RPL is septate uterus (spontaneous abortion [SAB] rate is high, about 65%) [20], followed by didelphys and bicornuate. Arcuate uterus has not been consistently associated with RPL. The relationship between RPL and acquired uterine abnormalities such as leiomyomata, adhesions, and endometrial polyps is not well established. Uterine synechiae (Asherman syndrome) and diethylstilbestrol (DES) exposure are associated with RPL. Myomata have been associated with decreased implantation rates in the

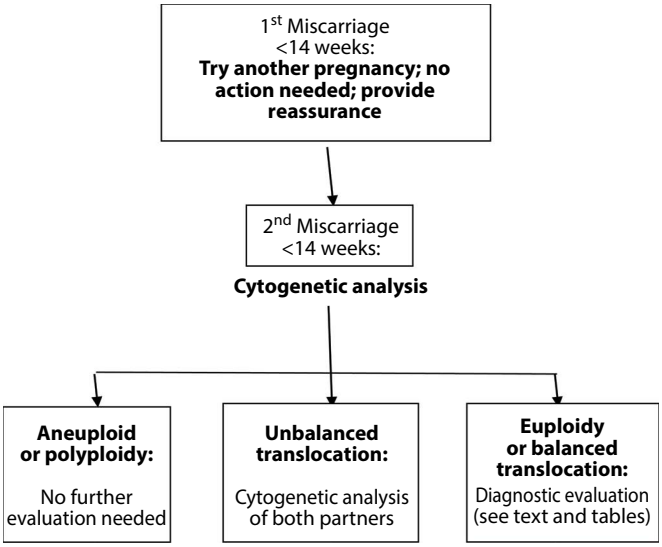


FIGURE 17.1 Evaluation of patients with early pregnancy loss based on cytogenetic analysis of products of conception. (Adapted from Ref. 7.)

in vitro fertilization (IVF) literature [21]. A maternal **uterine study** (sonohysterogram or hysterosalpingogram [HSG]) is recommended. Second-line tests (due to increased expense or invasive nature) such as MRI or hysteroscopy/laparoscopy may have a role as well. Available intervention is hysteroscopic resection of septum, synechiae, or submucous myomata. **Surgical correction may not improve chances of a successful pregnancy (see "Abnormal Uterine Cavity," later)**.

Endocrine evaluation

Endocrine factors may contribute to **8%–12% of RPL** [22]. Basic evaluation should consist of screening for **diabetes** (hemoglobin A1c [HgbA1c], fasting glucose, glucose tolerance testing) and screening for **thyroid** dysfunction (thyroid-stimulating hormone [TSH] and free thyroxine [T_4]); prolactin levels only if clinically suspicious.

Immunologic evaluation

Five to fifteen percent of women with RPL have antiphospholipid syndrome (APS) [7]. Testing, which includes aPL antibodies (lupus anticoagulant, anticardiolipin antibodies [ACAs], and beta-2 glycoprotein 1) should be positive twice, ≥12 weeks apart. See Chap. 28 in *Maternal-Fetal Evidence Based Guidelines* for details on diagnosis and other considerations in pregnancy.

Tests that cannot be routinely recommended

- POC molecular genetic abnormalities (e.g. X-chromosome inactivation) is associated with increasing maternal age, but is not associated with RPL [23].
- Endometrial biopsy or progesterone levels.
- Luteal phase deficiency (LPD) has been suggested as a cause of RPL. The corpus luteum fails to make enough progesterone to sustain pregnancy implantation and early growth. The diagnosis is hampered by inconsistent diagnostic criteria. The American Society for Reproductive Medicine (ASRM) has determined that there is no standard to diagnose LPD [24]. Screening is not recommended in RPL.
- Immunologic workup.

Although autoantibodies have been reported in women with RPL [25], there has been no consistent association and few intervention studies. Currently, testing for antinuclear antibody (ANA), anti–double-stranded DNA, and anti-smooth muscle antibodies is not recommended. There does appear to be an association with anti-thyroglobulin antibody based on a retrospective cohort. Further studies are needed [26].

Thrombophilia workup

Inherited thrombophilias (factor V Leiden [FVL], prothrombin G20210A gene mutation [PTM], antithrombin III deficiency, protein S, and protein C deficiencies) have not been consistently associated with RPL in the best designed prospective studies. However, a higher frequency of FVL carrier state has been shown in women with early RPL [27]. Second-trimester PL has been associated with thrombophilic mutations. There is **insufficient evidence regarding any interventions in women with RPL and inherited thrombophilias** (see Chap. 29 in *Maternal-Fetal Evidence Based Guidelines).*

Infectious workup

No infectious agent has been proven to cause RPL. *Listeria, Toxoplasma gondii,* and many viruses have been associated with sporadic early PL. *Chlamydia*, *Mycoplasma*/*Ureaplasma* (proposed diagnosis with endometrial biopsy, with treatment of woman and partner with either doxycycline 100 mg PO bid or ciprofloxacin 250 mg PO bid), and bacterial vaginosis are associated with sporadic pregnancy loss, but not RPL [28].

Male factor

A meta-analysis of prospective studies showed an association between sperm DNA fragmentation and RPL (mean difference 11.91, confidence interval [CI] 4.97–181.86) [29]. However, there is significant heterogeneity between the studies. Routine testing is not recommended.

Management

Prevention

Optimize preconception medical care of all maternal diseases.

Preconception care

In patients with RPL, workup should be performed prior to conception (Table 17.4). If workup is positive, patients should be counseled regarding specific associations. If workup is negative (>50% of couples), counseling should include the fact that **60%–70% of couples with unexplained RPL have successful pregnancies in the next gestation** (Table 17.3). This percentage, however, decreases to 40%–50% in women ≥40 years old. All women with RPL should be offered a **support group**. UNITE offers services that provide emotional support through parent-to-parent sharing on issues related to grieving. UNITE can assist in referral if additional professional support is needed [30].

Prenatal care

For recommend therapy specific for a positive workup, see next. In cases of RPL, especially with current vaginal bleeding but even in the absence of it, **progesterone** has shown benefit (see "Therapy" section). Offer early and frequent ultrasounds as needed given patient anxiety.

Therapy (specific for workup)

Abnormal parental chromosomes

Offer genetic counseling and prenatal diagnosis (termination is an option for affected pregnancies). **Preimplantation genetic screening with IVF** is **not beneficial, including in women with RPL** [31]. More data are needed; however, this intervention appears to be commonly used for couples who are translocation carriers. Gamete donation is another option.

Abnormal uterine cavity

Septum, synechiae, and/or submucous myomata can be resected hysteroscopically, but **there are no trials regarding this intervention**. However, there have been prospective studies suggesting higher live birth rates in women with uterine septa and RPL who undergo septum resection [32]. **Repair of the bicornuate or unicornuate uterus is not suggested** in these women, as outcomes are usually good without repair, whereas surgical correction is associated with higher risk of complications. Consider referral to a reproductive endocrinology specialist if necessary. There is a paucity of evidence to give a recommendation for women with fibroids and RPL. The available data suggest resection of submucosal fibroids may confer benefit [33].

Medical condition

If a medical condition is identified (e.g. diabetes mellitus [DM], thyroid disease), treat as indicated (see specific chapters in *Maternal-Fetal Evidence Based Guidelines).* Metformin has not been shown to reduce the risk of miscarriage in women with RPL and polycystic ovary syndrome [14, 34].

Antiphospholipid syndrome

Unfractionated heparin (UFH) combined with low-dose aspirin is associated with improved live birth compared to aspirin alone (relative risk [RR] 1.74, 95%CI 1.28–2.35, 2 trials, $n = 140$). There is no advantage in a higher dose of UFH over a prophylactic dose [35, 36]. **Low-molecular-weight heparin (LMWH) combined with low-dose aspirin** also shows improved live birth rates compared to low-dose aspirin (RR 1.20, 95% CI 1.04–1.38, 3 trials, $n = 1155$) [35, 36]. Either UFH or LMWH has been shown to reduce the risk of pregnancy loss (RR 0.48, 95% CI 0.32–0.71, 5 trials, $n = 1295$) and to increase the live birth rate (RR 1.27, 95% CI 1.09–1.49) (see Chap. 28 and Table 28.3) [36]. Therapy is usually begun once fetal viability is established. Low-dose aspirin is usually about 75–100 mg daily. For prophylactic UFH, the dose is 5000–7500 U in the first trimester, 7500–10,000 U in the second trimester, and 10,000 U in the third trimester SQ q12h. Prophylactic LMWH, 40 mg SQ a day, is often recommended due to once-daily dosing and fewer side effects. Aspirin alone (three trials), intravenous immunoglobulin (IVIG) plus UFH plus aspirin (two trials), and prednisone plus aspirin (three trials) have not shown significant benefit and should not be used [34].

In summary, **in women with RPL and APS**, available guidelines recommend a **combined therapy with low-dose aspirin and prophylactic doses of heparin**, although the available randomized controlled trials (RCTs) include heterogeneous groups of patients [36, 37].

Inherited thrombophilia

As stated earlier, a **workup for inherited thrombophilia is not indicated**. If positive inherited **thrombophilia** is **incidentally** or previously identified, **no intervention** has been consistently shown to improve outcomes in women with RPL. Please also refer to Chap. 16 and to Chap. 29 in *Maternal-Fetal Evidence Based Guidelines*.

Interventions for unexplained RPL

Progesterone

Women with recurrent miscarriage may benefit from the use of vaginal micronized progesterone (e.g. 400 mg twice daily) [38]. This was described in particular by two large RCTs: PROMISE (vaginal progesterone in recurrent miscarriage, $n = 836$) and PRISM (vaginal progesterone in women with early pregnancy bleeding, $n = 4153$) [39, 40]. While the primary outcomes for both trials were negative, preplanned subgroup analysis in PROMISE showed a nonsignificant trend toward the benefit of vaginal progesterone with an increasing number of miscarriages. In the PRISM RCT, prespecified subgroup analyses showed increasing benefit for vaginal progesterone with an increasing number of miscarriages. In women with one or more miscarriage(s) and current pregnancy bleeding, the live birth rate was improved ($n = 1515$, RR 1.09, 95% CI, 1.03–1.15, $p = 0.003$). The benefit was even greater for women with three or more prior miscarriages and current pregnancy bleeding ($n = 285$, RR 1.28, 95% CI 1.08–1.51, $p = 0.004$) [40].

Multiple meta-analyses have addressed progesterone in various routes and doses for women with RPL and generally show benefit. In a 2018 meta-analysis of 10 trials, 1684 women showed reduced miscarriage rate (RR 0.73, 95% CI 0.54–1.00) [41]. A previous 2016 meta-analysis of 10 trials, $n = 1586$, also showed benefit (RR 0.72, 95% CI 0.53–0.97) [42].

Thus, women with a history of miscarriage, and especially those with early pregnancy bleeding, may benefit from progesterone. There should be shared decision-making between patients and their providers regarding timing, route of administration, and dose.

Human chorionic gonadotropin

There is **not enough evidence to support the use of hCG** for RPL. In a meta-analysis of five trials (596 women), when these two studies were removed from analysis, there was no longer a significant benefit of hCG (RR 0.74, 95% CI 0.44–1.23) [43].

Low-dose aspirin

Compared with placebo, aspirin alone did not increase the chance of live birth (RR 0.94, 95% CI 0.80–1.11) in a pooled analysis of 256 women with unexplained recurrent miscarriage with or without thrombophilia [44]. Therefore, low-dose aspirin should not be recommended for women with recurrent unexplained early PLs.

Unfractionated heparin

There is **insufficient evidence** to assess the effect of UFH alone in women with unexplained RPL [45].

Low-molecular-weight heparin

There are several RCTs that show **no effect of LMWH alone in the prevention of pregnancy loss in women with unexplained RPL** [46–48].

Additionally, no reduction in pregnancy loss was observed when LMWH and low-dose aspirin were used in combination [44, 46].

Vitamins

Vitamin D deficiency (VDD) has been associated with RPL, although the underlying mechanism is not clear. Immune dysregulation has been theorized in RPL. A review of 11 studies of women with >2 RPLs showed a high prevalence of VDD in

women with RPL. Exposure to vitamin D promoted immune regulation and cytokine secretion. Vitamin D supplementation can be considered, but more studies are needed to investigate the association between VDD and RPL [47–49].

Diethylstilbestrol

DES should not be used in pregnancy for any indication. DES use in **pregnancy is significantly associated with several harmful consequences for both mother and baby** [50]. Exposed female offspring have an increased incidence of cancer, infertility, and genital tract abnormality.

Immunotherapy

Various forms of immunotherapy have been studied in the treatment of RPL. The theory is that the fetus is considered an allograft, and alteration of maternal immune response is needed for successful implantation. **IVIG and donor leukocytes** do not show significant differences between treatment and control groups in terms of subsequent live births [51, 52]. **Currently, immunotherapy should be used in the context of research and should not be used in routine clinical practice to improve reproductive outcomes**.

Antepartum testing

No specific testing indicated.

Delivery

No specific precaution.

Anesthesia

No specific precaution.

Postpartum/Breastfeeding

No specific precaution.

Future considerations

Effective treatment of an alleged alloimmune cause of recurrent miscarriage awaits more complete knowledge of the underlying pathophysiology. A specific assay to diagnose immune-mediated early PL and a reliable method to determine which patients might benefit from manipulation of the maternal immune system are needed. It is not presently known how many RPLs are the result of anembryonic or chromosomally abnormal conceptuses or anatomic or structural abnormalities and how many are embryonic or fetal deaths. **It is likely that some unexplained early losses are due to undefined subchromosomal genetic abnormalities impairing early development of the conceptus**. The currently available molecular genetic techniques, including comparative genomic hybridization and single nucleotide polymorphism microarray, may detect more of these abnormalities. New molecular techniques (e.g. whole-genome sequencing) should be directed at understanding the factors responsible for successful pregnancy, as well as PL.

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18

PRETERM BIRTH PREVENTION IN ASYMPTOMATIC WOMEN

Anju Suhag

Key points

- **Gestational age (GA) determination is of the utmost importance in preventing preterm birth (PTB) and the management of presumed threatened PTB**.
- **PTB** is defined as birth between $20^{0/7}$ and $36^{6/7}$ weeks. It is the **number-one cause of perinatal morbidity and mortality**, and these complications are inversely proportional to GA at birth. **Over 1 million babies die of the consequences of PTB every year in the world**, 1 every 30 seconds.
- An accurate history should be taken regarding risk factors for PTB, especially obstetric-gynecologic (ob-gyn) history, maternal lifestyle, and pre-pregnancy weight (Table 18.1). Consider preconception counseling for women with very early PTB or recurrent PTB or poor obstetric history.
- **Primary prevention strategies** for PTB aimed at the general population include family planning, avoidance of lifestyle risks, and proper nutrition. A reproductive-age woman should **avoid** (as feasible) **extremes of age, extremes of interpregnancy interval (18–23 months is the optimal interval between last delivery and next conception), induced termination of pregnancy (TOP) without ripening, multiple gestations, illegal drugs (e.g. cocaine), physical abuse, sexually transmitted infections (STIs)**, poverty, poor education, and **a pre-pregnancy weight of <50 kg (<120 lb)**. A normal BMI at the start of pregnancy, not dieting but instead a balanced diet during pregnancy, and achieving weight gain of >5 kg by 30 weeks for underweight and normal-weight women can certainly help avoid PTB. Consider low-dose aspirin for PTB prevention (if no contraindications).
- **Screening with transvaginal ultrasound (TVU) cervical length (CL) at 18–$23^{6/7}$ weeks should be offered to all singleton gestations. In singleton gestations without a prior spontaneous PTB (SPTB), if CL ≤25 mm develops, vaginal progesterone (e.g. 200 mg suppositories daily until 36 weeks) should be recommended. If CL is less than 10 mm, consider physical (e.g. speculum and digital) cervical examination to evaluate for physical examination–indicated cerclage**.
- **Secondary prevention of PTB** is based on identification and treatment (or avoidance) of risk factors. **A screening test aimed at prediction of PTB is only beneficial if an intervention reduces the outcome once the screening test is positive**. Secondary prevention of PTB has been shown in the following groups for the following interventions:
  - In women who **smoke, smoking cessation counseling**/support programs.
  - In women with **≥1 prior SPTBs** now carrying **a singleton gestation**, all the following interventions are associated with a significant decrease in recurrent PTB:
    - **Vaginal progesterone 200 mg every evening or 17 alpha-hydroxyprogesterone caproate** 250 mg IM weekly starting at 16–20 weeks until 36 weeks.
    - Moderate **fish intake**, up to three meals per week, before 22 weeks.
    - **Cerclage if the TVU CL is <25 mm before $24^{6/7}$ weeks. Therefore, all singleton gestations with prior SPTB should have serial TVU CL screening in the second trimester, usually at 16–23 weeks**.
    - In women with **≥3 prior early (usually <32 weeks) SPTBs or second-trimester losses (STLs), history-indicated cerclage**.
- Avoid bed rest and/or routine maintenance tocolytics during pregnancy for secondary prevention of PTB.
- In women with **cervical dilatation ≥1 cm before 24 weeks, physical exam-indicated cerclage** is associated with a significant decrease in PTB; consider amniocentesis beforehand to detect intra-amniotic infection.
- In women with **asymptomatic bacteriuria of >100,000 bacteria/mL, appropriate antibiotics** are associated with a significant decrease in PTB.
- In women with **asymptomatic group B streptococcus (GBS) bacteriuria of any colony count**, appropriate antibiotics (usually **penicillin)** are associated with a significant decrease in PTB.
- All other screening and treatment interventions for prevention of PTB are not supported by strong evidence for recommending their clinical use.

Background

Prevention of preterm birth (PTB) is the number-one issue in pregnancy, as being born preterm is the number-one cause of neonatal mortality and the second leading cause of all under-5 childhood mortality in many developed countries, including the United States [1, 2]. This chapter reviews evidence-based guidelines for women without symptoms related to PTB. The following two chapters deal with women with symptoms of PTB: First preterm labor (PTL) (Chap. 19), then preterm prelabor rupture of membranes (PPROM) (Chap. 20).

Diagnoses/Definitions

Gestational age (GA) determination is of the utmost importance in the prevention of PTB and management of presumed threatened PTB (see Chap. 4 for the best GA determination criteria).

Definitions regarding prematurity vary in different publications, but the ones most commonly accepted and used in trials are the following:

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TABLE 18.1: Selected Risk Factors for Spontaneous Preterm Birth

History:
- Obstetric-gynecological history: Prior SPTB; prior STL; prior D&Es; prior LEEP; prior cone biopsy; uterine anomalies; DES exposure; myomata; short interpregnancy interval (<6 months); ART; prior stillbirth <24 weeks; prior early twin SPTB; prior full-term cesarean delivery for second-stage arrest
- Maternal lifestyle (smoking, drug abuse)
- Maternal pre-pregnancy weight <120 lb (<50 kg) or low BMI (<19.8 kg/m^2), short height (<53 inches or 3SD below any race/ethnicity); poor nutritional status
- Maternal age (<19; >35 years old)
- Race (especially Afro-American)
- Education (<12 grades)
- Certain medical conditions (e.g., DM, HTN, renal disease and intrahepatic cholestasis of pregnancy)
- Low socioeconomic status
- Limited prenatal care
- Family history of SPTB
- Vaginal bleeding (especially during second trimester, subchorionic hematoma)
- Social or psychological stress (mostly related to earlier risks)
- Infections (bacterial vaginosis, chlamydia, gonorrhea, asymptomatic bacteriuria, urinary tract infection, periodontal disease)
- Higher number of lifetime sexual partners

Identifiable by screening:
- Anemia
- Infections (STIs, periodontal disease)
- TVU CL <25 mm (especially <24 weeks)
- fFN positive (≥50 ng/mL) (between 22 and 34 weeks)

Usually symptomatic:
- Uterine contractions

Not spontaneous (indicated/iatrogenic):
- Fetal demise/major fetal anomaly
- Multiple gestation/polyhydramnios
- Nonreassuring fetal heart tracing
- FGR
- Placenta previa
- Placental abruption
- Major maternal disease (HTN complications, DM, etc.)

Abbreviations: SPTB, spontaneous preterm birth; STL, second-trimester loss; LEEP, loop electrosurgical excision procedure; DES, diethylstilbestrol; ART, assisted reproductive technology; STI, sexually transmitted infection; BMI, body mass index; DM, diabetes mellitus; HTN, hypertension; TVU, transvaginal ultrasound; CL, cervical length; fFN, fetal fibronectin; FGR, fetal growth restriction.

PTB: Birth between $20^{0/7}$ and $36^{6/7}$ weeks [3]

- Very early PTB: Birth between $20^{0/7}$ and $23^{6/7}$ weeks
- Early PTB: Birth between $24^{0/7}$ and $33^{6/7}$ weeks
- Late PTB: Birth between $34^{0/7}$ and $36^{6/7}$ weeks

Pregnancy loss (PL): Spontaneous loss of pregnancy from conception to <20 weeks. The term spontaneous abortion is equivalent, but should be avoided since women associate negative feeling with this term. Miscarriage is a lay term for PL (see also Chaps. 16 and 17).

Second-trimester PL (aka second-trimester loss—STL): Birth between $14^{0/7}$ and $19^{6/7}$ weeks.

Cervical insufficiency (CI) (formerly called incompetence): Recurrent painless dilatation leading to STLs [4]. A better definition is a **cervical length (CL) <25 mm before 24 weeks in women with singleton gestations and prior SPTB <37 weeks**.

PTL: Uterine contractions (≥4 per 20 minutes or ≥8 per hour) and documented cervical change with intact membranes at 20–$36^{6/7}$ weeks. A better definition is **uterine contractions (≥4 per 20 minutes or ≥8 per hour) with TVU CL <20 mm, or 20–29 mm with positive fetal fibronectin (fFN)** at 20–$36^{6/7}$ weeks (see Chap. 19).

Prelabor preterm rupture of membranes (PPROM): Vaginal pooling, nitrazine, and/or ferning at 16–$36^{6/7}$ weeks (see Chap. 20).

- Early PPROM: PPROM between 24 and $33^{6/7}$ weeks
- Very early PPROM: PPROM between 16 and $23^{6/7}$ weeks

Epidemiology/Incidence

Incidence of PTB <37 weeks varies between about 5% and 18% in different countries [5]. The rate of PTB in the United States steadily increased from 9.4% in 1981 and peaked in 2006 at 12.8%. Since then, the rate of PTB in the United States dropped to 9.6% in 2014 (25% decline) [6, 7]. The incidence of PTB <32 weeks remains at about 2% in United States and ≤1% in most other high-income countries. **Over 1 million babies die of the consequences of PTB every year in the world, 1 every 30 seconds** [1]. The high incidence of PTB in many high-income countries may be due to assisted reproductive technology (ART)–related multiple gestations, older and sicker mothers, earlier GA of registered births and neonatal improvements, better and earlier timing of births (related to ultrasound), worsening socioeconomic factors, and other factors. In addition to the use of progesterone and cerclage in women at high risk for PTB, there are several other demographic factors which lead to reducing the national PTB rate. This decline in PTB in the United States appears to be related also to a reduced teen birth rate, lower rate of higher-order multiple births, smoking cessation counseling and bans, and improved institutional/national policies of preventing non-medically indicated PTB <39 weeks [8]. Early adoption of guidelines for the prevention of PTB has been shown to reduce the rate of PTB at a major academic center below the national average [9]. This study emphasizes a call for uniform implementation of protocols suggested by national societies like the Society for Maternal-Fetal Medicine (SMFM) and the American College of Obstetricians and Gynecologists (ACOG) to further decrease the U.S. national rates of PTB.

Genetics

While a genetic predisposition in certain ethnic groups and families has been reported, no clinical genetic studies are yet recommended for the prediction/prevention of PTB due to insufficient evidence [10].

Etiology/Basic pathophysiology

Just like cardiac disease, PTB is a final common manifestation with a multifactorial, complex etiology. Several processes leading to PTB are shown in Figure 18.1.

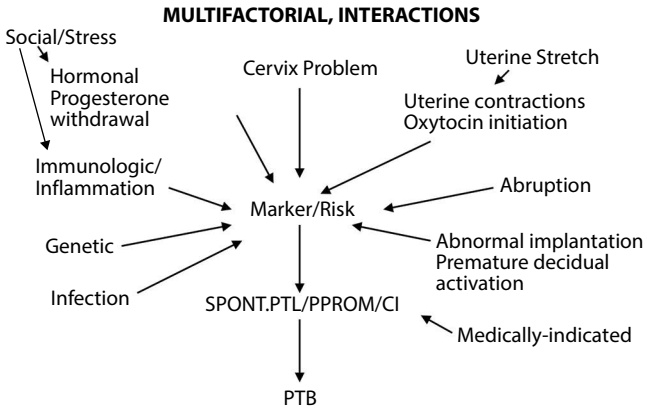


FIGURE 18.1 Preterm birth is the final common pathway of many associated possible etiologies. *Abbreviations:* SPONT. PTL, spontaneous preterm labor; PPROM, preterm prelabor rupture of membranes; CI, cervical insufficiency; PTB, preterm birth.

Classification

PTB can be spontaneous and follow PTL (50%; Chap. 19), PPROM (30%; Chap. 20), or, rarely, CI; or be iatrogenic (20%). CI may comprise about 1% of spontaneous PTB (SPTB) and/or STLs (see Risk: Cervical insufficiency (page 222, 2nd paragraph)). CI represents one extreme of SPTB, as PTB is continuous.

Risk factors/Associations

Most women who have a PTB have identifiable risk factors. Risk factors for SPTB (presenting as PTL, PPROM, or CI) are similar (Table 18.1). **All these risk factors should be reviewed in detail with every pregnant woman at the first prenatal visit**. The vast majority of U.S. pregnant women (96% on in one study) has at least one risk factor for PTB [11]. For many of these risks, interventions are associated with the prevention of PTB.

Complications

PTB is the **number-one cause of perinatal mortality**. Seventy-five percent of perinatal mortality occurs in preterm babies; more than two-thirds of perinatal mortality (60% of total) occurs in infants aged <32 weeks. **Mortality and morbidities are inversely associated with GA at birth** (Table 18.2) [12]. Morbidities include respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), sepsis, apnea, and retinopathy of prematurity [13]. The long-term neonatal morbidities from PTB include chronic lung disease, grade III/IV IVH, NEC, vision and hearing impairment, cerebral palsy, reduced cognition, academic difficulties, and attention deficit disorders [14, 15].

Prediction and prevention of PTB

A screening test aimed at predicting PTB is only beneficial if an intervention (prevention) reduces the outcome once the screening test is positive. Several predictive strategies have poor sensitivity and specificity.

Prevention is preferable, rather than treatment, once symptoms have been identified. Prevention can be divided into three categories (Table 18.3). Primary and secondary prevention are preferable, rather than tertiary prevention of symptomatic women with PTL or PPROM. This chapter refers to prevention of SPTB mostly in **singleton gestations** unless otherwise specified. Prevention of PTB in multiple gestations is also discussed in Chap. 46 in *Maternal-Fetal Evidence Based Guidelines.*

For women at risk for **iatrogenic (indicated) PTB**, one should aim to keep the pregnant woman as healthy as a nonpregnant adult. Appropriate prevention and therapy of any maternal medical or fetal/congenital anomaly disorder are paramount, as is appropriate prevention and therapy for preeclampsia and fetal growth restriction (FGR) (please see specific chapters in *Maternal-Fetal Evidence Based Guidelines)* [1].

All **pre-pregnancy evaluations** of the cervix (e.g. hysterosalpingogram, no. 8 Hegar dilator passage, and catheter traction test) aimed at screening for CI have either been inadequately studied or been shown not to be sufficiently predictive and therefore useful in a prevention program (no trial ever reported).

An accurate history should be taken regarding risk factors for PTB, especially ob-gyn history, maternal lifestyle, and pre-pregnancy weight (Table 18.1). A detailed history should include whether the prior PTB was spontaneous or indicated (iatrogenic). Spontaneous PTB is defined as PTB prior to 37 weeks due to PTL, PPROM, advanced cervical dilation (ACD), or cervical insufficiency. It is also important to document the sequence of events (antepartum) leading to a PTB, as this could help **counsel these women about their risk of recurrent PTB**, and **appropriate PTB prevention strategies** could be utilized. For example,

TABLE 18.2: Preterm Neonatal Morbidity and Mortality

		Delivery Gestational Age (Weeks)														
Outcome	**All**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**p-value**
Death	1.4	44.2	31.6	12.1	11.2	8.2	2.0	1.9	1.5	1.0	0.2	0.2	0.0	0.0	0.0	<0.001
Major morbidity[a]	7.9	44.2	52.6	54.8	52.1	40.3	21.9	22.5	13.7	7.1	8.7	4.2	4.4	2.8	1.8	<0.001
Minor morbidity[b]	37.6	9.3	15.8	31.5	34.9	48.4	73.5	69.0	78.6	81.7	76.3	63.5	51.0	27.2	15.9	<0.001
Survival without any of earlier morbidities	53.1	2.3	0.0	1.6	1.8	3.1	2.6	6.6	6.1	10.3	14.9	32.1	44.6	69.9	82.4	

Source: Modified from Ref. [11].

Note: Data presented as %; $n = 8334$.

[a] Includes persistent pulmonary hypertension, intraventricular hemorrhage grade 3/4, seizures, hypoxic-ischemic encephalopathy, necrotizing enterocolitis stage II/III, bronchopulmonary dysplasia.

[b] Includes intraventricular hemorrhage grade 1/2, necrotizing enterocolitis stage 1, respiratory distress syndrome, hyperbilirubinemia requiring treatment, hypotension requiring treatment.

TABLE 18.3: Definition of the Different Categories of Prevention of Preterm Birth

	Definition	Examples
Primary Prevention	Prevention strategies aimed at **all asymptomatic** pregnant women at risk for PTB (i.e. aimed at all pregnant women)	Encourage optimal (18–23 months) interpregnancy interval Limit higher order multiple births (ART)
Secondary Prevention	Prevention strategies aimed at **identifying asymptomatic women at high risk for PTB through screening**. Screen for predictive risk factor (prediction) in asymptomatic women and avoid/treat (preventive intervention)	Obtain comprehensive OB history and offer preventive interventions (progesterone, cerclage, CL screening) to appropriate candidates Smoking cessation Low-dose aspirin Screen for infection, and treat if indicated
Tertiary Prevention	Prevention strategies aimed at women with active **symptoms** of PTB	Interventions for women with PTL (Chap. 19) or PPROM (Chap. 20)

Abbreviations: ART, assisted reproductive technology; PTB, preterm birth; OB, obstetrical; CL, cervical length; PTL, preterm labor; PPROM, preterm prelabor rupture of membranes.

women with a history of ACD are at an increased risk of having cervical shortening (50% vs. 14.6% vs. 15.6%, p <0.01), recurrent PTB (55.2% vs. 27.2% vs. 32.2%, p <0.01), and a lower GA at delivery (34.0 vs. 37.2 vs. 37.0 weeks, p <0.01) in a subsequent pregnancy compared with women with prior PTB-associated PPROM or PTL, respectively [16].

A Creasy score or other similar history-based systems to predict PTB have been associated with a low (10%–30%) positive predictive value (PPV) for PTB and are not clinically useful, given negative intervention trials. There are **no trials on risk-scoring systems for predicting PTB** [17]. There is a need for prospective studies that evaluate the use of a risk-screening tool designed to predict PTB (in combination with appropriate consequent interventions) to prevent PTB, including qualitative and/or quantitative evaluation of their impact on women's well-being.

There are four main risk factors for which there are effective interventions for the prevention of PTB: Smoking, short TVU CL, prior SPTB, and asymptomatic bacteriuria (Table 18.4). **A TVU CL screening at 18–23 weeks is indicated in all women with a singleton gestation** (Figure 18.2).

Current evidence does not support the use of home uterine activity monitoring (HUAM) [18] or bacterial vaginosis (BV) screening [19] in asymptomatic, low-risk women. There are insufficient data to support the use of salivary estriol or fFN in asymptomatic women (even if fFN is one of the best predictive screening tests). Cytokines, matrix metalloproteinases, corticotropin-releasing hormone (CRH), salivary estriol, relaxin, human chorionic gonadotropin (HCG), prothrombin, fetal DNA, and many other tests remain research tools for the prediction of PTB and are not yet clinically beneficial, given the lack of intervention trials based on these screening tests.

Primary prevention

Primary prevention includes prevention strategies aimed at **all asymptomatic pregnant women** at risk for PTB (i.e. aimed at all pregnant women). Unfortunately, many primary prevention interventions have been so far either insufficiently studied or found not to be effective.

Preconception/Early pregnancy

Family planning

There are no trials to assess interventions. **Avoiding extremes of age, avoiding short interpregnancy interval <6 months** (18–23 months is the optimal interval between the last delivery and the next conception) [20], **and reducing the rate of multiple gestations** (through ART improvements) seem self-evident for efficacy in preventing PTB when feasible. Evidence suggests that risks of PTB, low birth weight (LBW), and small-for-gestational-age (SGA) infants are minimized when interpregnancy intervals are between 18 and 23 months [20, 21]. For an appropriate interpregnancy interval, physicians should pay close attention to plans for postpartum contraception. Improvements in postpartum contraceptive use have been associated with decreased incidence in PTB. For every month of contraception coverage, the odds of PTB <37 weeks decrease by 1.1% (odds ratio [OR] 0.98, 95% confidence interval [CI] 0.98–099) [22].

TABLE 18.4: Selected Effective Interventions for Prevention of Preterm Birth

Avoid (as feasible)	• Extremes of age • Interpregnancy interval <6 months • Induced termination of pregnancy without ripening • Multiple gestation • Illegal drugs (e.g. cocaine) • Physical abuse • STIs • Poverty • Poor education • Pre-pregnancy weight of <50 kg (<120 lb)
Risk	**Intervention**
Smoking	Smoking cessation programs
No prior spontaneous PTB *and* CL ≤25 mm (screen every singleton and twin with TVU CL at 18–$23^{6/7}$ wk)	Vaginal progesterone (e.g. 200 mg daily)
Prior spontaneous PTB (SPTB)[a]	Progesterone
Prior SPTB *and* CL <25 mm up to $23^{6/7}$ wk[a]	Ultrasound-indicated cerclage
Prior ≥3 early PTB/STL[a]	History-indicated cerclage
Asymptomatic bacteriuria	Appropriate antibiotics

[a] For singleton gestations.

Abbreviations: TVU, transvaginal ultrasound; CL, cervical length; PTB, preterm birth; SPTB, spontaneous PTB; STL, second-trimester loss; STIs, sexually transmitted infections; wk, weeks.

Induced TOP is associated with a higher risk of PTB, even if just one early TOP is performed [23]. Recent meta-analyses showed that dilation and curettage (D&C) compared with no D&C increases the risk of PTB <37 weeks (OR 1.29, 95% CI 1.17–1.42) [24, 25]. Women who had even just one uterine evacuation for either spontaneous or induced abortion have a higher risk of PTB (OR 1.44, 95% CI 1.09–1.90) [25]. The risk of PTB <37 weeks is noted to be even higher in women with a history of multiple D&Cs (OR 1.74, 95% CI 1.10–2.76) [24]. **Avoiding TOPs as feasible with effective contraception seems to be an effective preventive strategy to avoid PTB**. If TOP is unavoidable, the dilation and evacuation (D&E) should be performed with preoperative cervical ripening (e.g. misoprostol, mifepristone, or laminaria), as this is associated with no or very low risk for PTB [23].

Avoidance of lifestyle risks

There are no trials to assess interventions. **Avoiding illegal drugs** (e.g. cocaine and amphetamines), **physical abuse, and STIs** (chlamydia, gonorrhea, syphilis, HIV, etc.) seem self-evident for efficacy in preventing PTB [26]. **Poverty, poor education**, lack of women's empowerment, and several other social stressors (Table 18.1) are all linked profoundly to an increased risk of PTB and should be avoided as possible, especially through political and social changes. Workplace conditions are only weakly related or are not related to adverse pregnancy outcomes. In the third trimester, >42 hours of work per week, >6 hours of standing per day, and pesticide exposure are associated with PTB [27]. There are no trials on modifying other potential risks, such as a physically demanding job, prolonged standing, night work, or others.

Proper nutrition and weight gain

A pre-pregnancy weight of <50 kg (<120 lb) should be avoided. A recent meta-analysis of 17 randomized controlled trials (RCTs) showed the benefit of **nutrition education to increase energy and protein intake in decreasing the risk of PTB** (2 trials, 449 women) (relative risk [RR] 0.46, 95% CI 0.21–0.98, *low-quality evidence*), **and LBW** (one trial, 300 women) (RR 0.04, 95% CI 0.01–0.14) **among undernourished women** [28]. **A normal BMI at the start of pregnancy, not dieting but instead a balanced diet during pregnancy, and achieving a weight gain of >5 kg by 30 weeks for underweight and normal-weight women can certainly help to avoid PTB**.

The available evidence shows no benefit of balanced protein/energy supplementation in prevention of PTB [29]. A high-protein diet (>25% of total energy content) has no association with PTB prevention and is not recommended in pregnancy because of the increased risk of SGA (see also Chap. 2) [30].

Early pregnancy

Fish intake

Shark, swordfish, king mackerel, or tilefish contain high levels of mercury and should be avoided or eaten infrequently (≤1/week) in pregnancy. **Canned light tuna, salmon, pollock, grouper, mussels, scallops, shrimp, and catfish are common fishes low in mercury, and two portions (6 oz = 1 portion) of these per week can** (and probably should) **be safely eaten in pregnancy**. Albacore ("white") tuna has more mercury and should be consumed up to 6 oz/week. In general, for other fishes, smaller fishes have less mercury than larger ones. More information on fish and mercury intake in pregnancy is available at https://www.fda.gov/food/consumers/advice-about-eating-fish"-"https://www.epa.gov/fish-tech/epa-fda-advice-about-eating-fish-and-shellfish. There is **limited evidence suggesting the potential benefit of maternal fish intake on reduction of PTB**. A recent prospective cohort study reported a significant reduction in the risk of PTB in women choosing a "prudent" or a "traditional" dietary pattern, characterized by, for example, vegetables, cooking oil, fruit, berries, olive oil, rice, water as a beverage, whole grain cereals, yoghurt, poultry, lean fish, and boiled potatoes, as well as a low intake of processed meat products, white bread, and pizza/tacos [31].

Omega-3 fatty acids

Low-risk women without a prior PTB have a similar incidence of PTB <37 weeks when given 12 eggs with either 133 mg DHA or 33 mg DHA per week starting at 24–28 weeks [32]. Supplementation has been shown to prolong pregnancy by 3–8 days in different populations. When all RCTs are examined, women allocated to a marine oil supplement had a mean gestation that was 2.6 days longer than women allocated to placebo or no treatment. This was not reflected in a clear difference between the two groups in PTB <37 weeks, although women allocated to marine oil did have a **lower risk of PTB <34 weeks** (RR 0.69, 95% CI 0.49–0.99). Birth weight was slightly greater (47 g) in infants born to women in the marine oil group compared with controls. However, there were no overall differences between the groups in the proportion of LBW or SGA babies. There was no clear difference in the relative risk of preeclampsia between the two groups [33]. A large RCT found that DHA 800 mg supplementation before 21 weeks was associated with a decrease in PTB <34 weeks (RR 0.49, 95% CI 0.25–0.94) [34]. In contrast, in a recent meta-analysis of nine randomized trials including over 3800 asymptomatic women with singleton pregnancies and no prior PTB, **women who received omega-3 had a similar rate of PTB <37 weeks as women who received either a placebo or no supplementation** (7.7% vs. 9.1%; RR 0.90, 95% CI 0.72–1.11) [35]. The evidence suggests **minimal or no benefit of omega-3 supplementation in reduction in PTB <37 weeks in asymptomatic, low-risk singleton pregnancies**.

The PrimaCare vitamin supplement contains 150 mg of omega-3 fatty acids and has not been evaluated in a trial. The possible beneficial effects of omega-3 fatty acids to later fetal/neonatal/infant cognition remain not fully proven. For omega-3 supplementation in high-risk women, see the section "Risk: Prior PTB."

Probiotics

Women who report habitual intake of probiotic dairy foods (e.g. yogurt) have been associated with a lower incidence of PTB in non-RCTs [36]. Currently, there are **insufficient data** from RCTs to demonstrate any impact of probiotic food supplementation in low-risk women on PTB and its complications [37].

Other nutritional changes

There are no trials with the specific aim of preventing PTB to evaluate other nutritional changes, such as vitamin supplementation (see Chap. 2), HCG, and anticytokine supplements. **Pre-pregnancy weight <120 lb (<50 kg) is a significant risk factor for PTB and should be avoided if possible**. Suggested pregnancy weight gain in pregnancy is 25–35 lb for women with a normal BMI, but there are no trials on proper pre-pregnancy weight or pregnancy weight gain.

Vitamin C

Vitamin C supplementation alone is not associated with a reduced risk of PTB [38].

Vitamin E
Vitamin E supplementation alone or in combination with other supplements is not associated with the prevention of PTB [39].

Vitamins C and E
Maternal supplementation with vitamin C 1000 mg and vitamin E 400 mg daily from 9 to 16 weeks until delivery in nulliparous low-risk women is **not associated with a reduction in PTB** [40].

Vitamin D
Level II evidence suggests a protective effect of vitamin D supplementation in women with low 25-hydroxyvitamin D concentrations (at or prior to 20 weeks) on the rate of PTB in low-risk women [41]. Routine vitamin D level assessment and/or vitamin D replacement or supplementation is **not indicated** in women at risk for PTB until a well-designed RCT confirms these findings.

Calcium supplementation
Maternal supplementation of calcium versus placebo is **not associated** with a reduction in PTB [42].

Magnesium supplementation
There is **insufficient high-quality evidence** to show that dietary magnesium supplementation during pregnancy is beneficial. In the analysis of all trials, oral magnesium treatment before 25 weeks showed no significant effect of magnesium on perinatal mortality, SGA, preeclampsia, and PTB compared to placebo [43]. Of the ten trials included in the review, only two were judged to be of high quality and showed no association between magnesium and pregnancy outcomes.

Progesterone
The mechanism of action of progesterone for the prevention of PTB is poorly understood but probably involves an antiinflammatory action. Safety for the fetus/neonate has not been yet proven with 100% certainty, but progesterone is known not to be a teratogen, and long-term detrimental effects up to 18 years of age have not been shown. The effect of progesterone supplementation should be **evaluated according to different patient populations and according to the type of progesterone**. Here we review progesterone for low-risk women (see later for other risk groups).

In a small RCT including women in active military duty with only a 3% rate of prior PTB and unknown CL, 17α-hydroxyprogesterone (17P) 1000 mg IM weekly starting at 16–20 weeks was **not associated with any effect** on the incidence of PTB or perinatal outcomes compared with placebo [44]. No RCT has evaluated the effect of vaginal progesterone in this population.

In summary, there is **insufficient evidence to determine the impact on PTB of progesterone in singleton gestations with no prior PTB, with unknown or normal CL**.

Low-dose aspirin
Low-dose aspirin for the prevention of preterm delivery in nulliparous women with a singleton pregnancy (ASPIRIN trial) was studied in six low- and middle-income countries with 5780 women in the aspirin group and 5764 in the placebo group. This trial showed a significant reduction in PTB <37 weeks in women who took aspirin compared to those who took placebo (11.6% vs. 13.1%, RR 0.89 [95% CI 0.81–0.98], $p = 0.012$). Women in the aspirin group showed lower perinatal mortality, fetal loss, early PTB <34 weeks, and lower incidence of delivery before 34 weeks in women with hypertensive disorders of pregnancy [45]. **In summary, low-dose aspirin seems beneficial for the prevention of PTB**.

Secondary prevention
Secondary prevention strategies involve screening for a predictive risk factor (prediction) in asymptomatic women and avoiding it or treating it (preventive intervention) (Table 18.3).

Risk: Smoking
Intervention: Smoking cessation programs
It is estimated that 10%–15% of PTBs may be due to smoking. In the United States, about 23% of women start pregnancy as a smoker and 11% continue to smoke throughout pregnancy [46]. **Psychosocial interventions (e.g. counseling, health education, feedback, incentives, social support) to support women to stop smoking in pregnancy has been associated with an increase the proportion of women who stop smoking in late pregnancy and a reduction in LBW** (RR 0.82, 95% CI 0.71–0.94) **and PTB** (18% reduction, RR 0.82, 95% CI 0.70–0.96) [47]. The ACOG has recommended use of the five A's—ask, advice, assess, assist, arrange—approach [48]. The most effective intervention for smoking cessation in pregnancy is **social support and a reward component** (23% decrease) [49, 50]. If this approach is not successful, consider nicotine replacement therapy (NRT) (see Chap. 22 in *Maternal-Fetal Evidence Based Guidelines*).

Intervention: Nicotine replacement therapy
NRT is associated with a trend for a benefit in the reduction in the incidence of smoking (see Chap. 22 in *Maternal-Fetal Evidence Based Guidelines*) [51–53]. **There is limited evidence to assess the effect of NRT, or nicotine gum, or bupropion, on the incidence of PTB** (see Chap. 22 in *Maternal-Fetal Evidence Based Guidelines*).

Other interventions
Interventions to increase smoking cessation among the partners of pregnant women, with the additional aim of facilitating cessation by the women themselves, have been insufficiently studied (only one trial) [47]. Stages of change, or feedback, do not show benefit [47]. A recent RCT showed no benefit of combining supervised exercise and physical activity counseling to improve the effectiveness of behavioral support for smoking cessation in pregnancy [54]. There has been increased awareness and use of e-cigarettes, or electronic nicotine delivery system (ENDSs), in adolescents (especially in middle and high school students), the health impact of which is not clear [55, 56]. E-cigarettes are marketed as smoking cessation devices and as better alternatives to regular cigarettes. This perception of harm reduction in comparison to regular cigarettes may be prevalent due to the lack of FDA regulation on e-cigarette advertising, and this potentially can further increase use of e-cigarettes in adolescents/reproductive-age women and in pregnant women as well (see Chap. 22 in *Maternal-Fetal Evidence Based Guidelines*) [55, 57].

Risk: Short cervix on ultrasound
Intervention: Activity restriction
Activity restriction is **not associated with prevention of PTB** in asymptomatic singleton gestations with a TVU CL <30 mm, and in fact is associated with a **237% increase in PTB** incidence [58].

Intervention: Progesterone
Regarding 17P, a multicenter RCT evaluating the effect of 17P in women with singleton gestations, no prior PTB, and short CL <30 mm compared with placebo showed no difference in rate of PTB <37 weeks (25.1% vs. 24.2%, RR 1.03, 95% CI 0.79–1.35) [59].

In another smaller RCT including women with singleton pregnancies (66% of which had no prior PTB) with CL<25 mm between 16 and 24 weeks, 17P was associated with similar incidences of PTB and neonatal morbidity and mortality compared to cerclage [60]. Cerclage was significantly more effective than 17P at reducing the incidences of PTB <35 and <37 weeks in the subgroup with CL ≤15 mm [60]. In summary, **17P cannot be recommended for prevention of PTB in singleton gestations (no prior PTB) with a short TVU CL**.

Regarding vaginal progesterone, several RCTs are available. In 250 women with mostly (90%) singleton gestations and CL ≤15 mm at 20–25 weeks, of whom about 85% had no prior PTB, vaginal progesterone 200 mg nightly started at 24 weeks until 34 weeks was associated with a 44% significant decrease in SPTB <34 weeks (19% vs. 34%, RR 0.56, 95% CI 0.36–0.86), but no significant effects on neonatal morbidities (composite neonatal adverse outcomes: RR 0.57, 95% CI 0.23–1.31) [61]. A subgroup analysis of only women without prior PTB confirmed a significant benefit of progesterone in preventing PTB <34 weeks (RR 0.54, 95% CI 0.34–0.88) [61]. The incidence of CL ≤15 mm was 1.7%. Based on the frequency of short CL and effectiveness for the prevention of SPTB <34 weeks from the work of Fonseca et al., the number of women needed to be screened with CL in order to prevent one SPTB <34 weeks is approximately 387 if all women with a CL ≤15 mm receive vaginal progesterone. Once the short CL ≤15 mm is identified, the number needed to treat to prevent one PTB <34 weeks is 7.

In 458 women with singleton gestations and CL 10–20 mm at 19–23$^{6/7}$ weeks, of whom about 84% had no prior PTB, vaginal progesterone 90 mg daily started at 20–23$^{6/7}$ weeks until 36$^{6/7}$ weeks was associated with a 45% significant decrease in PTB <33 weeks (9% vs. 16%, RR 0.55, 95% CI 0.33–0.92) and 43% significant decrease in composite neonatal morbidity and mortality (8% vs. 14%, RR 0.57, 95% CI 0.33–0.99) [62]. The incidences of PTB <28 and <35 weeks and RDS were also significantly decreased. Analysis of only women without prior PTB confirmed a significant benefit of progesterone in preventing PTB <33 weeks (8% vs. 15%, RR 0.50, 95% CI 0.27–0.90) [62]. The incidence of CL 10–20 mm was 2.3%. Based on the frequency of short CL and effectiveness for prevention of PTB <33 weeks from this study [62], the number of women needed to be screened with CL in order to prevent one PTB <33 weeks is approximately 604 if all women with a CL 10–20 mm receive vaginal progesterone. Once the short CL 10–20 mm is identified, the number needed to treat to prevent one PTB <33 weeks is 14.

A recent systematic review and meta-analysis of individual patient data of randomized trials, including OPPTIMUM, noted a reduction of PTB and neonatal morbidity and mortality in singleton gestations with CL ≤25 mm with vaginal progesterone compared with placebo (STPB <33 weeks, RR 0.62, 95% CI 0.47–0.81, $p = 0.0006$; composite neonatal morbidity and mortality, RR 0.59, 95% CI 0.38–0.91) [63].

In summary, **in women with singleton gestations**, **no prior SPTB**, and short CL, vaginal progesterone is associated with a reduction in PTB and composite perinatal morbidity and mortality. Based on these results, **if a TVU CL ≤25 mm is identified at ≤24 weeks, vaginal progesterone should be offered for the prevention of PTB** [61, 63]. There is insufficient evidence that any of the vaginal preparations or doses are superior, as they have not been compared. **Vaginal progesterone 200 mg** suppository (which is cheaper) has been used in the trial for CL ≤15 mm [62], and 90 mg gel for the trial for CL 10–20 mm [62]. Therefore, CL, but also cost, availability, and other factors, may influence the preferred dosing [64, 65].

These results also support **universal screening with a single TVU assessment of CL at around 20 weeks (18–23 weeks range) in singleton gestations without prior SPTB** (Figure 18.2). TVU CL screening of singleton gestations fulfills all criteria for an effective screening program [66]. For example, multiple cost-effectiveness analyses evaluating universal CL screening in singleton gestations to identify those with a short CL eligible for vaginal progesterone have been published [64, 65, 67]. All reported that such a strategy would be cost-effective, and in fact cost-saving.

In one study, compared with other managements, including no screening, "universal" sonographic screening of CL in singletons was associated with a reduction of 95,920 PTBs <37 weeks annually in the United States, and was actually cost saving (almost $13 billion saved) [64]. Even when altering the variables (e.g. the cost of vaginal progesterone or of TVU screening), universal screening was the preferred strategy 99% of the time [64].

The other cost-effectiveness analysis, which looked at universal screening of singleton gestations without prior PTB with TVU CL at 18–24 weeks, calculated over $12 million saved, 424 quality-adjusted life-years (QALY) gained, and 22 neonatal deaths or long-term neurologic deficits prevented for every 100,000 women screened, compared to no screening. Even when altering the variables (e.g. the cost of vaginal progesterone or of TVU screening), universal screening was cost-effective over 99% of the time [65].

It should be noted that only 1.7%–2.3% of women were identified to have a short CL in the two large trials published [61, 62] and that the incidence of CL ≤20 mm at 18–24 weeks is even lower (about 0.8%) in singletons without prior SPTB [66].

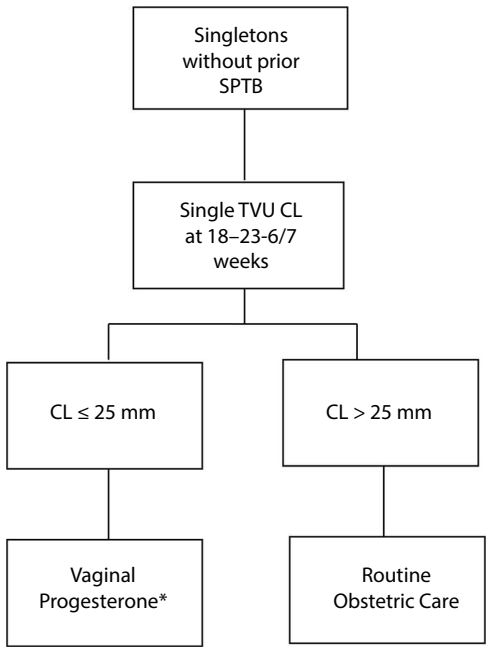


FIGURE 18.2 Transvaginal ultrasound cervical length screening for the woman with a singleton gestation and no prior spontaneous preterm birth. (Adapted from Ref. 68.) *For example, daily 200 mg suppository or 90 mg gel from time of diagnosis of short CL to 36 weeks. *Abbreviations:* SPTB, spontaneous preterm birth at 16–36$^{6/7}$ weeks; TVU, transvaginal ultrasound; CL, cervical length.

There are more limited data to evaluate the effectiveness of vaginal progesterone for CL 21–25 mm [63].

Guidelines from SMFM and ACOG state that implementation of universal TVU CL screening should be viewed as reasonable and can be considered by individual practitioners; third-party payers should not deny reimbursements for this screening [68, 69]. The International Federation of Gynecology and Obstetrics (FIGO) recommends TVU CL screening [70]. TVU CL exams should be done following strict quality criteria, in the United States via CLEAR and the Perinatal Quality Foundation (https://clear.perinatalquality.org) [71], and in Europe through the Fetal Medicine Foundation [72]. **Only TVU, and not transabdominal ultrasound, should be used for CL screening** [68, 69].

Screening with TVU CL at about 20 weeks (18–23 weeks range) should be offered to all singleton gestations without prior SPTB. If CL ≤25 mm, vaginal progesterone (e.g. 200-mg suppositories every evening until 36 weeks) should be recommended [61–63].

Intervention: Cerclage (ultrasound-indicated cerclage)

An **ultrasound-indicated cerclage** (UIC) involves the first screening of pregnancies with TVU of the cervix to determine during pregnancy the risk of PTB, since the majority of even women at high risk by obstetric risk factors for PTB do not develop a short CL and deliver at term even without intervention. A short CL (<25 mm) on TVU in the second trimester (between 14 and $23^{6/7}$ weeks) significantly increases the risk of PTB in all populations studied [73]. UIC is defined as a cerclage performed because a short CL has been detected on TVU during pregnancy, usually in the second trimester. This cerclage has also been called therapeutic, salvage, or rescue cerclage, but these terms are confusing and should be avoided. UIC has differing effects in different populations.

In women with **singleton gestations**, **no prior PTB or other risk factors for PTB**, and **CL <25 mm** before 24 weeks, cerclage is associated with a nonsignificant reduction in PTB <35 weeks (RR 0.76, 95% CI 0.52–1.15; $n = 275$) [74]. A recent individual patient data meta-analysis of five RCTs (with 419 women) showed no significant association between cervical cerclage and the reduction of SPTB <35 weeks or neonatal outcomes in asymptomatic singleton women with a short cervix less than 25 mm and without prior SPTB [75].The planned subgroup analysis noted **a significant decrease in SPTB <35 weeks in women with a cervical length ≤10 mm, with adjunct treatment with indomethacin and one dose of antibiotics** (39.5% vs. 58.0%; RR, 0.68; 95% CI 0.47–0.98, 0.98; I^2 =0%). **TVU CL ≤11 mm may identify a subgroup of patients at high risk for asymptomatic cervical dilation (30% risk of being ≥1 cm dilated) and poor perinatal outcome** [76]. Physical examination for evaluation of cervical dilation should be performed in singletons with TVU CL ≤11 mm. If cervical dilation is noted, physical examination–indicated cerclage is recommended (see later, under "risk: cervical dilation intervention: cerclage (physical-exam indciated cerclage"). Therefore, **cerclage can be considered for singleton gestations with prior SPTB and TVU CL ≤10 mm before 24 weeks, but more research is needed**.

For singleton gestations with prior PTB and a short TVU CL, see later, under "Risk: Prior PTB and Short Cervix on Ultrasound."

Intervention: Pessary

There is contradictory evidence regarding the efficacy of a pessary to prevent PTB in women with singleton gestations and a short TVU CL ≤25 mm in the second trimester. All studies so far used the Arabin pessary. While the first RCT revealed a 82% decrease in PTB <34 weeks associated with pessary use [77], subsequent, other (some larger) RCTs have not shown any benefit in PTB or neonatal outcomes [78, 79]. All these RCTs included mostly (about 85%–90%) singletons without a prior SPTB. A systemic review and meta-analysis of three RCTs ($n = 1420$), Arabin pessary placement did not reduce the risk of SPTB <37 weeks or improve neonatal outcomes in singleton gestations with short cervix 25 mm or less at 20–24 weeks [80]. A small RCT of singleton gestation with short cervix 25 mm or less without a history of prior PTB showed no difference in the rate of SPTB <37 weeks in pessary versus nonpessary groups (43% vs. 40%; relative risk 1.09; 95% CI 0.71–1.68) [81]. In summary, **pessary cannot be recommended for the prevention of PTB in singleton gestations (without prior PTB) with a short TVU CL**.

Intervention: Indomethacin

There is **insufficient evidence** to evaluate the effect of indomethacin on the incidence of PTB in women with a short CL on TVU [82], as no RCTs have been performed.

Intervention: Antibiotics

There is **insufficient evidence** to evaluate the effect of antibiotics on the incidence of PTB in women with a short CL on TVU, as no RCTs have been performed.

Risk: Pregnancy high-risk for PTB

Intervention: Activity restriction/bed rest

Activity restriction and/or bed rest are probably the most commonly prescribed interventions for PTB prevention despite no proven benefit and potential for increased maternal morbidity. There is no evidence supporting bed rest or activity restriction to prevent PTB [83, 84]. Per ACOG, bed rest should not be routinely recommended for the prevention of PTB [85]. **Bed rest (rest 1 hour TID) in asymptomatic and symptomatic "high-risk" singleton pregnancies is not associated with the prevention of PTB over no bed rest** [86]. Bed rest can be associated with an increased incidence of complications; in-hospital extended strict bed rest for PTL or PPROM is associated with an up to 1%–2% incidence of thromboembolic disease. Moreover, muscle wasting, cardiovascular deconditioning, bone demineralization, impaired glucose tolerance, heartburn, constipation, failure of volume expansion, headaches, dizziness, fatigue, depression, anxiety, and stress, as well as lost wages, lost domestic productivity, and other costs may be other detrimental consequences of bed rest. A secondary analysis of Maternal-Fetal Medicine Units' (MFMUs) preterm prediction study evaluated a cohort of 1086 singleton gestations at high risk of PTB, of which 9.7% ($n = 105$) of women were recommended activity restriction and 37.1% ($n = 39$) of these women had SPTB <37 weeks. In the group with no recommended activity restriction ($n = 981$), 14.3% ($n = 140$) delivered SPTB <37 weeks. The authors and national societies (including SMFM) **discourage the routine use of activity restriction in women at high risk for preterm birth** [87, 88].

It is true that rest decreases uterine activity and exercise increases it, but these are small effects that do not change the rates of PTB. In nonrandomized studies, **exercise in pregnancy has been associated with a decrease in PTB** [89], while physically demanding work, prolonged standing, shift and night work, and high cumulative work fatigue score have been associated with PTB. Despite its use in about 20% of pregnancies, **bed rest or any activity restriction for the prevention of PTB cannot**

be recommended. These interventions should be studied in trials before clinical use. If prescribed bed rest, women should be allowed to ambulate to the bathroom a few times a day to limit complications of strict bed rest. It is possible that women at high risk of PTB from the previously noted or other risk factors have not been studied adequately with this intervention of bed rest.

Intervention: Support

Programs of additional support during at-risk pregnancy (varying definitions), usually by a professional (social worker, midwife, or nurse), **do not reduce PTB** or LBW [90]. "Additional support" was defined as some form of emotional support (e.g. counseling, reassurance, and sympathetic listening) with or without additional information/advice, occurring during home visits, clinic appointments, and/or by telephone; most of the time, these were intensive programs started in the first or second trimesters to the end of pregnancy. Other significant outcomes are as follows: Antenatal hospital admission and cesarean delivery are decreased [90].

Intervention: Weekly manual exams, education

A program of weekly manual cervical exams in addition to education for women at high risk for PTB (≥10 on Creasy score) **does not reduce PTB** [91–93].

Intervention: Antibiotics

See the section "Intervention: Antibiotics" under "Risk: Prior PTB."

Intervention: Cerclage

Different specific clinical scenarios have been studied for the possible benefit of cerclage. For efficacy of history-indicated cerclage, transabdominal (TA) cerclage, UIC, physical exam–indicated cerclage, and in twins, see earlier and later.

Risk: Prior PTB (Figures 18.3 and 18.4) [**94**]

Intervention: Low-dose aspirin

A recent secondary analysis of an RCT (underpowered) showed no association between preconception low-dose aspirin in women with one or more prior pregnancy loss and PTB on overall PTB rates [95].

Intervention: Fish intake

Moderate fish intake, up to three meals per week, before 22 weeks is associated with a reduction in repeat PTB, compared with women eating fish less than once per month (OR 0.60, CI 0.38–0.95) [96]. **Moderate fish intake should be encouraged in women with prior PTB for the prevention of recurrent PTB** (see also the text earlier for low-risk women).

Intervention: Omega-3 fatty acids

In one RCT, omega-3 fatty acids (fish oil, Pikasol: 32% eicosapentaenoic acid [EPA], 23% DHA, and 2 mg tocopherol/mL; 4 capsules/day: 1.3 g EPA and 0.9 g DHA, total 2.7 g/day; started ≥16 weeks at an average of 29–30 weeks) were associated with a reduction in PTB <37 weeks by 46% and PTB <34 weeks by 68% in women with a prior PTB <37 weeks and a singleton gestation. The same omega-3 fatty acid regimen does not reduce PTB in women with twins [97]. In another larger RCT, in singleton gestations with prior SPTB and on 17P 250 mg IM, omega-3 supplementation (1200 mg EPA and 800 mg DHA) from 16 to 22 weeks until 36 weeks was associated with similar incidences of PTB

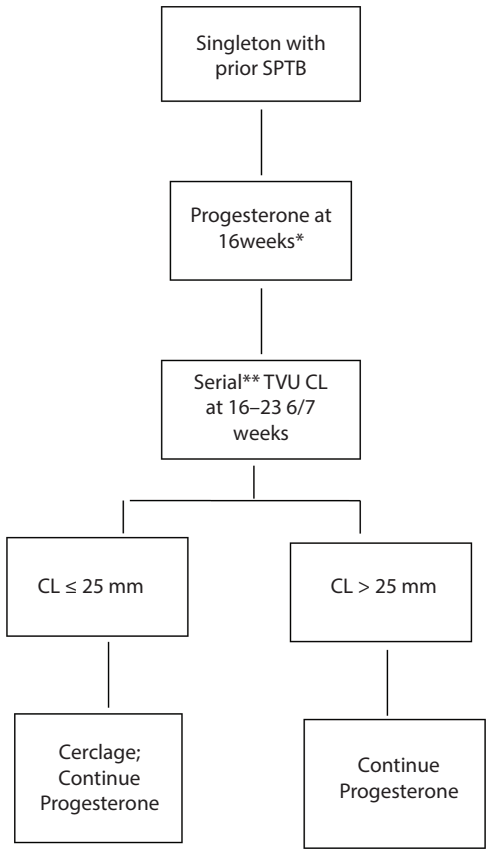


FIGURE 18.3 Transvaginal ultrasound cervical length screening for the woman with a singleton gestation and prior spontaneous preterm birth(s). (Adapted from Ref. 69.) *Vaginal progesterone, usually 200 mg every night; or 250 mg IM every week, from 16–20 weeks to 36 weeks. **Every 2 weeks; if 26–29 mm, repeat in 1 week. *Abbreviations*: SPTB, spontaneous preterm birth at 16–$36^{6/7}$ weeks; TVU, transvaginal ultrasound; CL, cervical length.

<37 weeks (38% vs. 41%; RR 0.91, 95% 0.77–1.07) and PTB <35 weeks (RR 0.95, 95% CI 0.72–1.25) [98]. Meta-analysis of these two RCTs revealed that women who received omega-3 had similar rates of PTB at <37 weeks (34.5% vs. 39.8%; RR, 0.81; 95% CI 0.59–1.12) and PTB at <34 weeks (12.0% vs. 15.4%; RR, 0.62; 95% CI 0.26–1.46) compared with controls. The omega-3 groups had a statistically significantly longer latency (mean difference, 2.10 days; 95% CI 1.98–2.22) and higher birth weight (mean difference, 102 g; 95% CI 20–185) compared with control subjects [99]. In summary, **in singleton gestations with prior SPTB on 17P, omega-3 supplementation does not seem to be beneficial in preventing recurrent PTB**. The benefits in longer latency and higher birth weight may deserve further study (see also earlier for low-risk women).

Intervention: Antibiotics

Antibiotics to prevent PTB in women with prior PTB have been evaluated either as preconception (one RCT) or as prenatal intervention. In women with prior PTB <34 weeks, **preconception** oral azithromycin 1 g twice (4 days apart) and metronidazole 750 mg daily for 7 days are not associated with an effect of subsequent PTB or miscarriage rates [100].

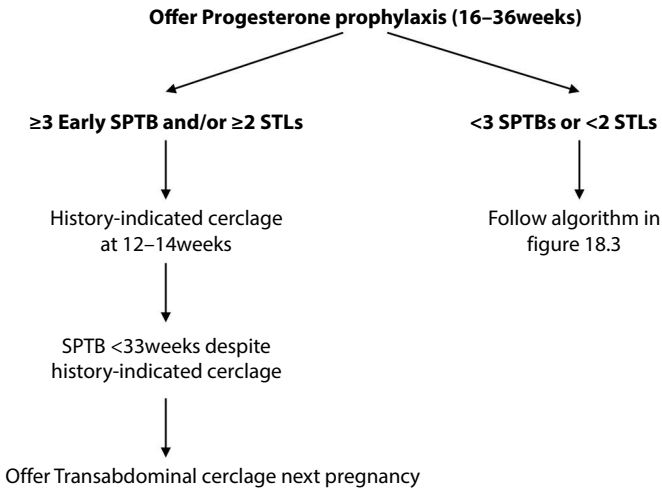


FIGURE 18.4 Clinical algorithm for care of asymptomatic women with multiple prior PTB or STLs (see text). (Adapted from Ref. 94.) *Abbreviations:* SPTB, spontaneous preterm birth; STL, second-trimester loss.

Clindamycin cream 2% for 7 days at 26–32 weeks does not reduce PTB <37 weeks in women with a prior PTB 24–36 weeks but may increase PTB <34 weeks, especially in women without BV, so that antibiotics in this setting may actually be detrimental [101].

Cefetamet pivoxil (not available in the United States) 2 g × 1 at 28–32 weeks in women in Nairobi with prior PTB, fetal death, or LBW did not affect GA at delivery (PTB was not reported) [102].

Metronidazole 250 mg TID × 7 days and erythromycin base 333 mg TID × 14 days in women with a prior PTB or pre-pregnancy weight <50 kg do not prevent PTB <37 weeks but may increase PTB <34 weeks [103, 104].

In summary, **antibiotics given just because of a prior PTB do not prevent recurrent PTB**.

Intervention: Progesterone

The effect of progesterone supplementation should be evaluated according to different patient populations and according to the type of progesterone. Here we review progesterone for prior PTB.

For 17P, there are at least two RCTs available in women with prior PTB. In 43 women with mostly (>90%) singleton gestation and either prior PTB or prior >1 spontaneous abortion, 17P 250 mg IM weekly started as soon as prenatal care began was associated with a significant reduction in PTB <37 weeks and perinatal mortality compared with placebo [105]. In 463 women with a singleton gestation and prior SPTB at 20–$36^{6/7}$ weeks of a singleton gestation, compounded 17P 250 mg IM weekly started at 16–$20^{6/7}$ weeks was associated with a reduction in the incidences of PTB <37 weeks (RR 0.66, 95% CI 0.54–0.81), PTB <35 weeks, and <32 weeks, as well as of supplemental oxygen, NEC, and IVH, compared with placebo [106]. The number needed to treat to prevent one recurrent PTB was 5.4. Based mostly on this clinical trial, 17P 250 mg IM weekly started at 16–20 weeks is recommended for all women with prior SPTB 20–$36^{6/7}$ weeks (Figure 18.3) [107–109]. The estimated number of prevented PTBs <37 weeks in the United States by this policy is about 9870.

For vaginal progesterone, there are at least two RCTs available in women with prior PTB. In 142 women with singleton gestations and mostly (>90%) prior PTB, vaginal progesterone 100 mg nightly from 24 to 34 weeks was associated with a significant reduction in the incidences of PTB <37 weeks (RR 0.48, 95% CI 0.25–0.96) and <34 weeks, as well as contraction frequency, compared with placebo [110]. In 659 women with singleton gestation and prior SPTB 20–$35^{0/7}$ weeks, vaginal progesterone 90 mg every morning starting at 18–$22^{6/7}$ weeks until $37^{0/7}$ weeks was not associated with significantly different rates of PTB <37, 36, 33, and 29 weeks and neonatal morbidity and mortality [111]. Several women screened for this trial were excluded because of short CL [106]; therefore, vaginal progesterone cannot be recommended for the prevention of recurrent PTB when data against placebo is considered.

For a **comparison of 17P versus vaginal progesterone**, there are three RCTs. In 518 women with singleton gestation and prior PTB between 20 and 34 weeks, 17P 250 mg IM weekly was associated with similar incidences of PTB and neonatal morbidities and mortality compared with vaginal progesterone 90 mg (Crinone) daily, except for significant lower incidences of PTB 28–$31^{6/7}$ weeks, neonatal intensive care unit (NICU) admission, and maternal side effects in the vaginal progesterone group [112]. Another RCT reported similar outcomes, including incidence of PTB, with either vaginal progesterone or 17P in women with singleton gestations and prior PTB [113]. Another recent nonblinded randomized trial of 78 singleton pregnancies from Iran compared effectiveness of vaginal progesterone with 17P in women with either prior PTB or short cervix TVU CL <25 mm. The authors concluded that vaginal progesterone and intramuscular progesterone have the same level of effectiveness and reported a similar rate of PTB in the two groups [114]. In 145 women with singleton gestations (16–20 weeks) and prior PTB, weekly intramuscular administration of hydroxyprogesterone caproate (250 mg) and daily vaginal progesterone suppository (100 mg) exhibited similar efficacy in reducing the rate of recurrent PTB <37 weeks (43.9% vs. 37.9%, p=0.05) [115]. Overall these RCTs do not appear to be high quality, and the study results should be used cautiously. A systematic review and meta-analysis of three RCTs (680 women) showed that daily vaginal progesterone (either suppository or gel) started at about 16 weeks' gestation is a reasonable, if not better, alternative to weekly 17-OHPC injections for the prevention of SPTB in women with singleton gestations and prior SPTB [116].The level of the summary estimates was low or very low as assessed by GRADE; therefore, **more data are necessary to evaluate how 17P and vaginal progesterone compare in efficacy in singletons with a prior PTB**, but **vaginal progesterone seems to be at least equivalent, if not possibly more efficacious, than 17P in preventing recurrent PTB in women with prior SPTB**.

For **oral progesterone**, there are two small RCTs. In 150 women with singleton gestation and prior SPTB 20–$36^{6/7}$ weeks, oral micronized progesterone 100 mg twice a day was associated with significantly reduced incidences of PTB <37 weeks (39.2% in the oral progesterone vs. 59.5% in the placebo group, p = 0.002) and NICU admission compared with placebo [117]. In 33 women with singleton gestation and prior PTB 20–$36^{6/7}$ weeks, oral progesterone 400 mg daily was associated with nonsignificant reductions in the incidence of PTB <37 weeks (26% vs. 57%) and ventilator use (0% vs. 21%) compared with placebo [118]. A meta-analysis and systematic review of the three trials on oral progesterone vs. placebo (involved 386 patients: 196 in oral progesterone and 190 in placebo) showed a significant decrease in the risk of PTB <37 weeks' gestation (42% vs. 63%; p = 0.0005; RR 0.68; 95% CI 0.55–0.84) and reduction in perinatal morbidity and mortality [119]. This study did not note any serious adverse effects and

reported a higher rate of maternal adverse effects with oral progesterone that included dizziness, somnolence, and vaginal dryness. In summary, there is **insufficient but promising evidence** to assess the efficacy of oral progesterone for the prevention of PTB in women with prior PTB.

In summary, in women with prior SPTB and singleton gestation, progesterone administration is beneficial in preventing recurrent PTB. Comparison RCTs seem to show vaginal progesterone is an effective alternative to 17P [112, 114]. **So either vaginal progesterone 200 mg every night or 17P 250 mg IM weekly, starting at 16–20 weeks until 36 weeks, should be recommended to women with singleton gestations and prior SPTB 20–36$^{6/7}$ weeks** [106]. After the Meis publication, ACOG and SMFM recommended progesterone supplementation (17P or vaginal progesterone) to reduce the risk of recurrent PTB in women with a prior SPTB [69, 120]. A recent meta-analysis of 17P vs. placebo or no treatment for prevention of recurrent PTB identified four RCTs, including the Meis trial. This meta-analysis showed a reduction in recurrent PTB at <37, <35, and <32 weeks by 29% (RR 0.71; 95% CI 0.53–0.96; $p = 0.001$), 26% (RR 0.74; 95% CI 0.58–0.96; $p = 0.021$), and 40% (RR 0.60; 95% CI 0.42–0.85; $p = 0.004$), respectively, in the 17-OHPC group compared with placebo or no treatment [121].

The Meis trial lead to FDA approval of Makena in 2011 [122]. The requirement of FDA approval led to a confirmatory second trial called PROLONG (Progestin's Role in Optimizing Neonatal Gestation), which was a multicenter, international, double-blind, randomized, placebo-controlled trial of 1700 women from 93 sites in nine countries (with approximately 25% of women from the United States) with a history of spontaneous PTB that was conducted from 2009 through 2018 with co-primary outcomes of PTB <35 weeks and neonatal composite index. The PROLONG study showed the incidence of PTB at less than 35 weeks of gestation (17a-hydroxyprogesterone caproate–treated group 11.0% vs. placebo 11.5%, $p = 0.72$) and the percentage of neonates with the morbidity and mortality composite index (5.6% vs. 5.0%, $p = 0.73$) [123]. The discordant results of the Meis and PROLONG trials have been extensively reviewed by ACOG and SMFM and other experts in the field [124–126]. The differences in these two trials include different study populations, especially with respect to the baseline risk of PTB, characteristics of prior PTBs, and additional demographic and reproductive characteristics (such as ethnicity, marital status, and smoking) [125]. The SMFM statement concluded, "On the basis of the evidence of effectiveness in the Meis study, with the largest number of US patients, and given the lack of demonstrated safety concerns, SMFM believes that it is reasonable for providers to use 17-OHPC in women with a profile more representative of the very-high-risk population reported in the Meis trial. For all women at risk of recurrent SPTB, the risk/benefit discussion should incorporate a shared decision-making approach, taking into account the lack of short-term safety concerns but uncertainty regarding benefit. It is important to consider that 17-OHPC use is associated with substantial health care costs, injection-site pain, and extra patient visits and that long-term potential maternal and neonatal effects are unknown" [125].

Intervention: Cerclage

A history-indicated cerclage is placed based solely on prior obgyn history (previously called a prophylactic or elective cerclage). Trials on women with only one or two prior PTBs have not shown benefit from history-indicated cerclage [127, 128]. **A history-indicated cerclage has been associated with the prevention of PTB in women with three or more STLs or** early (e.g. <32 weeks) **PTBs** [129]. Cerclage decreases the incidence of PTB <37 weeks from 53% (with no cerclage) to 32% and the incidence of PTB <32 weeks from 32% (with no cerclage) to 15% in women with three or more prior PTBs or STLs (Figure 18.4) [129].

The other clinical indication for history-indicated cerclage might include CI, defined by some as prior painless cervical dilatation leading to recurrent STLs. Unfortunately, **no trial has been done to confirm the efficacy of history-indicated cerclage in reducing PTB in women with a diagnosis of CI**. Other indications such as prior cone biopsy, Mullerian anomaly, diethylstilbestrol (DES) exposure, prior PTB not associated with CI, and Ehlers-Danlos syndrome have occasionally been used clinically but have not been confirmed by any trial as indications that benefit from history-indicated cerclage. History-indicated cerclage is usually performed at 12–15 weeks' gestation, and its techniques have been well described [73].

TA cerclage has been associated with less recurrent PTB compared with controls receiving transvaginal cerclage in women with a **history of a failed (SPTB <33 weeks despite cerclage) transvaginal history–indicated cerclage** in a case-control study [130]. It should be noted that in this study antibiotics and progesterone were uniformly given to the TA cerclage women. There is no RCT on TA cerclage. The efficacy of TA cerclage for other clinical scenarios such as a cervix with no intravaginal portion has not been adequately studied. TA cerclage can be performed prophylactically at around 10–12 weeks, and its technique has been well described [73, 130]. TA cerclage has been successfully performed also laparoscopically and robotically, in particular pre-pregnancy, but also in the early first trimester [131].

In summary, **the vast majority of women with prior PTB (e.g. those with only one or two prior SPTBs) does not benefit from universal history-indicated cerclage** and can **instead be followed with serial TVU CL screening starting usually at 16 weeks**. A policy of TVU CL screening with cerclage for short CL is associated with similar incidences of PTB <37 weeks (31% vs. 32%; RR 0.97, 95% CI 0.73–1.29), PTB <34 weeks (17% vs. 23%; RR 0.76, 95% CI 0.48–1.20), and perinatal mortality (5% vs. 3%; RR 1.77, 95% CI 0.58–5.35) compared with universal history-indicated cerclage and omits an obviously unnecessary cerclage in about 58% of these women [132]. **Therefore, all singleton gestations with a prior spontaneous PTB should be screened with serial TVU CL starting at 16 weeks, every 2 weeks, until 23$^{6/7}$ weeks. If the CL is 26–29 mm, repeat TVU CL can be done in 1 week instead of 2 weeks. If the CL <25 mm is detected before 24 weeks, singleton gestations with prior PTB should undergo ultrasound-indicated cerclage** (Figure 18.3) (see also the section "Risk: Short Cervix on Ultrasound") [133].

If cerclage is performed, it should be performed according to the best technique. McDonald cerclage, with suture (usually Mersilene tape) placed as close to the internal os as possible (as high as possible), under spinal anesthesia, is recommended. There is usually no need for preoperative antibiotics or tocolytics [134]. A double suture might improve outcomes compared to one suture, but the evidence is still insufficient for a recommendation [135]. Cervical occlusion has no significant additional effect on cerclage [136].

Intervention: Oral tocolytics

There is insufficient evidence (only one small old RCT) to support the use of prophylactic oral betamimetics for preventing PTB in women with prior PTB with a singleton pregnancy [137].

For a summary of care of pregnant women with prior PTB, see also Ref. [89].

Risk: Prior PTB and short cervix on ultrasound

Intervention: Progesterone

In a secondary analysis of an RCT evaluating just 46 singleton gestations with prior SPTB <35 weeks and short CL <28 mm at 18–22$^{6/7}$ weeks, **vaginal progesterone** 90 mg daily started at 18–23$^{6/7}$ weeks until 37 weeks was associated with significant decreases in the incidences of both PTB <32 weeks and NICU admission compared with placebo [138].

In a small RCT which did not recruit the planned sample size, **17P** in singleton gestations at high risk for PTB (56% with prior PTB) with TVU CL <25 mm 20–31$^{6/7}$ weeks was noted to have no benefit in prolonging pregnancy compared to no 17P. The sample size was too small, and the intervention probably too late, to show significance [139].

In a randomized trial that did not recruit the planned sample size, **17P** and **cerclage** had a similar effect in women for CL <25 mm for the prevention of PTB, but cerclage was more effective in women with CL <15 mm [60]. So, while cerclage seems to be more efficacious (lower RRs) as the CL is shorter [140, 141], progesterone seems to be most efficacious in cases of "moderate" short CL [61, 62].

Until further evidence is available, we suggest continuation of 17P in women with prior PTB and short cervix in the index pregnancy. Some instead have suggested switching from 17P to vaginal progesterone, but not based on RCT data [142]. There is no good evidence suggesting the benefit of the addition of vaginal progesterone in women with a prior PTB on 17P who are noted to have a short cervix [142]. In summary, **women with prior PTB should be screened with TVU CL from 16 to 23 weeks**. **Vaginal progesterone or 17P should be recommended to women with prior SPTB starting at 16 weeks**, as described earlier. If the cervix shortens, there is insufficient evidence to assess efficacy of a different progesterone therapy, and therefore it is reasonable to continue 17P until 36 weeks.

Intervention: Cerclage

In women with a **singleton gestation, prior SPTB, and CL <25 mm** before 24 weeks, **cerclage is associated with a significant 30% reduction in PTB <35 weeks** (28.4% vs. 41.3%; RR 0.70, 95% CI 0.55–0.89); **significant reductions in PTB <37, <32, <28, and <24 weeks**; and a **significant 36% decrease in composite perinatal mortality and morbidity** (15.6% vs. 24.8%; RR 0.64, 95% CI 0.45–0.91), compared to no cerclage [133]. Therefore, **cerclage is recommended in women with a singleton gestation, prior SPTB, and CL <25 mm before 24 weeks** [68, 69].

There are no randomized trials on the **management of subsequent pregnancy in women who required UIC in their prior pregnancy**. Level II evidence suggests similar outcomes with TVU CL screening with UIC for short cervix of 25 mm or less or planned history-indicated cerclage (HIC) in the subsequent pregnancy, in singleton gestations with prior UIC. The authors reported less than 50% of the TVU CL screening group required a repeat UIC in the subsequent pregnancy [143]. Another retrospective study of women with a prior UIC also reported that the majority of women who underwent CL surveillance in the next pregnancy did not require intervention for a short cervix. The authors reported a higher rate of PTB in women who received HIC in the subsequent pregnancy, which was not justified based on their risk status [144]. Based on the available level II evidence, **TVU CL screening with UIC for a short cervix is acceptable and possibly more effective than a routine HIC in women with UIC in prior pregnancy**. A consideration can be given to **HIC in the small subset of women who delivered prior to 32 weeks in their prior pregnancy despite UIC** [143].

There is insufficient evidence to suggest an upper limit of GA at UIC placement [145]. A retrospective study of 426 singleton gestations who underwent UIC in previable (16 to <22 weeks) and periviable (22 to <24 weeks) GA showed similar obstetric outcomes. The authors showed a lower risk of recurrent PTB <36 weeks in women who had a periviable cerclage compared to those with previable cerclage placement (26.6% vs. 38.3%, respectively, p <0.04) [146]. The authors support continued use of UIC up until 24 weeks. Further well-designed randomized studies on the safety and efficacy of cerclage at or beyond 24 weeks are suggested.

If the TVU CL shortens again later after the UIC has been placed, a second "reinforcing" cerclage has not been associated with the prevention of PTB [147, 148].

For singleton gestations without a prior PTB and with a short TVU CL, see the earlier sections "Risk: Short Cervix on Ultrasound" and "Intervention: Cerclage."

Intervention: Adjunctive treatment at cerclage

There is insufficient evidence to evaluate the effect of combining a tocolytic (indomethacin) and antibiotics (cefazolin/clindamycin) with cervical cerclage compared with cervical cerclage alone for preventing spontaneous PTB in women with singleton pregnancies undergoing HIC. Further well-designed randomized trials are warranted [149].

Intervention: Vaginal progesterone vs. cerclage

There is no RCT comparing directly vaginal progesterone to cerclage in this population, and therefore there is insufficient evidence for a recommendation. While an indirect meta-analysis reported that either vaginal progesterone or cerclage is equally efficacious in the prevention of PTB in women with a sonographic short cervix in the mid-trimester, singleton gestation, and previous PTB, the populations compared were not similar, introducing significant bias [150]. We offer progesterone based on the prior PTB, and cerclage for the short CL, based on data reviewed earlier.

Intervention: 17P vs. cerclage

Progesterone in addition to cerclage

There is **insufficient evidence** to assess the size of any cumulative effect of 17P for prior PTB in singletons already with cerclage for short CL. 17P was associated with a reduction in PTB <35eeks in women with UIC in the current pregnancy for TVU CL<25 mm, but the sample size was too small to show significance [151, 152]. Another retrospective study showed a 69% reduction in PTB <24 weeks in women with cerclage plus 17P compared to cerclage alone [153]. The secondary analysis of ultrasound indicated– and physical exam–indicated cerclage showed a 91% and 89% reduction in delivery at less than 24 and less than 28 weeks of gestation, respectively (CI 0.004–0.6 and CI 0.02–0.46; p <0.05) in women with cerclage plus 17P compared to cerclage alone [153]. A recent systematic review and meta-analysis of adjuvant 17P in UIC showed no benefit [154]. The results should be interpreted with caution due to insufficient evidence and lack of randomized trials confirming or refuting the benefit. Expert opinions recommend continuation of progesterone supplementation after cerclage placement [155].

Cerclage in addition to progesterone

There is insufficient evidence to assess the size of any cumulative effect of cerclage for short CL in singletons already on 17P for prior PTB. UIC was associated with a reduction in PTB <35 weeks in women already on 17P for prior PTB in the current pregnancy, but the sample size was too small to show significance [156].

Risk: Cervical insufficiency

Intervention: Cerclage

No intervention has been specifically studied in this population (see earlier under prior PTB). There are no randomized trials evaluating the role of HIC in women with prior PTB or pregnancy loss due to cervical insufficiency. There is insufficient evidence to recommend an HIC in women with fewer than three prior PTBs or STLs. **A policy of TVU CL screening with UIC if the CL shortens to <25 mm at <24 weeks has been shown to be equivalent to a policy of universal HIC in women with one or more than one prior SPTB** [73, 132, 157].

Intervention: 17P in addition to cerclage

There is insufficient evidence to assess the possible cumulative effect of 17P on PTB <35 weeks in women with an HIC [158].

Risk: IVF ART

Intervention: Progesterone or HCG

17∝-hydroxyprogesterone caproate or HCG supplementation in the first trimester **is associated with an increase in the incidence of fetal heart activity on ultrasound by 238% and of pregnancy ≥24 weeks' rate by 380%** compared with placebo [159].

Risk: Amniocentesis

Intervention: Progesterone

Natural progesterone 200 mg IM daily for 3 days post-amniocentesis followed by 17∝-hydroxyprogesterone caproate 340 mg IM twice a week until the second week after the amniocentesis **did not reduce PTB** <25 weeks in women undergoing amniocentesis [160].

Risk: Uterine contractions detected by home uterine activity monitoring

Intervention: Varied, per obstetrician

Uterine contractions have been associated with PTB, but their predictive value is poor. HUAM usually consists of 1 hour of tocomonitoring twice daily at 24–36 weeks. **HUAM with or without nursing contact and education is not associated with prevention of PTB**. Some studies show earlier (at lower cervical dilatation) detection of PTL. The lack of benefit in prevention of PTB might have been secondary to a lack of effective intervention (usually tocolysis) once PTL was diagnosed. Three different populations of women at high risk for PTB have been studied: Singleton gestations with risk factors for PTB (e.g. prior PTB), twin gestations, and women status-post an episode of PTL. Unfortunately, there is no published meta-analysis of all trials, and most trials do not report results for each population specifically and also report differing outcomes. A meta-analysis of published data shows no decrease in PTB <37 weeks in any of these three subgroups: Mostly singletons at high risk (9 trials; $n = 3613$) [161–170]: RR 1.01, 95% CI 0.91–1.11; twins (5 trials; $n = 998$) [64, 67, 69–71]: RR 0.91, 95% CI 0.80–1.04; or women status-post PTL episode (4 trials; $n = 218$) [67, 72–74]: RR 1.21, 95% CI 0.92–1.60. The largest study [170] and a recent meta-analysis [18] showed more unscheduled antenatal visits and prophylactic tocolytic use in the HUAM group compared to controls. Therefore, **HUAM should not be routinely provided for prevention of PTB**.

Risk: Cervical dilatation

Intervention: Cerclage (physical exam–indicated cerclage)

Physical exam–indicated cerclage (PEIC; aka emergency, urgent, or heroic) is the cerclage placed because of changes in the cervix (dilatation, effacement, etc.) detected by physical (manual) examination. Since about 50% of women with asymptomatic cervical dilatation ≥2 cm in the second trimester have microbial invasion of the amniotic cavity, **an amniocentesis should be considered before offering PEIC**.

There are limited data to assess the efficacy of PEIC in women with cervical dilatation in the second trimester, as only one small trial has been reported. In women with membranes at or beyond the external os at around 20–24 weeks, **PEIC (and indomethacin) is associated with a delay in delivery of about 4 weeks** compared with controls (30 vs. 26 weeks) [171]. The major limitations of this study are the small sample size and the inclusion of twins. Over 25 retrospective observational series, mostly with no controls, have claimed benefit of PEIC. The largest cohort study reported a significant decrease of 92% in the prevention of PTB <28 weeks with PEIC, compared with no cerclage, in singletons with ≥1 cm of cervical dilatation before 26 weeks [172]. A recent meta-analysis reported that PEIC is associated with a significant increase in neonatal survival and prolongation of pregnancy of approximately 1 month when compared with no cerclage. The strength of this conclusion is limited by the potential for bias in the included studies [173]. For PEIC, perioperative indomethacin and antibiotics have been associated with a significant 28-day prolongation of pregnancy [174]. In summary, **PEIC in singleton gestations with a cervix dilated to ≥1 cm in the second trimester is associated with a prevention in PTB and neonatal benefits**. Clearly a large, well-designed randomized trial is needed to confirm these benefits.

Intervention: Indomethacin

There is **insufficient evidence** to evaluate the effect of indomethacin on the incidence of PTB in women with a short CL on TVU [175], as no RCT has been performed. An RCT of perioperative indomethacin and antibiotics in women receiving a PEIC between 16 and 23 weeks showed a significant prolongation of gestation by 28 days compared to control [174].

Intervention: Perioperative considerations and surgical technique of PEIC

Observation for 12–24 hours for evaluation of PTL, PROM, chorioamnionitis and placental abruption, and appropriate cervical and vaginal sample collection to evaluate for cervicitis and vaginitis may be warranted by clinical evaluation. Amniocentesis can be considered especially in women with 2 cm or more cervical dilation and/or prolapsed membrane to rule out intraamniotic infection. **Perioperative antibiotics (one dose just before cerclage, e.g. cephalexin) and tocolytics (i.e. indomethacin 100 mg then 50 mg per rectum every 6 hours for 48 hours peri-cerclage) should be given** (details provided earlier). Cerclage technique and suture selection is per the surgeon's preference. If the cervix is flushed, consideration can be given to a modified Shirodkar technique. Various techniques have been described to avoid iatrogenic rupture of

membranes, including but not limited to lithotomy position with deep Trendelenburg position, tocolytics, and retrograde refill of bladder to assist with repositioning the membrane in the uterus. Other options include placement of ring forceps on the external os followed by gentle easing of the membranes into the uterus [176].

Intervention: Progesterone

There is no randomized trial to evaluate the effect of adjuvant progesterone supplementation after PEIC. A small retrospective study of 53 singleton gestations with PEIC at 17–24 weeks showed an association with reduction of SPTB <36 weeks (17% vs. 51%, p <0.05), low birth weight, and NICU admission with adjuvant vaginal progesterone therapy. The authors noted this association of reduction in SPTB<36 weeks after adjusting for confounding variables such as a visible membrane size of ≥4 cm, GA, prior SPTB, and use of amnioreduction (adjusted odds ratio [aOR] 0.12, 95% CI 0.02–0.69, p <0.05) [177]. Further well-designed trials are suggested.

Prior PEIC and subsequent pregnancy outcomes are not very well studied. Limited data from a retrospective study of a rare cohort of women with prior PEIC showed similar outcomes if they received either TVU CL screening with UIC for CL ≤25 mm or planned HIC in the subsequent pregnancy. The authors noted 87.5% of the women in TVU CL screening require a repeat UIC in the subsequent pregnancy [178].

Risk: Positive fFN

Intervention: Antibiotics

fFN is a basement membrane protein present between the decidua/uterus and fetal membranes/placenta and produced by the trophoblast. Its presence (>50 ng/mL) at ≥22 weeks in the cervicovaginal canal has been associated with an increased risk for PTB. In fact, fFN is one of the best predictors of PTB in all populations, including asymptomatic low- and high-risk women, twins, and women in PTL. Even at 13–22 weeks, higher (using the 90th percentile) fFN levels are associated with a twofold to threefold increased risk in subsequent SPTB. In women found to be fFN positive at 21–25 weeks, treatment with metronidazole 250 mg TID and erythromycin 250 mg QID × 10 days is associated with similar incidences of PTB <37 weeks to placebo. Among women with a prior SPTB, this antibiotic regimen is associated with a significantly higher incidence of PTB <37 weeks than the placebo group [179]. In women with at least one other risk factor for PTB (e.g. prior PTB), and positive fFN at 24–27 weeks, metronidazole 400 mg orally TID for 7 days was associated with no effect on the reduction of PTB and maternal and perinatal outcomes compared with placebo; rather, the authors reported that metronidazole use can be detrimental due to a trend of higher PTB rate, antenatal admission, and LBW in the metronidazole group compared with placebo [180]. In summary, **screening low-risk or high-risk asymptomatic pregnant women for fFN is not effective**, as no intervention (the one tried used antibiotics) has been shown to alter outcomes.

Risk: Prior FGR or preeclampsia

Intervention: Low-dose aspirin

Compared to no aspirin or placebo, **low-dose aspirin (usually 50–150 mg) is associated with a decreased incidence of PTB** (RR 0.22, 95% CI 0.10–0.49) **in women at high risk for pregnancy complications, such as those with prior preeclampsia or prior FGR** (see Chaps. 1 and 47 in *Maternal-Fetal Evidence Based Guidelines*) [181]. A large systematic review showed an 8% reduction in the rate of PTB <37 weeks in women (many with prior preeclampsia or fetal growth restriction [FGR]) treated with antiplatelet agents (RR 0.92, 95% CI 0.88–0.97) [182]. This reduction in the rate of PTB was higher if low-dose aspirin therapy is initiated at or prior to 16 weeks compared to after 16 weeks (RR 0.35, 95% CI 0.22–0.57, compared with RR 0.90, 95% CI 0.83–0.97, respectively) [183]. **Low-dose aspirin started earlier than 16 weeks is recommended for women at high risk of recurrent preeclampsia due to prior history of preeclampsia or FGR leading to early (<34 weeks) PTB**.

Risk: Periodontal disease

Intervention: Periodontal therapy

Periodontal disease has been associated with an increased risk of PTB in several observational studies. Periodontal treatment such as scaling, root planning, plaque control, and daily rinsing have been evaluated as an intervention to decrease PTB in women with periodontal disease [184, 185].

Periodontal treatment has not been associated with a decrease in PTB in women with periodontal disease (RR 0.63, 95% CI 0.32–1.22), even when controlling for probing depth and attachment loss for periodontitis criteria, multiparity, prior PTB, or genitourinary infections [186].

Infections

Risk: Asymptomatic bacteriuria

Intervention: Antibiotics

Asymptomatic bacteriuria occurs in 2%–10% of pregnancies, can lead to pyelonephritis, and is associated with an increased risk of PTB. **Screening for asymptomatic bacteriuria and treating for urine colony count of >100,000 bacteria/mL reduce the incidence of PTB** by 73% (RR 0.27, 95% CI 0.11–0.62, 2 studies, n = 242) [187]. The optimal time to perform the urine culture is unknown; it seems reasonable to perform the urine culture and treat, as done in most studies, at the first prenatal visit. Quantitative urine culture of a midstream or clean-catch urine is the gold standard for detecting asymptomatic bacteriuria in pregnancy. The choices of a sulfonamide or sulfonamide-containing combination, a penicillin, or nitrofurantoin, based on the results of susceptibility testing, are appropriate regimens for the management of asymptomatic bacteriuria. A short (3–7 days) course of therapy for asymptomatic bacteriuria has become accepted practice and is as effective as longer therapy. A single-dose regimen of antibiotics may be less effective than a short (4–7 days) regimen [188]. Women with asymptomatic bacteriuria in pregnancy should be treated by the standard regimen of antibiotics until more data become available on the cure rate of a shorter course (3–5 days) compared with the standard regimen. Although it is recommended that a urine culture be done following treatment, with retreatment as necessary, the evidence is insufficient to specifically evaluate the effectiveness of this strategy. Treatment of asymptomatic pregnant women with lower colony counts is not currently recommended, but further study of appropriate strategies to manage these women is warranted. **Asymptomatic women with even low** (100+) colony-forming units (CFUs) of **group B streptococcus (GBS) in the urine culture at 27–31 weeks have decreased PTB <37 weeks (5.4% in the penicillin group vs. 38% in the placebo group, p <0.002) when treated with penicillin 1 million IU three times per day for 6 days** compared with placebo [189].

Antibiotic treatment compared with placebo or no treatment is effective in clearing asymptomatic bacteriuria. Antibiotic treatment of asymptomatic bacteriuria is then clinically indicated to reduce the risk of pyelonephritis in pregnancy. If untreated, the overall incidence of pyelonephritis is about 21%. Overall, the number of women needed to treat to prevent one episode of pyelonephritis is seven, and treatment of asymptomatic bacteriuria will lead to approximately a 75% reduction in the incidence of pyelonephritis (RR 0.23, 95% CI 0.13–0.41; 11 studies, $n = 1932$) [187]. The apparent reduction in PTB is consistent with current theories about the role of infection as a cause of PTB. Prevention of pyelonephritis, which in early studies prior to the availability of effective antimicrobial therapy was associated with PTB, may be a factor, but treatment of bacteriuria with antibiotics may also eradicate organisms colonizing the cervix and vagina that are associated with adverse pregnancy outcomes. The use of tetracycline is contraindicated in pregnancy. Insufficient data are available to determine the effectiveness of treatment to prevent recurrent bacteriuria during pregnancy. There is a need to define the appropriate frequency of follow-up cultures and retreatment strategies [187]. See Chap. 18 in *Maternal-Fetal Evidence Based Guidelines*.

Risk: Bacterial vaginosis
Intervention: Antibiotics

BV is a massive overgrowth of organisms such as anaerobes, *Gardnerella, Mycoplasma,* and others in the vagina. Most of these organisms are normally present in the vagina, but are at higher concentrations in BV, while predominant normal flora such as lactobacilli is decreased.

The diagnosis of BV is usually made clinically with at least three out of four of these (Amsel) criteria: pH >4.5 (most important), clue cells, thin homogenous discharge, and "amine" test, while in many studies Nugent criteria (≥7 on Gram stain) are used for diagnosis. All these screening tests are not very accurate in predicting PTB (PPV 6%–49% depending on PTB prevalence and patient population) in both asymptomatic and symptomatic women.

Antibiotic therapy is effective at decreasing the presence of BV during pregnancy. In nonselected women, antibiotic treatment is not effective in reducing the incidence of PTB <37 weeks, PTB <34 weeks, PTB <32 weeks, or PPROM [190]. However, **treatment before 20 weeks** may reduce the risk of PTB <37 weeks (OR 0.72, 95% CI 0.55–0.95).

In women with a previous PTB, treatment did not affect the risk of subsequent PTB <37 weeks, with a 17%–25% nonsignificant trend for benefit [166, 167]. It may decrease the risk of PPROM and LBW. Subgroup analysis of treatment with metronidazole or clindamycin does not alter the incidence of PTB <37 weeks [191].

Risk: Trichomonas vaginalis
Intervention: Antibiotics

Antibiotics (**metronidazole** was the only one tested) **do not prevent PTB** in women with asymptomatic *T. vaginalis* (TV) infection [191–195]. In fact, metronidazole as studied (two 2-g doses 48 hours apart—possibly an excessive dose) is associated with a 78% higher incidence of PTB <37 weeks [194] and similar incidences of PTB <32 weeks and perinatal mortality [105]. Even in women with a prior PTB, metronidazole is associated with an 84% higher risk of PTB [191]. Metronidazole does eradicate TV in >90% of pregnant women. Therefore, at least for the purpose of decreasing PTB, asymptomatic women should not be screened for TV and treated with metronidazole at doses studied so far if positive for TV. **Symptomatic** women with TV should still be adequately treated with metronidazole as a **single 2-g oral dose, or 500 mg twice a day for 7 days** (see Chap. 38 in *Maternal-Fetal Evidence Based Guidelines).*

Risk: BV, Candida, and Trichomonas
Intervention: Antibiotics

In one large RCT, **screening for BV** (treatment: Clindamycin 2% vaginal cream for 6 days), ***Candida*** (treatment: Local clotrimazole 100 mg for 6 days), and *Trichomonas* (treatment: Local metronidazole 500 mg for 7 days) was **associated with lower risks of PTB <37 weeks** (3% vs. 5%; RR 0.55, 95% CI 0.41–0.75). The incidence of PTB for BW <2500 g and <1500 g were significantly lower in the intervention group (RR 0.48, 95% CI 0.34–0.66 and RR 0.34; 95% CI 0.15–0.75, respectively) compared to screening, with results unavailable to the managing physician [196]. Very few women were positive for *Trichomonas,* while about 21% of women had either BV or *Candida*, or both.

Risk: GBS vaginal-cervical colonization
Intervention: Antibiotics

GBS colonization of the cervicovaginal tract is common in pregnancy (10%–20%), and has been associated with a slight (OR 1.5–3, usually) increased risk of PTB. Antibiotic therapy with erythromycin does not prevent PTB in women with GBS colonization or affect stillbirths. Subanalysis by heavy colonization did not change the results [197].

Risk: Ureaplasma vaginal-cervical colonization
Intervention: Antibiotics

Ureaplasma urealyticum and/or *Mycoplasma hominis* colonization of the cervicovaginal tract is common in pregnancy and has been associated with a possible increased risk of PTB. **There is insufficient evidence to show whether giving antibiotics to women with *Ureaplasma* in the vagina prevents PTB**. The only trial did not report data on PTB [198]. Compared to placebo, erythromycin is associated with a nonsignificant 30% decrease in the incidence of LBW <2500 g (RR 0.70, 95% CI 0.46–1.07). Although some studies appeared to meet the inclusion criteria for this review, in most studies *Ureaplasma* was not an essential entry criterion or studies reported just a post hoc subgroup analysis of *Ureaplasma*.

There is insufficient information at this time to evaluate other interventions such as pessary. These therefore cannot be recommended for clinical use, unless in a research trial.

Multiple gestations

See Chap. 46 in *Maternal-Fetal Evidence Based Guidelines.*

Bed rest

In uncomplicated twin pregnancies, **prophylactic bed rest in the hospital does not reduce PTB, perinatal mortality, LBW**, and other complications of pregnancy [199]. **In fact, the incidence of PTB <34 weeks is significantly increased by 84%** [200–204].

In twin pregnancies with cervical dilatation, bed rest in the hospital does not decrease PTB in women in Zimbabwe [205]. In the trial in which it was recorded, only 6% of women appreciated in-hospital bed rest. For complications, see the section "Intervention: Bed Rest" (for singleton pregnancies).

Reduction

There is no trial to assess the effect of multifetal reduction to prevent PTB. Compared to triplets/higher-order multiples, triplets/

higher-order multiples reduced to twins have a higher incidence of loss <24 weeks, but lower incidences of PTB <32 weeks and better neonatal outcome of the remaining twins after reduction in case-control studies. See Chap. 44 in *Maternal-Fetal Evidence Based Guidelines.*

Cervical length screening

Routine second-trimester TVU assessment of CL in twin gestation is not associated with improved outcomes when incorporated into the standard management of otherwise low-risk twin pregnancies in an RCT [206]. See later for information on progesterone, cerclage, and pessary as interventions for short CL in twins.

17P

17P is not associated with prevention of PTB or neonatal adverse outcomes in more than six RCTs including twins [207–212]. A meta-analysis revealed no benefit of 17P in unselected twin pregnancies [213].

In **twins with short CL**, there was **no effect** of 17P on PTB rates, but numbers are limited [210, 214]. A meta-analysis showed that 17-alpha-hydroxy progesterone caproate is not beneficial in reducing PTB or adverse perinatal outcomes in 175 twin pregnancies (with >90% of mothers with no prior spontaneous PTB) with a TVU CL ≤25 mm before 24 weeks.

In women with **twins and prior PTB**, 17P did not affect incidence of PTB [211].

In **triplet gestations**, 17P is not associated with an effect on the incidence of PTB [215, 216].

Vaginal progesterone

Vaginal progesterone 90 mg daily starting at 24 weeks for 10 weeks, in 500 women with **unselected twin** gestation, was **not associated with significant effects in incidences of PTB** or perinatal morbidity and mortality [217]. Other RCTs also showed no effect of vaginal progesterone in unselected twins [218, 219]. A recent double-blinded, placebo-controlled RCT on nonselected twin pregnancies with no prior PTB investigated the use of daily vaginal progesterone or placebo from 18–21 weeks to 34 weeks for prevention of PTB <34 weeks [220]. There was no difference in mean GA at delivery, the rate of SPTB <34 weeks (18.5% in the progesterone group and 14.6% in the placebo group, OR 1.32, 95% CI 0.24–2.37), and no reduction of neonatal morbidity and mortality. Another RCT evaluated two different doses of vaginal progesterone (200 mg vs. 400 mg daily) to placebo in dichorionic multiple gestations and showed no difference in the rate of PTB <37 weeks in the three groups [221]. A meta-analysis revealed no benefit from vaginal progesterone in unselected twins [213]. **In summary, vaginal progesterone should not be given to unselected twin pregnancies for prevention of PTB**.

A systematic review and metanalysis including **twins with short mid-trimester CL ≤25 mm** showed that **vaginal progesterone**, compared with placebo or no treatment, was associated with a statistically significant **reduction in the risk of preterm birth <33 weeks' gestation** (31.4% vs. 43.1%; RR, 0.69 95% CI, 0.51–0.93; *moderate-quality evidence*). Vaginal progesterone administration was associated with a significant decrease in the risk of **PTB <35, <34, <32, and <30 weeks' gestation** (RRs ranging from 0.47 to 0.83), **neonatal death** (RR 0.53 95% CI 0.35–0.81), **RDS** (RR 0.70 95% CI 0.56–0.89), **composite neonatal morbidity and mortality** (RR, 0.61 95% CI 0.34–0.98), **use of mechanical ventilation** (RR 0.54 95% CI 0.36–0.81), and **birth weight <1500 g** (RR, 0.53 95% CI 0.35–0.80; *all moderate-quality evidence*) [222]. Another meta-analysis found that vaginal progesterone was not beneficial in preventing PTB at <34 weeks in 58 twin pregnancies (with >95% of mothers with no prior spontaneous PTB) with a TVU CL ≤25 mm before 24 weeks, but was associated with a significant 43% decrease in adverse perinatal outcome [213]. A Cochrane review on antenatal progesterone treatment in multiple gestations concluded that administration of progesterone (IM or vaginal) does not appear to be associated with a reduction in the risk of PTB or improved neonatal outcomes. Further well designed meta-analyses and randomized trials are needed [223]. **In summary, vaginal progesterone in multiple gestations with a short cervix ≤25 mm is associated with prevention of PTB and neonatal benefits**.

Women with twins with prior SPTB can be offered progesterone, e.g. vaginal progesterone 200mg daily starting at 16 weeks, until 36 weeks, but the evidence for this intervention is limited.

There is insufficient evidence to assess the effect of vaginal progesterone on unselected triplet gestations [218].

In summary, **the evidence is insufficient to recommend the use of any type of progesterone for the prevention of PTB in unselected multiple gestations**. **Vaginal progesterone in women with both multiple gestations and short CL is associated with PTB prevention and neonatal benefits**. Therefore, TVU CL at around 20 weeks can be reconsidered as routine in multiple gestations.

Cerclage

HIC does not prevent PTB in unselected twin gestations in one small RCT [224].

There is insufficient evidence to assess the efficacy of **UIC** in twin pregnancies with a short TVU CL. UIC **does not prevent PTB** in a meta-analysis of the 49 twin gestations and TVU CL <25 mm included in the three RCTs published so far [74]. An individual patient-level data meta-analysis of three RCTs showed no benefit of cerclage compared to no cerclage in preventing PTB <34 weeks [225]. For multiple gestations, there is no evidence that cerclage is an effective intervention for preventing PTBs and reducing perinatal deaths or neonatal morbidity [226]. A recent retrospective cohort study of asymptomatic twin gestation with short cervix (TVU CL ≤25 mm) between 16 and 24 weeks showed UIC was not associated with perinatal outcomes compared to controls. However, **in a planned subgroup analysis of asymptomatic twin pregnancies with TVU CL ≤15 mm before 24 weeks, UIC was associated with a significant prolongation of pregnancy by almost 4 more weeks, significantly decreased SPTB <34 weeks by 49%, and admission to NICU by 58% compared with controls** [227]. **Given the available evidence, with lack of large RCT data, UIC cannot yet be recommended for twin gestations with a short TVU CL, and further research is warranted**.

Regarding the effectiveness of **PEIC** in twins, a recent multicenter, open-label RCT of diamniotic twins with asymptomatic cervical dilation before 24 weeks of gestation showed a **significant decrease in PTB <34 weeks** (RR 0.71; 95% CI 0.52–0.96) with a combination of PEIC, indomethacin, and antibiotics [228]. The mean GA at delivery of cerclage vs. the "no cerclage" group was 29.05 ± 1.7 vs. 22.5 ± 3.9 weeks (p <0.01), respectively; the mean interval from diagnosis of cervical dilation to delivery was 8.3 ± 5.8 vs. 2.9 ± 3.0 weeks (p = 0.02), respectively. **PEIC in twins with a dilated cervix before 24 weeks should be recommended**.

Pessary

In unselected twin gestations, the largest RCT found no benefit of pessary use [229]. **In summary, there is sufficient evidence**

to recommend against pessary use for prevention of PTB in unselected twins.

There is contradictory evidence regarding the efficacy of a pessary to prevent PTB in women with **twin gestations and a short TVU CL** in the second trimester. All studies so far used the Arabin pessary. One RCT on twins with TVU CL ≤25 mm revealed that SPTB <34 weeks was significantly less frequent in the pessary group than in the expectant management group (11/68 [16.2%] vs. 26/66 [39.4%]; RR 0.41; 95% CI 0.22–0.76) [230]. A secondary analysis of an RCT suggests pessary use is associated with a decreased rate of PTB <28 weeks and <32 weeks (but not <37 weeks) in twin pregnancies with TVU CL <38 mm before 23 weeks GA [231]. In the largest RCT so far, pessary use on twins with TVU CL ≤25 mm was not associated with prevention of PTB ≤34 weeks (33/106 [31%] vs. 28/108 [26%]; RR 1.20; 95% CI 0.78–1.83) or other PTB or neonatal outcomes [229]. A multicenter RCT of asymptomatic diamniotic twins with TVU CL of ≤30 mm at 18 weeks 0 days to 27 weeks 6 days were randomized to receive either the Biotequecup cervical pessary or no pessary. This study was underpowered; however, the authors showed no significant differences between the pessary and no-pessary groups in rate of primary outcome, PTB <34 weeks (39% vs. 35%; RR 1.13 95% CI 0.53–2.40) [232]. **In summary, there is insufficient evidence to recommend pessary use for prevention of PTB in twins with short CL**, and this intervention **should not be recommended for the prevention of PTB in multiple gestations with a short TVU CL outside of research trials**.

For **preconception counseling, prenatal care, antepartum testing, mode of delivery, anesthesia, and postpartum/breastfeeding in multiple gestations**, see Chap. 46 in *Maternal-Fetal Evidence Based Guidelines*. For preterm labor, see Chap. 19. For PPROM, see Chap. 20. For consequences of PTB for the infant and child, see Chap. 32.

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19

PRETERM LABOR

Rebecca Horgan

Key points

- See Chap. 18 for primary and secondary prevention of preterm birth (PTB) in asymptomatic women and for risk factors and complications.
- The diagnosis of preterm labor (PTL) is based on the clinical criteria of regular **uterine contractions (≥4 per 20 minutes or ≥8 per hour)** at 20–$36^{6/7}$ weeks **with either:**
  - **Manually detected cervical dilatation of ≥ 3 cm**
  - **Transvaginal ultrasound (TVU) cervical length (CL) <20 mm**
  - **Positive fetal fibronectin (FFN) and TVU CL 20–29 mm**
- Threatened PTL (regular uterine contractions (≥4 per 20 minutes or ≥8 per hour) at 20–$36^{6/7}$ weeks) should be assessed and managed with knowledge of **TVU CL; and of FFN** results if TVU CL 20–29 mm (Figure 19.1).
- Women with threatened PTL but TVU CL ≥30 mm have a ≤2% chance of delivering within 1 week and a >95% chance of delivering ≥35 weeks without therapy and should therefore not receive any treatment.
- **Corticosteroids** (e.g. **betamethasone 12 mg IM every 24 hours × 2 doses**) given to pregnant women at high risk for PTB (either spontaneous or indicated) between 23 and $33^{6/7}$ weeks are **effective in preventing respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), and neonatal mortality and should therefore be recommended**. They can also be considered for pregnant women at high risk for PTB between $22^{0/7}$ and $22^{6/7}$ weeks.
- Corticosteroids (e.g. betamethasone 12 mg IM every 24 hours × 2 doses) given to pregnant women at high risk for birth (either spontaneous or indicated) between $34^{0/7}$ and $36^{6/7}$ weeks decrease neonatal respiratory morbidity and can be considered. However, delivery should not be delayed.
- A **single rescue course** of antenatal corticosteroids should only be considered if more than 2 weeks have elapsed since the initial course of corticosteroids and a new episode of PTL or preterm prelabor rupture of membranes (PPROM) or impending risk of PTB presents again at <34 weeks. A single rescue course of betamethasone, two 12-mg doses 24 hours apart, received before 33 weeks at least 14 or more days after the first course, which was administered before 30 weeks, is associated with decreased RDS, ventilatory support, surfactant use, and composite neonatal morbidity. A repeat course of antenatal corticosteroids given prior to 34 weeks to women at risk of PTB is associated with reduced likelihood of the neonate requiring respiratory support. More than two courses of corticosteroids for fetal maturity should be avoided.
- **Intravenous magnesium sulfate** (loading dose of 4–6 g infused for 20–30 minutes, followed by a maintenance infusion of 1–2 g/hour) given at 24–$31^{6/7}$ weeks immediately (within 12 hours) before PTB **is associated with a significant decrease in the incidence of cerebral palsy**.
- Other interventions studied to prevent PTB in women with PTL and intact membranes, including bed rest, hydration, sedation, and antibiotics, have not been shown to be beneficial in the management of PTL.
- **No tocolytic** agent has been shown to **improve perinatal mortality**.
- Tocolytics should not be used without concomitant use of corticosteroids for fetal maturity.
- **No tocolytic** agent has been shown to be superior in terms of safety and effectiveness. **Cyclooxygenase (COX) inhibitors** are the only class of primary tocolytics shown to **decrease PTB <37 weeks** compared with placebo. **COX inhibitors and oxytocin receptor antagonists (ORAs)** have been shown to significantly **prolong pregnancy by 48 hours and by 7 days compared with placebo**. **COX inhibitors, calcium channel blockers (CCBs), and ORAs** have significantly **fewer side effects than betamimetics**. **CCBs and COX inhibitors are the tocolytic agents best supported by evidence for safety and effectiveness**.
- In general, **maintenance tocolysis has not been proven** to **prevent PTB or reduce perinatal morbidity/mortality, and therefore maintenance tocolysis should not be used**.
- There is insufficient evidence to evaluate multiple tocolytic agents for primary tocolysis, refractory (primary agent is failing, so another is started) tocolysis, or repeated (after successful primary tocolysis) tocolysis.
- **In preterm neonates, delayed cord clamping for 30–60 (maximum 120) seconds** is associated with **fewer transfusions for anemia, better circulatory stability, less intraventricular hemorrhage**, and **lower risk of necrotizing enterocolitis** compared to early clamping at <30 seconds.

Diagnosis

Preterm labor (PTL) was often defined in the past as regular uterine contractions (≥4 per 20 minutes or ≥8 per hour) with either manually detected cervical change, or cervical effacement ≥80%, or cervical dilatation ≥3 cm at 20–$36^{6/7}$ weeks [1]. A more evidence-based definition using current diagnostic technology is regular **uterine contractions (≥4 per 20 minutes or ≥8 per hour) with transvaginal ultrasound (TVU) cervical length (CL) <20 mm, or positive fetal fibronectin (FFN) and TVU CL 20–29 mm** at 20–$36^{6/7}$ weeks. Threatened PTL can be defined as regular uterine contractions (≥4 per 20 minutes or ≥8 per hour) between 20 and $36^{6/7}$ weeks, before cervical dilatation and TVU CL have been assessed.

Symptoms

Symptoms of PTL are often nonspecific and include menstrual-like cramps, abdominal "tightenings," mild irregular contractions,

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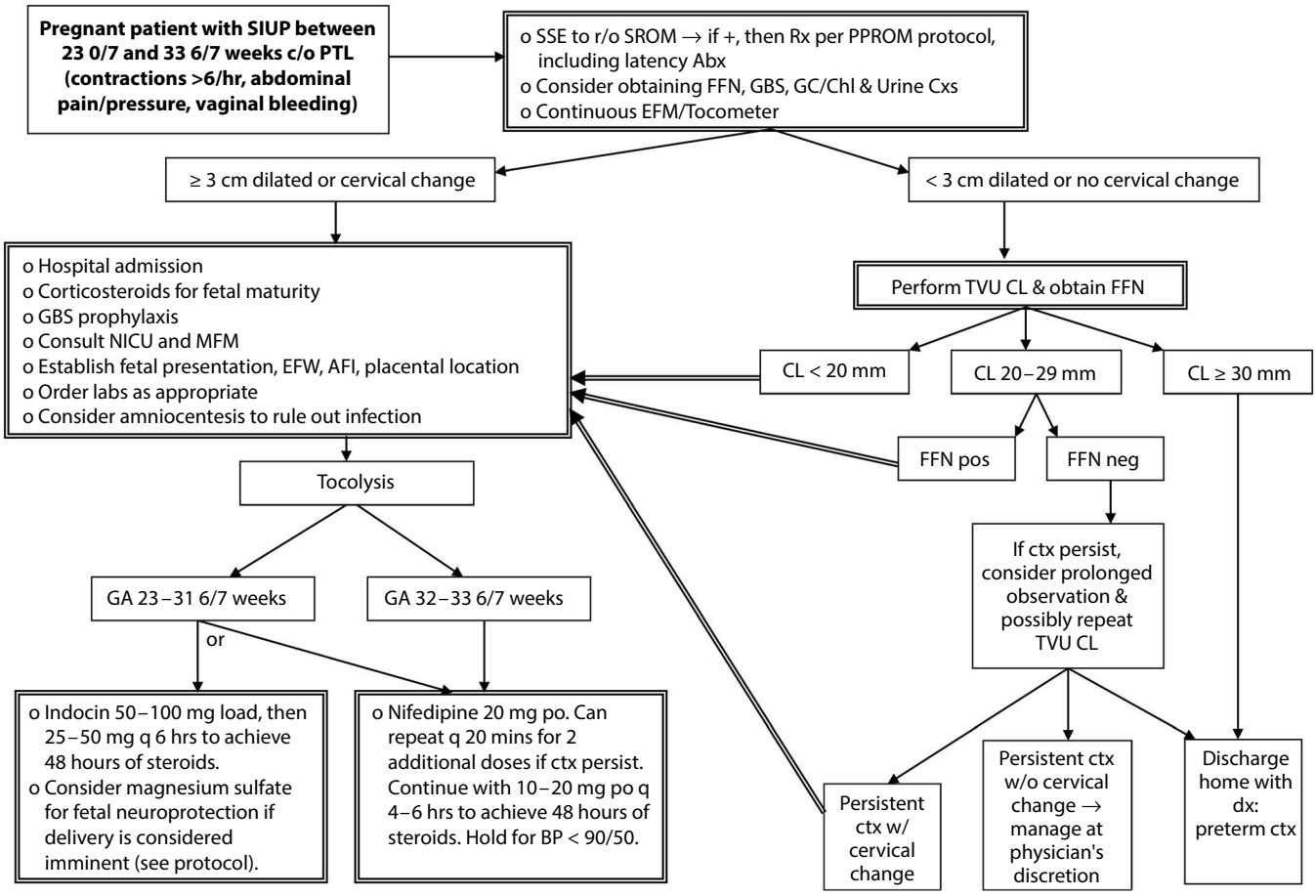


FIGURE 19.1 Suggested algorithm for the management of PTL. *Abbreviations.* PTL, preterm labor; SLIUP, single live intrauterine pregnancy; R/O, rule out; CTX, contractions; SSE, sterile speculum exam; SROM, spontaneous rupture of membranes; Rx, treat; PPROM, preterm prelabor rupture of membranes; FFN, fetal fibronectin; Amnio, amniocentesis; GBS, group B streptococcus; GC, gonorrhea; Chl, chlamydia; EFM, external fetal monitoring; TVU CL, transvaginal ultrasound cervical length; dx, diagnosis; NICU, neonatal intensive care unit; MFM, maternal-fetal medicine specialist; EFW, estimated fetal weight; GA, gestational age; AFV, amniotic fluid volume; IVF, intravenous fluids; BP, blood pressure.

low backache, pelvic pressure, increased vaginal discharge, spotting, or bleeding.

For **epidemiology/incidence, genetics, etiology/basic pathophysiology, classification, risk factors/associations**, and **complications**, see Chap. 18.

Workup (Figure 19.1)

- History: Ensure correctness of gestational age (GA) estimation; evaluate signs and symptoms of PTL, and *all* risk factors for preterm birth (PTB) (Table 19.1).
- Physical exam: Maternal vital signs; frequency, intensity, and duration of uterine contractions; fetal heart rate pattern; assess uterine tenderness, firmness, fetal position.
  Perform speculum exam:
  - Estimate cervical dilatation [2]
  - Assess presence/amount of uterine bleeding
  - Assess for preterm prelabor rupture of membranes (PPROM) (nitrazine, pooling, ferning)

TABLE 19.1: Estimated Incidences of Intraamniotic Infection in Women in Different Clinical Scenarios

Condition	Percent
GA <37 weeks	
Asymptomatic second trimester	0.5
PTL (intact membranes)	13
PPROM, no labor	25
PPROM, labor	39
Cervix ≥2 cm/80% in second trimester	50
GA ≥37 weeks	
Labor	19
PROM	34

Abbreviations: GA, gestational age; PPROM, preterm prelabor rupture of membranes; PTL, preterm labor.

- Obtain swab for FFN testing
- If no PPROM, perform digital cervical exam
- If cervix <3 cm dilated, send FFN swab and perform TVU CL
- If cervix ≥3 cm dilated, discard FFN swab and manage PTL

- Laboratory tests: Rectovaginal group B streptococcus (GBS) culture; gonorrhea and chlamydia; urinalysis and urine culture (Figure 19.1); FFN in women <34 weeks gestation with cervical dilation <3 cm and TVU CL 20–29 mm.

TVU CL

Symptomatic women with CL ≥30 mm have a low risk (<5%) of delivering preterm, regardless of FFN result. For women with CL 20–29 mm, the PTB rate is somewhat increased but still <5% within 7 days if the FFN test is negative. A CL <20 mm is associated with a high risk (>25%) of PTB within 7 days. With this degree of cervical shortening, FFN testing does not improve the predictive accuracy of CL measurement alone [3, 4].

Compared to no knowledge, **knowledge of TVU CL results** is associated with a **statistically significant decrease in PTB <37 weeks** (22.1% versus 34.5%; relative risk [RR], 0.64, 95% confidence interval [CI], 0.44–0.94). Delivery occurred at a later GA (by about 4–5 days) in the knowledge versus no-knowledge groups [5, 6]. Given the clinical and cost-effectiveness of TVU CL in the assessment of suspected PTL, **TVU CL should be used in the management of women with threatened PTL** (Figure 19.1).

Fetal fibronectin

FFN testing has been shown to predict PTB with moderate accuracy in symptomatic women resulting in health care cost benefits by identifying women who do not require intervention [7]. In a meta-analysis of six randomized controlled trials (RCTs), compared to no knowledge, **knowledge of FFN results in women with threatened PTL is not associated with effects on the incidence of PTB <37 weeks or any other outcome**, maternal or neonatal, including time in triage; PTB <34, 32, or 28 weeks; GA at delivery; birth weight less than 2500 g; perinatal death; maternal hospitalization; tocolysis; or steroids for fetal lung maturity [8, 9]. The benefit in knowledge of FFN was seen only in one RCT, in which TVU CL was the main screening test, with FFN used only for "indeterminate" results (Figure 19.1) [10]. Recent evidence suggests that placental alpha-microglobulin-1 (PAMG-1) may be more effective at predicting PTB in symptomatic women with a short CL than FFN, but further evidence is necessary before guidance can be provided [11].

Management

Principles of management

Before treatment is considered, the diagnosis and risk of PTB must be established. **Women with preterm uterine contractions but negative FFN and TVU CL ≥30 mm have a <2% chance of delivering within 1 week and a >95% chance of delivering ≥35 weeks without therapy, and should therefore not receive any treatment** (Figure 19.1) [4].

Women with **preterm uterine contractions and cervical dilatation ≥3 cm, TVU CL <20 mm, or TVU CL 20–29 mm and positive FFN, have a moderate to high risk of PTB within 7 days and are those with true PTL** and should be managed with strong consideration for admission, steroids, magnesium for neuroprophylaxis, and possibly tocolysis, depending on GA.

If PTL is diagnosed without using TVU CL, about 70%–80% of women diagnosed with the condition deliver at term. Women without cervical change do not have PTL and should not receive tocolysis. Women with multiple gestations should not be treated differently than those with singletons, except that their risk of pulmonary edema is greater when exposed to betamimetics or magnesium sulfate [12].

Referral to a tertiary care center should be considered if the neonatal ICU is not adequate for the GA of the potential neonate. There is insufficient evidence to justify the use of steroids for fetal maturity and tocolysis before 23 weeks. Amniocentesis may be considered to assess intraamniotic infection (IAI) (incidence about 5%–15%) and fetal lung maturity (especially between 33 and 35 weeks). IAI (documented by amniotic fluid culture) rates can be estimated by pregnancy status (Table 19.1). IAI rates can also be estimated by TVU CL [13].

Counseling regarding morbidity and mortality for preterm infant, using recent and ideally national or institutional data, should be provided (Table 19.2) [14]. Neonatal consult at 22–34 weeks is indicated for counseling regarding prognosis and

TABLE 19.2: General Guidance Regarding Obstetric Interventions for Periviable Birth[a]

	20^0–21^6 weeks	22^0–22^6 weeks	23^0–23^6 weeks	24^0–24^6 weeks
Neonatal assessment for resuscitation	Not recommended	Consider	Consider	Recommended
Antenatal steroids	Not recommended	Consider	Consider	Recommended
Tocolytics to allow steroids	Not recommended	Not recommended[b]	Consider	Recommended
Magnesium sulfate for neuroprotection	Not recommended	Not recommended[b]	Recommended	Recommended
Antibiotics for PPROM to prolong latency	Consider	Consider	Consider	Recommended
Antibiotics for GBS prophylaxis	Not recommended	Not recommended[b]	Consider	Recommended
Continuous intrapartum electronic fetal monitoring	Not recommended	Not recommended[b]	Consider	Recommended

Source: Adapted from Refs. [16, 20].

[a] Survival of infants born in the periviable period is dependent on resuscitation and support. Several factors (e.g. intrauterine growth restriction, small fetal size, the presence of fetal malformations or aneuploidy, and pulmonary hypoplasia due to prolonged membrane rupture) can impact the potential for survival and the determination of viability. Personal and family values should be extensively discussed, allowing individual decisions. See text.

[b] Limited data for efficacy at this early gestation, but gestational age when interventions start to be offered continues to be moved earlier in pregnancy, with 22 weeks becoming currently the lower limit when interventions are beginning to possibly be considered.

For example, persistently abnormal fetal heart rate patterns or biophysical testing (category II–III), malpresentation.

Abbreviation: GBS, group B streptococcus; PPROM, preterm prelabor rupture of membranes.

neonatal management. Current **neonatal survival** in the United States is **0% at 21 weeks, 5%–15% at 22 weeks, 15%–40% at 23 weeks, 60%–75% at 24–25 weeks, 75%–95% at 26–28 weeks, and >95% at 29–30 weeks**, whereas intact survival at 18 months is about 50% after 25 weeks [15]. Disabilities in mental and psychomotor development, neuromotor function (including cerebral palsy), or sensory and communication function are present in at least 50% of fetuses born ≤25 weeks' gestation [16].

Pregnancies at risk for **periviable** PTB are particularly challenging to counsel and manage. The periviability period varies according to several factors, including by level of care provided in the hospital and the country where the care is being provided. In many developed countries, this period, in 2015, was between 22 and 24 weeks. Table 19.2 provides some guidance for care, but should be adjusted according to local capabilities [16]. Patients with an intrauterine demise or undergoing pregnancy termination are not to be included in this group. For patients in whom the GA has not been clearly established, plans for intervention and information provided to the patient should be based on the best estimate of GA. Several algorithms have been developed to provide patient-specific mortality and morbidity information [17], as well as an online calculator [18]. Status can be reevaluated with each additional gestational week.

Prophylaxis to prevent neonatal morbidity/Mortality from PTB (fetal maturation)

Corticosteroids

Betamethasone, dexamethasone (only two corticosteroids that cross the placenta reliably).

Dose: One course: Betamethasone 12 mg SQ q24h × 2 doses or dexamethasone 6 mg SQ q12h × 4 doses.

Mechanism of action: Enhanced maturational changes in lung architecture and induction of lung enzymes resulting in biochemical maturation.

Evidence for effectiveness: Corticosteroids given prior to PTB (either spontaneous or indicated) are effective in preventing respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC) and neonatal mortality [19]. Antenatal administration of 24 mg of **betamethasone (12 mg intramuscularly q24h),** or of 24 mg of **dexamethasone (6 mg intramuscularly q12h),** to women expected to give birth preterm is associated with a significant **28% reduction in neonatal mortality, 34% reduction in RDS and respiratory support, 45% reduction in IVH, 50% reduction in NEC, 32% reduction in requirement for mechanical ventilation, and 40% reduction in systemic infections in the first 48 hours of life** in preterm infants. There are also decreased needs for surfactant, oxygen, and mechanical ventilation in the neonatal period. Treatment with antenatal corticosteroids does not increase risk to the mother of death, chorioamnionitis, or puerperal sepsis [19].

These benefits apply to **gestational ages of at least 23–33$^{6/7}$ weeks** and are not limited by gender or race. There are insufficient data to assess effectiveness before these GAs. However, if neonatal resuscitation is to be attempted, corticosteroids can be considered from 22 weeks' gestation [20]. At 22–25 weeks, cohort studies have shown benefit in decreasing neonatal death [21]. The **effects are optimal at 48 hours to 7 days from the first dose** [21], but treatment should not be withheld even if delivery appears imminent. Antenatal corticosteroids should be administered when PTB is considered imminent within 7 days, the GA estimate is accurate, adequate neonatal care is available, and there is no clinical evidence of maternal infection.

Recent evidence has demonstrated that **steroids are associated with neonatal benefits also at ≥34 weeks**, as three RCTs have been done on steroids 34–36$^{6/7}$ weeks in women at risk of PTB and two RCTs in women at ≥37 weeks [22]. Women who received antenatal corticosteroids ≥34 weeks had a significantly lower incidence of RDS (RR 0.76, 95% CI 0.62–0.93), mild RDS (RR 0.40, 95% CI 0.23–0.69), moderate RDS (RR 0.39, 95% CI 0.18–0.89), transient tachypnea of the newborn (RR 0.62, 95% CI 0.50–0.77), severe RDS (RR 0.66, 95% CI 0.53–0.82), use of surfactant (RR 0.61, 95% CI 0.38–0.99), mechanical ventilation (RR 0.62, 95% CI 0.41–0.94), significantly lower time on oxygen (mean difference [MD] –2.06 hours, 95% CI –2.17 to –1.95), lower maximum inspired oxygen concentration (MD –0.66%, 95% CI –0.69 to –0.63), lower length of stay in the NICU (MD –7.64 days, 95% CI –7.65 to –7.64), and higher Apgar score at 1 and 5 minutes (MD 0.06, 95% CI 0.05–0.07) compared to those who did not. **Administration of steroids to women >34 weeks at risk of PTB who have not previously received antenatal corticosteroids is now recommended to decrease respiratory morbidity, except in the presence of clinical chorioamnionitis** [23]. However, tocolysis should not be attempted in the late preterm period to delay delivery in order to administer steroids [23]. Limited evidence also suggests late preterm steroids are cost-effective [24].

Type of steroid: There is **no clear evidence of superiority between betamethasone and dexamethasone**. Based on a recent Cochrane review, dexamethasone was associated with a reduced risk of IVH compared to betamethasone (RR 0.44, 95% CI 0.21–0.92) [25]. There were no statistically significant differences in other perinatal outcomes, including perinatal death, RDS, and NICU admissions, however. In one study, infants exposed to dexamethasone had a significantly shorter stay in the NICU. Results for biophysical parameters were inconsistent, but no important differences were seen for these or other secondary outcomes. Indirect comparisons of betamethasone and dexamethasone suggested that betamethasone is more effective in reducing RDS risk than dexamethasone, while chorioamnionitis and puerperal sepsis were more likely with dexamethasone [25].

Oral dexamethasone significantly increased the incidence of neonatal sepsis (RR 8.48, 95% CI 1.11–64.93) compared to intramuscular dexamethasone in one trial of 183 newborns [25].

Betamethasone administered at 12-hourly compared to 24-hourly intervals has been associated with reduced maternal length of stay, but no other differences in maternal or neonatal outcomes [25].

In an international cluster-randomized trial designed to increase the use of antenatal corticosteroid therapy in low-resource settings involving almost 100,000 pregnant women, identification of women at risk for PTB and increased use of antenatal corticosteroids increased overall newborn mortality by 12% (RR 1.2, 95% CI 1.01–1.22), perinatal mortality by 11% (RR 1.11, 95% CI 1.04–1.19), and suspected maternal infection rate by 45% (odds ration [OR] 1.45, 95% CI 1.33–1.58) [26]. Possible explanations for these unexpected findings in low-resource settings include unreliable dating criteria to establish GA, the reliance on birth weight rather than estimated GA to define PTB and evaluate other important outcomes, and the coding of suspected maternal infection by treatment rather than by diagnosis. Inconsistent access and limited resources to provide optimal neonatal intensive care and potential targeting of term, low-birth-weight infants for antepartum corticosteroid treatment may have also contributed to these results. As reaffirmed by the World Health Organization, the study's findings should not alter current

recommendations regarding the use of antenatal corticosteroids to improve newborn outcomes [27].

Weekly repeat courses of antenatal corticosteroids: Evidence for repeating antenatal corticosteroids weekly is provided by a recent Cochrane systematic review of 10 trials (4738 women/5700 babies) [28]. Administration of repeat dose(s) to women who remained at risk for PTB 7 or more days after the initial dose was associated with a reduction in the risk of RDS (RR 0.83, 95% CI 0.75–0.91) and the risk of serious neonatal adverse outcome (RR 0.84, 95% CI 0.75–0.94). In the largest international multicenter RCT, multiple repeat doses were associated with decreased birth weight, length, and head circumference at birth [29]. At early childhood follow-up, no statistically significant differences were seen for infants exposed to repeat prenatal corticosteroids compared with unexposed infants for the primary outcomes (total deaths, survival free of any disability or major disability, disability, or serious outcome) or in the secondary outcome growth assessments [28].

Single repeat (rescue) course of antenatal corticosteroids: Given the potential short- and long-term adverse effects of multiple doses of corticosteroids combined with the optimal benefit 7 days following administration, **timing the first course is extremely important**. A single rescue course should only be considered if PTB has not occurred within 14 days of the initial dose, current GA is <34 weeks, and subsequent clinical assessment demonstrates a new episode of PTL or PPROM and PTB appears highly likely within 7 days [12, 30]. A repeat course of antenatal corticosteroids given prior to 34 weeks to women at risk of PTB who had received their first course of antenatal corticosteroids >7 days previously was associated with a reduced likelihood of requiring respiratory support, with a number needed to treat of 21 patients (RR 0.91, 95% CI 0.85–0.97, $n = 5791$ infants) [23, 31]. Given the concerns regarding multiple courses of corticosteroids, **more than two courses should be avoided** [23].

Contraindications: None.

Side effects: When used for only one course, no significant side effects are seen, except for **transient maternal hyperglycemia** from 12 hours to about 5–7 days after the dose. This effect results in false-positive glucose screening tests or difficulty in managing diabetes. There is no significant increase in maternal or fetal/neonatal infection. If ≥4 courses are used, there is an association with birth weight <10th percentile and probably with small (<10th percentile) neonatal head circumference, with evidence of later "catch-up" [28, 29]. No adverse consequences of prophylactic corticosteroids for PTB in either mothers or infants, even at 10+ years follow-up, have been identified, but long-term follow-up data are limited.

Thyrotropin-releasing hormone

Prenatal thyrotropin-releasing hormone (TRH), in addition to corticosteroids, given to women at risk of very PTB does not improve infant outcomes and can cause maternal side effects [32]. Overall, prenatal TRH, in addition to corticosteroids, does not reduce the risk of neonatal respiratory disease or chronic oxygen dependence and does not improve any of the fetal, neonatal, or childhood outcomes. Prenatal TRH may actually have adverse effects for women and their infants. Side effects (nausea, vomiting, lightheadedness, urgency, flushing) are more likely to occur in women receiving TRH. Among infants, prenatal TRH increases by 16% the risk of needing ventilation, by 48% at having a low Apgar score at 5 minutes, and was associated with poorer childhood outcomes at follow-up [29].

Phenobarbital

The use of prophylactic maternal phenobarbital administration prior to preterm delivery does not prevent periventricular hemorrhage (PVH) or protect from neurologic disability in preterm infants [33]. Prenatal maternal phenobarbital is associated with a significant 35% reduction in the rates of all grades of PVH and a 59% reduction in severe grades PVH (3 and 4) in the infants. The results were influenced by poor-quality trials that excessively influenced the analysis due to their higher rates of severe PVH. When only higher-quality trials were included, phenobarbital was not associated with any beneficial effects, including similar incidences of all grades of PVH and severe grades of PVH to placebo. No difference in the incidence of neurodevelopmental abnormalities at childhood follow-up assessed between 18 and 36 months of age was observed. Maternal sedation is a common side effect in women receiving phenobarbital [33].

Vitamin K

Vitamin K administered to women prior to very PTB has not been shown to significantly prevent PVHs or other neurodevelopmental abnormalities in preterm infants. Antenatal vitamin K is associated with a nonsignificant reduction in all grades of PVH (RR 0.76, 95% CI 0.54–1.06) and a significant reduction in severe PVH (grades 3 and 4) (RR 0.58, 95% CI 0.3–0.91) [34]. When the two quasi-randomized trials are excluded, antenatal vitamin K is not associated with a reduction in all grades of PVH (RR 0.87, 95% CI 0.60–1.26) or severe PVH (RR 0.82, 95% CI 0.49–1.36). Treatment with vitamin K results in a significant reduction in the Bayley Mental Development Index at 2 years of age, but these results are derived from one trial with a high lost to follow-up rate. No difference is found in the incidence of other neurodevelopmental abnormalities at childhood follow-up at 18–24 months or 7 years of age between children exposed to vitamin K and children not exposed [34].

Ambroxol

Giving ambroxol to women at risk of PTB to prevent neonatal RDS is not supported by available evidence. Prenatal administration of ambroxol to reduce the risk of RDS in preterm infants has not been shown to reduce the incidence of RDS or perinatal mortality when compared to betamethasone or placebo. Maternal adverse effects were similar in ambroxol- and betamethasone-treated women. Since the trials included in the Cochrane systematic review were of very low to moderate quality, there is insufficient evidence to support or refute this intervention [35].

Magnesium sulfate for neuroprotection

Antenatal magnesium sulfate therapy given to women at risk of PTB significantly reduces the risk of cerebral palsy in their child (RR 0.68, 95% CI 0.54–0.85) [36–38]. There was also a significant **reduction in the rate of substantial gross motor dysfunction** (RR 0.61, 95% CI 0.44–0.85). No statistically significant effect of antenatal magnesium sulfate therapy is detected on pediatric mortality (RR 1.04, 95% CI 0.92–1.17) or on other neurologic impairments or disabilities in the first few years of life. There are higher rates of minor maternal side effects in the magnesium groups, but no significant effects on major maternal complications [36].

Magnesium sulfate should be administered to women with singleton or twin pregnancies $23^{0/7}$–$31^{6/7}$ weeks for neuroprotection when PTB is imminent. Imminent PTB is defined as a high

likelihood of birth due to active labor with ≥4 cm cervical dilatation, with or without PPROM or planned PTB for maternal or fetal indications. Women with an indicated PTB anticipated within 2–24 hours (e.g. for severe preeclampsia) are candidates for magnesium sulfate. **The optimal timing of magnesium sulfate to reduce the risk of cerebral palsy in preterm neonates is within 12 hours of delivery** [39].

Intravenous magnesium sulfate is administered with a loading dose of 4–6 g infused for 20–30 minutes, followed by a maintenance infusion of 1–2 g/hour [27]. If delivery has not occurred after 12 hours and is no longer considered imminent (e.g. if the patient is not having regular uterine contractions), the infusion should be discontinued and resumed when delivery is deemed imminent again (e.g. when contractions develop). If at least 6 hours have passed since the discontinuation of the magnesium sulfate, another loading dose should be given. Administration of magnesium sulfate for prevention of cerebral palsy **should not delay the delivery**.

Nontocolytic interventions for PTL

Bed rest

Bed rest in hospital or at home in **singleton gestations** complicated by PTL or PPROM has been evaluated in one multiintervention RCT [40]. Bed rest offered **no benefit** over no treatment or placebo in preventing PTB. In multiple pregnancies, bed rest in the hospital **did not reduce the risk of PTB or perinatal mortality**, whether uncomplicated **twin pregnancy or twin or triplet pregnancy with cervical dilatation** [41].

Hydration

There is **no benefit** of intravenous hydration in preventing PTB. Intravenous hydration does not seem to be beneficial, even during the period of evaluation soon after admission, in women with PTL. Women with evidence of dehydration may, however, benefit from the intervention. **Compared with bed rest alone, hydration is associated with similar incidences of PTB <37 weeks, <34 weeks, or <32 weeks** and **of admission to the NICU** [34]. Cost of treatment was slightly higher (US$39) in the hydration group for hospital costs during a visit of less than 24 hours. Women studied were at low risk, as only 30% of women required tocolysis and <30% had PTB. No studies evaluated oral hydration [42].

Screen for infections

Several infections are associated with a higher risk of PTL and PTB. These include chlamydia, gonorrhea, syphilis, trichomoniasis, and others, as well as bacterial vaginosis (see Chap. 18). There is **insufficient evidence** to assess the effect of screening and treating for genitourinary infections in women with PTL, as no RCTs have been performed. However, a recent meta-analysis demonstrated a 9% prevalence of chlamydia in women with threatened PTL, which was significantly increased in comparison to controls, and further studies are necessary to assess the effectiveness of screening and treating vaginal infections in PTL [43].

Antibiotics

There is **no evidence of benefit** with the use of prophylactic antibiotic treatment for PTL with intact membranes on important neonatal outcomes [44]. PTB <36 or 37 weeks was similar in antibiotics and placebo groups. There is **a trend for a 52% increase in neonatal mortality for those who received antibiotic**s (RR 1.52, 95% CI 0.99–2.34), with similar overall perinatal mortality (RR 1.22, 95% CI 0.88–1.70) [35]. The only benefit is a 26% reduction in maternal infection with the use of prophylactic antibiotics. Use of antibiotics in women with PTL and intact membranes is associated with an increased risk of functional impairment and cerebral palsy [12, 36, 45]. Given these data, **antibiotics should not be used for prevention of PTB in women with PTL and intact membranes**. However, among preterm patients at imminent risk of delivery with an unknown GBS status, antibiotics for GBS prophylaxis is recommended, with optimal timing of antibiotics 4 hours prior to delivery [46].

Cervical pessary

There are conflicting data regarding the effectiveness of a cervical pessary following an episode of arrested PTL to decrease the risk of PTB in singleton pregnancies. One RCT ($n = 130$) found that use of a cervical pessary did not reduce the risk of delivery <37 weeks or improve perinatal outcome. However, another RCT ($n = 357$) found no decrease in PTB <34 weeks with pessary use (RR 0.78; 95% CI 0.45–1.38) but did report a decrease in the rate of spontaneous PTB <37 weeks (RR 0.58; 95% CI 0.3–0.90; $p = 0.01$), threatened PTL recurrence (RR 0.23; 95% CI 0.11–0.47; $p < 0.0001$), and PPROM (RR 0.28; 95% CI 0.09–0.84; $p = 0.01$) [47].

There is one RCT ($n = 132$) examining the use of cervical pessary following an episode of arrested PTL to decrease the risk of PTB in women with twin gestations. The trial found a decreased risk of spontaneous PTB <34 weeks (RR 0.51; CI 0.27–0.97; $p = 0.03$) [48]. However, due to limited evidence, further studies are required before recommendations regarding the effectiveness of cervical pessaries in both singleton and twin pregnancies after an episode of arrested PTL can be made.

Tocolysis

Principles

Tocolytic therapy may provide short-term prolongation of pregnancy, allowing antenatal corticosteroid administration, magnesium sulfate for neuroprotection, and/or maternal transport to a tertiary care facility. However, there is no evidence that treatment of PTL with tocolytic agents improves perinatal outcomes [27]. Calcium channel blockers (CCBs) and cyclooxygenase (COX) inhibitors are the agents best supported by evidence of safety and effectiveness (see Table 19.3).

With regard to the use of a combination of tocolytic agents, a recent Cochrane review concluded that the effectiveness of combination regimens in terms of maternal and neonatal outcomes is unclear due to a lack of data. The review noted that there are no RCTs examining combinations of commonly used tocolytics [49].

Contraindications

See Table 19.4.

Primary tocolysis: Single agent

Betamimetics

Types: Ritodrine, terbutaline.

Dose: Ritodrine: 50–100 mg/minute IV initial dose, increase 50 mg/minute q10min (max 350 mg/min) [PO: 1–20 mg q2–4h]. Terbutaline: 0.25 mg SQ q20min at first, then 2–3 hours; or 5–10 mg/min IV, max 80 mg/min; or 2.5–5 mg PO q2–4h (hold for maternal HR >120/minute).

Mechanism of action: Stimulate B2 receptors through cyclic adenosine monophosphate (AMP), so no free calcium for myometrial contraction.

Evidence for effectiveness (Table 19.5): **Compared with placebo, betamimetics are associated with a decrease in the**

TABLE 19.3: Principles of Tocolytic Therapy

- **At 23–33$^{6/7}$ weeks, steroids for fetal maturation should be given if tocolysis is initiated.** Tocolytics should not be used without concomitant use of steroids for fetal maturation.
- Tocolysis is typically used for 48 hours to allow steroid effect. Given side effects, consider stopping tocolytic therapy at 48 hours after steroids given if PTL under control.
- **No tocolytic agent has been shown to improve perinatal mortality**.
- There is no tocolytic agent that is more safe and efficacious. **COX inhibitors** are the only class of primary tocolytics shown to decrease PTB <37 weeks compared with placebo. COX inhibitors and **ORAs** have been shown to significantly prolong pregnancy at 48 hours and 7 days compared with placebo. COX inhibitors, **CCBs**, and ORAs, properly used, have significantly fewer side effects than betamimetics. Currently, **CCB and COX inhibitors are the tocolytic agents best supported by evidence for safety and effectiveness**.
- There is no maintenance tocolytic that prevents PTB or perinatal morbidity/mortality, and therefore **maintenance tocolysis should in general not be used**. There is insufficient evidence to evaluate multiple tocolytic agents for primary tocolysis, refractory (primary agent is failing, so another is started) tocolysis, or repeated (after successful primary tocolysis) tocolysis.

Abbreviations: COX, cyclooxygenase; ORA, oxytocin receptor antagonists; CCB, calcium channel blockers; PTB, preterm birth; PTL, preterm labor.

number of women in PTL giving birth within 48 hours (RR 0.68, 95% CI 0.53–0.88) and **a decrease in the number of births within 7 days** (RR 0.80, 95% CI 0.65–0.98) but there was no reduction in PTB <37 weeks [50]. No benefit is demonstrated for betamimetics on perinatal or neonatal death or on RDS. A few trials reported the following outcomes, with no difference detected: Cerebral palsy, infant death, and NEC. Betamimetics are significantly associated with the following side effects (see later): **Withdrawal from treatment due to adverse effects, chest pain, dyspnea, tachycardia, palpitation, tremor, headaches, hypokalemia, hyperglycemia, nausea/vomiting, nasal stuffiness, and fetal tachycardia** [42]. There is insufficient evidence to assess which of the studied betamimetics is most effective and/or associated with fewer side effects, with most data reported for ritodrine. For comparison with other tocolytics, RCTS are too small and varied to make meaningful comparisons [50].

Specific contraindications: Cardiac arrhythmia or other significant cardiac disease, diabetes mellitus (DM), poorly controlled thyroid disease (for ritodrine).

Side effects:

Maternal: Hyperglycemia (glucose 140–200 mg/dL in 20%–50%; mechanism: Decreased peripheral insulin sensitivity and increased endogenous glucose production; hyperinsulinemia; hypokalemia (K <3 mEq/L in 50%); tremors, nervousness, shortness of breath (10%), chest pain (5%–10%), tachycardia/palpitations, arrhythmia (3%); ECG changes (2%–3%); hypotension (2%–3%); pulmonary edema (<1%–5%); mechanism: Reduced sodium excretion—sodium and therefore fluid retention). Ritodrine: Altered thyroid function, antidiuresis.

Fetal/neonatal: Ritodrine: Neonatal tachycardia, hypoglycemia, hypocalcemia, hyperbilirubinemia, hypotension, IVH. Terbutaline: Tachycardia, hyperinsulinemia, hyperglycemia, myocardial and septal hypertrophy, myocardial ischemia.

TABLE 19.4: Contraindications to Tocolytic Therapy

Maternal:
Chorioamnionitis
Severe vaginal bleeding/abruption
Preeclampsia
Medical contraindications to specific tocolytic agent[a]
Other maternal medical condition that makes continuing the pregnancy inadvisable
Fetal:
Death
Major (especially if lethal) fetal anomaly or chromosome abnormality
Other fetal conditions in which prolongation of pregnancy is inadvisable
Documented fetal maturity

[a] See text.

Calcium channel blockers

Types: Nifedipine, nicardipine.

Dose: Nifedipine 20–30 mg × 1, then 10–20 mg q4–8h (max 90 mg/day) (similar dosing for nicardipine).

Mechanism of action: Impairs calcium channels, so inhibits influx of calcium into cell and therefore myometrial contraction.

Evidence for effectiveness (Table 19.5): Two small RCTs comparing CCB with placebo showed a **reduction in PTB <48 hours (RR 0.30, 95% CI 0.21–0.43) and an increase in maternal adverse effects**, with insufficient evidence to assess effect on PTB within 7 days and <37 weeks [44].

When compared with other tocolytic agents (betamimetics, nonsteroidal antiinflammatory drugs [NSAIDs], glyceryl trinitrate [GTN], magnesium sulfate and oxytocin receptor antagonists [ORAs]), **CCBs increased the interval from initiation of treatment to delivery, increased GA at birth, and decreased preterm and very preterm birth. RDS, NEC, IVH, hyperbilirubinemia, and admission to the NICU were also decreased** [44]. **CCB also reduced the requirement for women to have treatment ceased for adverse drug reaction**. There are insufficient data regarding the effects of different dosage regimens and formulations of CCBs on maternal and neonatal outcomes; the most studied is nifedipine, at the dosage shown earlier. **CCBs should be preferred to betamimetics for tocolysis**.

Specific contraindications: Cardiac disease; hypotension (<90/50); concomitant use of magnesium; caution in renal disease.

Side effects:

Maternal: Flushing, headache, dizziness, nausea, transient hypotension. Caution in women with hypotension and renal disease, as well as women on magnesium (cardiovascular collapse).

Fetal/Neonatal: None.

Cyclooxygenase inhibitors

Types: Nonselective COX inhibitors: Indomethacin (Indocin). Selective COX inhibitors (preferential COX-2 inhibitor): sulindac, rofecoxib (Vioxx), celecoxib, nimesulide.

Dose: Indomethacin: 50–100 mg loading dose (rectal or vaginal route preferred, oral otherwise), then 25–50 mg q6h **for 48 hours**

TABLE 19.5: Summary of the Evidence for Tocolytic Therapy

Tocolytics	<48 Hours	<7 Days	<34 Weeks	<37 Weeks	Perinatal mortality
Primary—Single Agent versus Placebo					
Betamimetics	**0.68 (0.53–0.88)** [*n* = 1209]	0.84 (0.46–1.55) [*n* = 1332]	NC	0.95 (0.88–1.03) [*n* = 1212]	0.90 (0.27–3.00) [*n* = 1174]
CCB	**0.30 (0.21–0.43)** [*n* =173]	NC	NC	NC	NC
COX	0.20 (0.03–1.28) [*n* = 70]	0.41 (0.10–1.66) [*n* = 70]	NC	**0.21 (0.07–0.62)** [*n* = 36]	0.80 (0.25–2.58) [*n* = 106] (NND)
Mg	0.56 (0.27–1.14) [*n* = 182]	NC	NC	**0.62 (0.46–0.83)** [*n* = 265]	4.56 (1.00–20.86) [*n* = 257]
ORA	1.05 (1.15–7.43) [*n* = 152]	**0.74 (0.61–0.91)** [*n* = 302][a]	1.33 (0.84–2.14) [*n* = 287][a]	1.17 (0.99–1.37) [*n* = 501]	2.25 (0.79–6.30) [*n* = 566]
NOD	1.19 (0.74–1.90) [*n* = 186]	NC	0.93 (0.61–1.41) [*n* = 153]	NC	0.43 (0.06–2.89) [*n* = 186] (NND)
Progesterone	NC	NC	0.62 (0.30–1.27) [*n* = 62]	**0.62 (0.39–0.98)** [*n* = 293]	0.31 (0.01–7.41) [*n* = 83]
Comparisons					
CCB vs. Betamimetics	0.86 (0.67–1.10) [*n* = 1505]	**0.76 (0.59–0.99)** [*n* = 242]	**0.78 (0.66–0.93)** [*n* = 1505]	0.89 (0.76–1.05) [*n* = 389]	0.80 (0.53–1.22) [*n* = 630]
COX vs. Betamimetics	**0.27 (0.08–0.96)** [*n* = 100]	0.88 (0.52–1.46) [*n* = 146]	NC	**0.53 (0.28–0.99)** [*n* = 80]	0.99 (0.27–3.57) [*n* = 237] (NND)
COX vs. CCB	1.08 (0.59–2.01) [*n* = 230]	0.26 (0.52–1.46) [*n* = 146]	0.92 (0.70–1.21) [*n* = 148]	1.08 (0.94–1.25) [*n* = 148]	2.81 (0.82–9.62) [*n* = 249] (NND)
COX vs. Mg	0.87 (0.59–1.29) [*n* = 547]	NC	0.84 (0.64–1.11) [*n* = 128]	0.88 (0.52–1.47) [*n* = 216]	1.59 (0.59–4.29) [*n* = 570]
Mg vs. Betamimetics	1.09 (0.72–1.65) [*n* = 503]	NC	NC	1.03 (0.77–1.39) [*n* = 473]	0.49 (0.05–5.12) [*n* = 263]
Mg vs. CCB	1.19 (0.86–1.65) [*n* = 588]	NC	0.89 (0.55–1.45) [*n* = 88]	1.06 (0.87–1.29) [*n* = 362]	0.27 (0.03–2.29) [*n* = 292]
Mg vs. COX	1.08 (0.91–1.27) [*n* = 318]	NC	NC	NC	0.98 (0.06–15.35) [*n* = 117]
ORA vs. Betamimetics	0.89 (0.66–1.22) [*n* = 1389]	0.91 (0.69–1.20) [*n* = 731]	NC	NC	0.55 (0.21–1.48) [*n* = 816]
ORA vs. CCB	1.06 (0.92–1.22) [*n* = 790]	1.04 (CI 0.89–1.21) [*n* = 890]	NC	NC	NC
NOD vs. Betamimetics	0.96 (0.87–1.05) [*n* = 420]	1.03 (0.92–1.15) [*n* = 679]	0.71(0.36–1.42) [*n* = 365]	0.73 (0.50–1.05) [*n* = 679]	2.06 (0.19–22.38) [*n* = 191]
NOD vs. CCB	0.97 (0.77–1.21) [*n* = 50]	NC	NC	NC	NC
Maintenance Therapy after Treatment of PTL (versus Placebo or No Treatment)					
Betamimetics	NC	NC	2.41 (0.86–6.74) [*n* = 681]	1.11 (0.91–1.35) [*n* = 644]	2.96 (0.72–12.14) [*n* = 467]
CCB	0.46 (0.07–3.00) [*n* = 128]	NC	1.07 (0.88–1.30) [*n* = 540]	0.97 (0.87–1.09) [*n* = 681]	1.36 (0.35–5.33), [*n* = 787]
COX	NC	NC	NC	NC	NC
Mg	NC	NC	NC	1.05 (0.80–1.40) [*n* = 99]	5.00 (0.25–99.16) [*n* = 50]
ORA	NC	NC	0.85 (0.47–1.55) [*n* = 285]	0.89 (0.71–1.12) [*n* = 510]	0.77 (0.21–2.83) [*n* = 512]
Progesterone	NC	NC	OR 0.80 (0.60, 1.08) [*n* = 1307]	OR 0.77 (0.62–0.96) [*n* = 1411]	NC

Note: Data are shown as relative risk (95% confidence intervals) unless otherwise stated. Significant results are shown in bold.

[a] Data courtesy of Vincenzo Berghella.

Abbreviations: PTB, preterm birth; NC, not calculable from the available reports; CCB, calcium channel blocker; COX, cyclooxygenase; ORA, oxytocin receptor antagonists; NOD, nitric oxide donors; NND, neonatal death; Mg, magnesium sulfate; Rx, therapy; excl. cong. anom, excluding congenital anomalies.

max, and **always <32 weeks**. Sulindac 200 mg PO q12h × 48 hours. Ketorolac: 60 mg IM, then 30 mg IM q6h × 48 hours.
Mechanism of action: Inhibits prostaglandin synthesis, therefore inhibits myometrial contraction.
Evidence for effectiveness (Table 19.5): (The nonselective COX inhibitor indomethacin was used in most trials.) When compared with placebo, COX inhibition (indomethacin only) results in a **79% reduction in PTB <37 weeks** in a small trial, an increase in GA of 3.5 weeks, and a >700 g increase in birth weight [51]. No difference was shown in birth within 48 hours of initiation of treatment (RR 0.20, 95% CI 0.03–1.28). No differences were detected in neonatal morbidity or mortality.
Compared with other betamimetics, COX inhibition resulted in a 47% reduction in PTB <37 weeks' gestation and a 73% reduction in PTB within 48 hours [51]. No differences were detected in the fetal or neonatal outcomes such as perinatal mortality, RDS, IVH, NEC, premature closure of the ductus, or persistent pulmonary hypertension of the newborn (PPHN). No differences were found when COX inhibitors were compared to magnesium sulfate or CCBs [51].

A comparison of nonselective COX inhibitors versus selective COX-2 inhibitors did not demonstrate any differences in maternal or neonatal outcomes [51]. Due to small numbers, all estimates of effect are imprecise and need to be interpreted with caution.
Specific contraindications: Renal or hepatic disease, active peptic ulcer disease, poorly controlled hypertension, NSAID-sensitive asthma, coagulation disorders/thrombocytopenia.
Side effects: When used for only 48 hours, no serious maternal and fetal/neonatal side effects occur, and fetal surveillance is not indicated. Usually COX inhibitors are better tolerated by the mother than other tocolytics such as magnesium and betamimetics.

Maternal: As with any NSAIDs, mild gastrointestinal (GI) upset—nausea, heartburn (take with some food/milk) (COX-1). GI bleeding (COX-1), coagulation, and platelet abnormalities (COX-1), asthma if aminosalicylic acid (ASA)-sensitive. May obscure elevation in temperature. Long-term rofecoxib (Vioxx) use in adults has been associated with stroke, so this drug is now not available in many countries.

Fetal/neonatal: In trials, 403 women received short-term tocolysis (up to 48 hours) with COX inhibitors (mainly indomethacin), and there was only one case of antenatal **closure of the ductus arteriosus**. There was no increase in the incidence of patent ductus arteriosus (PDA) postnatally (eight treated with COX inhibitors versus eight treated with placebo or other tocolytics) [52]. No difference in incidences of IVH, bronchopulmonary dysplasia (BPD), PDA, NEC, or perinatal mortality was noted in a review of trials aimed at evaluating safety [53]. Use for **>48 hours**, especially ≥32 weeks, is associated with significant fetal effects such as constriction of the ductus arteriosus, which can lead to hydrops, pulmonary hypertension and death, and **renal insufficiency**, manifested in utero by oligohydramnios. Other effects with prolonged use, such as hyperbilirubinemia, NEC, and IVH, have not been shown with <72 hours use. Selective COX-2 inhibitors have not been shown consistently to be any safer for the fetus/neonate than nonselective COX inhibitors such as indomethacin. Therefore, **continuous use of COX inhibitors for >48 hours and ≥32 weeks is contraindicated.**

Magnesium sulfate ($MgSO_4$)

Dose: 40 g $MgSO_4$ in 1 L half normal saline (NS). Initial: 4–6 g/30 minutes, then 2–4 g/hour. A dose of 5 g/hour has not been shown to be beneficial in perinatal outcomes compared with a dose of 2 g/hour and is associated with significant side effects [54]. Weaning $MgSO_4$ tocolysis has no benefits and a few harmful side effects compared with stopping $MgSO_4$ abruptly [55].
Mechanism of action: Intracellular calcium antagonist.
Evidence for effectiveness (Table 19.5): Compared with placebo, there is **insufficient evidence** to show if $MgSO_4$ reduces the incidence of PTB or perinatal morbidity and mortality [56].

Compared with all controls (including other tocolytics), $MgSO_4$ did not prevent PTB at 48 hours, PTB <37 weeks, or PTB <32 weeks. Perinatal death was higher (only two perinatal deaths), while perinatal morbidities were similar. Dose of magnesium did not affect efficacy. Given these results, there is **no convincing evidence for recommending magnesium for tocolysis** [57].

Management: Aim for 4–7 $MgSO_4$ level. Monitor urinary output. Follow deep tendon reflexes: ↓ at level ≥8, absent ≥10. At ≥10, respiratory depression; at ≥15, risk of cardiac arrest.

Specific contraindications: Myasthenia gravis.

Side effects:

Maternal: Flushing, lethargy, headache, muscle weakness, diplopia, dry mouth, pulmonary edema (1%; mechanism: Intravenous overhydration), cardiac arrest.

Fetal/neonatal: Lethargy, hypotonia, hypocalcemia, respiratory depression. Prolonged use: Demineralization.

Oxytocin receptor antagonists

Types: Atosiban (Tractocile); barusiban.
Dose: Atosiban 6.75 mg bolus, then 300 mg/minute IV × 3 hours, then 100 mg/minute (max 45 hours).
Mechanism of action: Competitive inhibitor of oxytocin via blockade of oxytocin receptor.
Evidence for effectiveness (Table 19.5): **Compared with placebo, atosiban does not reduce the incidence of PTB or improve neonatal outcome** [58]. In one trial, atosiban was associated with an increase in extreme PTB <28 weeks and infant deaths at 12 months of age compared with placebo [58]. However, this trial randomized significantly more women to atosiban before 26 weeks' gestation. Compared with betamimetics, atosiban is associated with similar incidences of PTB and perinatal morbidity/mortality and with fewer maternal drug reactions requiring treatment cessation [58]. Recent data comparing atosiban and nifedipine for tocolysis found no difference in pregnancy prolongation or perinatal outcome but fewer maternal side effects associated with atosiban [59, 60]. However, nifedipine was more cost-effective than atosiban [61]. There is insufficient evidence to assess the effectiveness of a different ORA, barusiban, as only one RCT has tested it against placebo at 34–35 weeks, with no changes in recorded outcomes [62]. Therefore, **as per magnesium, the only evidence supporting the use of ORAs for primary tocolysis is that they have fewer side effects than the (effective) betamimetics**.
Side effects: Minimal to none.

Nitric oxide donors

Type: Nitroglycerine.
Dose: Nitroglycerine transdermal patch 0.4 mg/hour.
Mechanism of action: Direct relaxation of uterine muscle.
Evidence for effectiveness (Table 19.5): There is currently **insufficient evidence** to support the routine administration of nitric oxide donors (NODs) for prevention of PTB in women with PTL [63]. Compared with placebo, there was no evidence that

NOD prolonged pregnancy beyond 48 hours or improved neonatal outcomes. When compared with other tocolytic agents (betamimetics, magnesium sulfate, CCBS, or a combination of tocolytics), there was no evidence that NODs perform better than other tocolytics. Nitroglycerine has been the only NOD used in trials.

Specific contraindications: NODs should not be used in women with hypotension or with preload-dependent cardiac lesions, such as aortic insufficiency.

Side effects:

Maternal: NODs cause dilatation of arterial smooth muscle and commonly cause headache and may result in hypotension. Other side effects include dizziness, flushing, and palpitations.

Fetal/neonatal: Although maternal hypotension could compromise utero-placental blood flow, no adverse fetal or neonatal effects have been reported.

Progesterone

There are **insufficient data** to assess the efficacy for progesterone as a primary tocolysis. There are some data suggesting that progesterone may reduce PTB and increase birth weight and that progesterone may reduce uterine contractility, prolong pregnancy, and attenuate cervical shortening. However, current evidence does not support a role for progesterone as a tocolytic agent [64].

Primary tocolysis: Multiple agents simultaneously

Indomethacin, ampicillin-sulbactam, and magnesium versus magnesium alone

Compared with placebos, indomethacin and ampicillin-sulbactam did not prevent PTB in women in PTL already receiving magnesium sulfate tocolysis [65].

Nifedipine and sildenafil citrate versus nifedipine alone

One RCT with 239 women found the combination of nifedipine and vaginal sildenafil citrate in comparison to nifedipine alone for acute tocolysis was associated with a decreased likelihood of delivery within 7 days (9.1% versus 20.3%; $p = 0.014$), prolonged latency (29 versus 7 days; $p = 0.002$), fewer admissions to neonatal intensive care units (31.4% versus 44.1%; $p = 0.043$), fewer preterm deliveries from 28 to 32 weeks (20.7% versus 38.1%; $p = 0.043$), and increased neonatal birth weight (1900 versus 1500 g; $p = 0.018$). Although these data are promising, further studies are necessary before recommendations can be made [66].

Primary tocolysis: Additional agents versus one agent only

Progesterone vs. placebo in addition to ritodrine

Compared with placebo, in women receiving ritodrine tocolysis, the addition of progesterone was not associated with a significant reduction in PTB <37 weeks (16% versus 33% in placebo) in a very small trial [67]. In detail, in this RCT, in 44 women with mostly (>90%) singleton gestations and threatened PTL at less than 35 weeks treated with ritodrine, natural progesterone 400 mg orally q6h × 24 hours (then 400 mg q8h for next 24 hours, and then 300 mg q8h onward) was associated with a similar incidence of PTB, with less quantity of ritodrine administered and shorter maternal hospital stay compared with placebo [67].

Refractory tocolysis: Primary agent is failing

Indomethacin was similar to sulindac in the prevention of PTB in women failing primary magnesium sulfate tocolysis in a small trial [68].

Maintenance tocolysis: After successful primary tocolysis

Betamimetics (oral)

Dose: Ritodrine: 1–20 mg PO q2–4h. Terbutaline: 2.5–5 mg PO q2–4h.

Evidence for effectiveness: Compared with **placebo**, oral betamimetic therapy for maintenance tocolysis **does not prevent PTB, recurrent PTL, recurrent hospitalizations, or perinatal morbidity and mortality** [69]. Some adverse effects such as tachycardia are more frequent in the betamimetics group. Given this ample evidence from 13 trials, there is **absolutely no evidence** to support the use of oral betamimetics after PTL has resolved.

Terbutaline pump

Dose: 0.05 mg/hour.

Evidence for effectiveness: Compared with **placebo**, terbutaline pump does not prevent PTB or improve perinatal morbidity and mortality. Side effects and costs associated with this therapy further **advise against its use** [70].

Calcium channel blockers

A meta-analysis examining the use of oral nifedipine for maintenance tocolysis found no difference in the incidence of perinatal death (RR 1.36; 95%, 95% CI 0.35–5.33), IVH ≥grade II (RR 0.65; 95% CI 0.16–2.67), NEC (RR 1.15; 95% CI 0.50–2.65), infant respiratory distress syndrome (IRDS) (RR 0.98;95% CI 0.51–1.85), and prolongation of pregnancy (hazard ratio 0.74; 95% CI 0.55–1.01) [71]. Therefore, maintenance tocolysis with nifedipine is not recommended.

COX inhibitors

Compared with **placebo**, after successful tocolysis, oral sulindac either 200 mg q12h × 7 days or 100 mg q12h until 34 weeks does not reduce PTB compared with placebo [63, 64]. Given the association with fetal/neonatal complications with COX inhibitor use for >48 hours, COX inhibitors should not be used for maintenance tocolysis [72].

Compared with oral **terbutaline**, oral indomethacin is associated with a similar incidence of PTB when used for maintenance tocolysis after successful IV tocolysis, but indomethacin is associated with significant constriction of ductus arteriosus and oligohydramnios when used for >48 hours [73]. Therefore, indomethacin should not be used for maintenance tocolysis, especially after 26 weeks.

Magnesium sulfate

Compared with **placebo** or **no treatment**, magnesium maintenance therapy **does not prevent PTB** (RR 1.05, 95% CI 0.80–1.40) **or affect perinatal morbidity and mortality** (mortality, RR 5.00, 95% CI 0.25–99.16) [74]. It has a similar effect on PTB as alternative tocolytic drugs (RR 0.99, 95% CI 0.57–1.72) (i.e. it is equally ineffective). Therefore, magnesium sulfate should not be used as a maintenance tocolytic.

Oxytocin receptor antagonists

Compared with **placebo**, ORA (atosiban) maintenance therapy (30 μg/minute) via pump up to 36 weeks does not prevent PTB or affect perinatal morbidity and mortality, with a 5-day (32.6 versus 27.6, $p = 0.02$) longer interval to delivery in one trial [75]. There are no side effects compared with placebo except for injection-site reactions. ORAs are not available in oral form for maintenance.

Progesterone

There is conflicting evidence regarding the effectiveness of progesterone for maintenance tocolysis. Women with a singleton gestation who received **17P maintenance tocolysis** for arrested PTL had a **similar rate of PTB** <37 weeks (42% versus 51%; RR 0.78; 95% CI 0.50–1.22) and PTB <34 weeks (25% versus 34%; RR 0.60; 95% CI 0.28–1.12) compared to controls [76, 77]. Women who received 17P had significantly later GA at delivery (MD 2.28 weeks; 95% CI 1.46–13.51), longer latency (MD 8.36 days; 95% CI 3.20–13.51), and higher birth weight (MD 224 g; 95% CI 71–378) as compared to controls. As 17P for maintenance tocolysis is associated with a significant prolongation of pregnancy and significantly higher birth weight [76, 77], further research is suggested.

One study examining maintenance tocolysis with **vaginal progesterone** for arrested PTL found its use was associated with a **significantly lower rate of PTB** <37 weeks (42% versus 58%; RR 0.71; 95% CI 0.57–0.90), significantly longer latency (mean difference 14 days), later GA at delivery (MD 1.3 weeks), lower rate of recurrent PTL (24% versus 46%; RR 0.51; 95% CI 0.31–0.84), and lower rate of neonatal sepsis (2% versus 7%; RR 0.34; 95% CI 0.12–0.98) compared to placebo or no treatment [78]. However, due to the poor quality of the trials, maintenance therapy with vaginal progesterone should be studied further before a strong recommendation can be made.

A recent RCT examining the effectiveness of vaginal progesterone and 17-OHP for maintenance tocolysis among women with threatened PTL and a CL <25 mm but without a history of a prior PTB found no difference in the rate of PTB in either group compared to the control group [79]. A 2017 meta-analysis, which again included both the use of vaginal and 17-OHP progesterone for maintenance tocolysis, found the overall pooled analysis favored treatment effect regarding delivery <37 weeks (OR 0.77, 95% CI 0.62–0.96). However, this was not sustained when only high-quality RCTs were considered (OR 1.23, 95% CI 0.91, 1.67) [80].

In summary, **there is insufficient evidence to recommend progesterone for prevention of PTB in women who remain pregnant after an episode of PTL, but recent evidence about vaginal progesterone for maintenance tocolysis is encouraging**.

PTL resolved: Home versus in-hospital care

After PTL has resolved (and cervical dilatation has not progressed ≥4 cm), **home management is associated with similar incidences of reaching ≥36 weeks compared with hospital management** [81, 82]. Hospitalization may increase maternal stress, vaginal examinations, time in recumbent position (and its consequences), and decreased plasma volume. **For the many women with arrested PTL, continued hospitalization after steroid administration is unnecessary**. Women sent home with a diagnosis of false PTL are not at increased risk for early (<34 weeks) PTB or neonatal mortality, but they are at risk for later (≥34 weeks) PTB [1].

Preconception counseling

Given its major impact of perinatal morbidity and mortality, it is important to **review risk factors for PTB in every pregnant woman**. In the woman with a risk factor (e.g. prior PTB), it is important to review the prognosis, possible complications, and management of a future pregnancy (see earlier).

Prenatal care

Preconception counseling as noted earlier, if not already done. Management should follow recommendations as discussed (Table 19.3). See also Chap. 2.

Antepartum testing

No specific fetal testing is indicated. Home uterine activity monitoring (HUAM), discussed in Chap. 18, is not effective in preventing any complication.

Delivery

Mode

There is **insufficient evidence** to evaluate the use of a policy for uniform planned cesarean delivery (CD) compared with expectant management and selective CD for preterm (24–36 weeks) infants [65, 84]. Mothers in the planned CD group had more morbidity. There was no significant difference between planned CD and expectant management in perinatal morbidity or mortality or in abnormal childhood follow-up. Differentiation of data between breech and vertex presentations is difficult, with numbers too small for definite conclusions.

Delayed cord clamping

In preterm neonates, delayed cord clamping by about 30–60 seconds (120 maximum) is associated with **fewer transfusions for anemia, less hypotension, and less IVH** than early clamping at less than 30 seconds [83]. In addition, delayed cord clamping likely decreases the risk of neonatal death [83].

Milking of the cord has been evaluated only in small RCTs in preterm neonates, so there is insufficient evidence for recommendation. Compared with 30-second delayed cord clamping, milking of the cord four times achieved a similar amount of placento-fetal blood transfusion [85]. However, compared with no milking, milking of the cord has been associated with a similar need for fetal blood transfusions and increased risk of the neonate requiring phototherapy [86].

Analgesia/Anesthesia

No specific changes from term intrapartum management (see Chap. 12).

Postpartum/Breastfeeding/Counseling

As in other pregnancies, breastfeeding is encouraged as tolerated for the preterm infant. Milk expression using a breast pump is also encouraged. Extensive counseling should be provided regarding the rate of recurrence of PTB and future management in pregnancy. Treatment with antibiotics before pregnancy does not prevent recurrent PTB. **In women with a prior spontaneous PTB <34 weeks, oral azithromycin and metronidazole every 4 months after the PTB and before the next conception does not significantly reduce subsequent PTB** [87]. Vaginal and IM progesterone has been shown to reduce the risk of recurrent PTB and adverse perinatal outcomes in women with a history of spontaneous singleton PTB. Following spontaneous singleton PTB, women should be counseled about the benefits of progesterone prophylaxis in subsequent pregnancies [88]. (See also Chap. 18.)

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20

PRETERM PRELABOR RUPTURE OF MEMBRANES

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Key points

- Definite diagnosis is by direct visualization of fluid **("pooling")**, with **pH test** or **ferning** as usual confirmatory tests. In equivocal cases, biochemical tests may aid in the diagnosis, but these **additional tests should not be used without other clinical assessments** because of concerns about inaccurate interpretation.
- **Complications** of preterm prelabor rupture of membranes (PPROM) include **premature labor/delivery** with related complications of prematurity such as **respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL), infection, and necrotizing enterocolitis (NEC)**; maternal or neonatal infections **(chorioamnionitis, endometritis, and sepsis); abruptio placentae**; **cord prolapse**; and, especially for PPROM <24 weeks, **perinatal death, pulmonary hypoplasia (PH), compression deformities, long-term infant morbidities, increased need for cesarean delivery (CD)**, and **retained placenta**.
- **Corticosteroids** should be administered in women with PPROM at $23^{0/7}$–$33^{6/7}$ weeks, as this intervention is associated with **lower** incidences of **RDS**, **IVH**, **NEC**, and **perinatal death rate**. Corticosteroid administration should probably be avoided after 35 weeks in most cases.
- **Antibiotics** are associated with less **chorioamnionitis, preterm birth (PTB) within 48 hours, PTB within 7 days, neonatal infection, surfactant use, oxygen therapy,** and **abnormal cerebral ultrasound scan** (including IVH). **RDS** and **NEC** are also decreased with ampicillin and erythromycin treatment. A combination of **ampicillin and macrolides is suggested**.
- **Tocolytic therapy in women with PPROM is not associated with maternal or perinatal benefits** and should, in general, be avoided.
- **Cervical cerclage should, in general, be removed when the diagnosis of PPROM is made**. Cerclage might be left in place to allow corticosteroid therapy, especially at < 28 weeks.
- **Delivery is indicated for nonreassuring fetal heart rate tracing (NRFHT), preterm labor (PTL), chorioamnionitis, or >37 weeks** (Figure 20.1). **Before 34 weeks**, **conservative management** is **recommended**, if possible. Between 34 and $36^{6/7}$ weeks, in the absence of overt signs of infection or fetal compromise, either delivery or a policy of expectant management with delivery at $37^{0/7}$ weeks is suggested.
- There are limited data to assess the benefit of interventions for PPROM <23 weeks. **Deciding upon a threshold of viability is challenging**. High variability in live birth rates is reported. Perinatal outcomes are related to whether or not families and clinicians agree on aggressive neonatal intervention after counseling. **From 23 weeks, active management (corticosteroids and [re]admission)** should be considered.
- In general, the management of PPROM in **twin pregnancies** should **not differ from that of singletons**.

Definition

Preterm prelabor rupture of membranes (PPROM) refers to chorioamniotic membrane rupture before the onset of labor in pregnancies at <37 weeks of gestation.

Diagnosis

Diagnosis is made in the majority of cases by **history** and direct visualization of fluid **(pooling)** in the posterior vaginal fornix at sterile speculum examination. History of persistent leakage of fluid and ultrasonographic diagnosis of oligohydramnios are two other confirmatory, but not diagnostic, findings.

Traditional confirmatory tests:

- **Ferning test**: The presence of arborization on a slide of amniotic fluid collected in a sterile way from the posterior vaginal fornix. Arborization represents the crystallization of amniotic fluid due to its high contents of salts and proteins. False-positive results for contamination by cervical-vaginal mucus, seminal fluid, fingerprints, and urine crystals. False-negative results for blood or meconium contamination or inadequacy in slide preparation.
- **pH test (nitrazine test)**: The normal pH of vaginal secretions is generally 3.8–4.5, whereas amniotic fluid usually has a pH of 7.1–7.3. False-positive test results may occur in the presence of blood or semen, alkaline antiseptics, certain lubricants, *Trichomonas*, or bacterial vaginosis. Alternatively, false-negative test results may occur with prolonged membrane rupture and minimal residual fluid.

In equivocal cases, additional tests could be used. Statistical measures (sensitivity, specificity, positive predictive value, negative predictive value) of the main prelabor rupture of membranes (PROM) diagnostic tests are reported in Table 20.1 [1–4]. The American College of Obstetricians and Gynecologists (ACOG) published 2020 guidelines [5] reminding health care providers that these **tests should not be used without other clinical assessments** because of concerns about "misuse, overreliance, and inaccurate interpretation" of lab test results used to detect rupture of membranes. These can lead to serious adverse events, including fetal death, infection, and other health complications in pregnant women.

Main biochemical tests:

- **Placental alpha microglobulin test** (AmniSure): Placental alpha microglobulin-1 (PAMG-1) is a placental glycoprotein of amniotic fluid (2000–25000 ng/mL); it can be detected also in lower concentrations in maternal blood (5–25 ng/mL) and in cervical-vaginal secretions (0.05–0.2 ng/mL) if fetal membranes are intact [6]. PAMG-1 is a good marker for PROM diagnosis due to this different concentration between amniotic fluid and cervical-vaginal secretions. PAMG-1 is dosed by an immune-chromatographic test able

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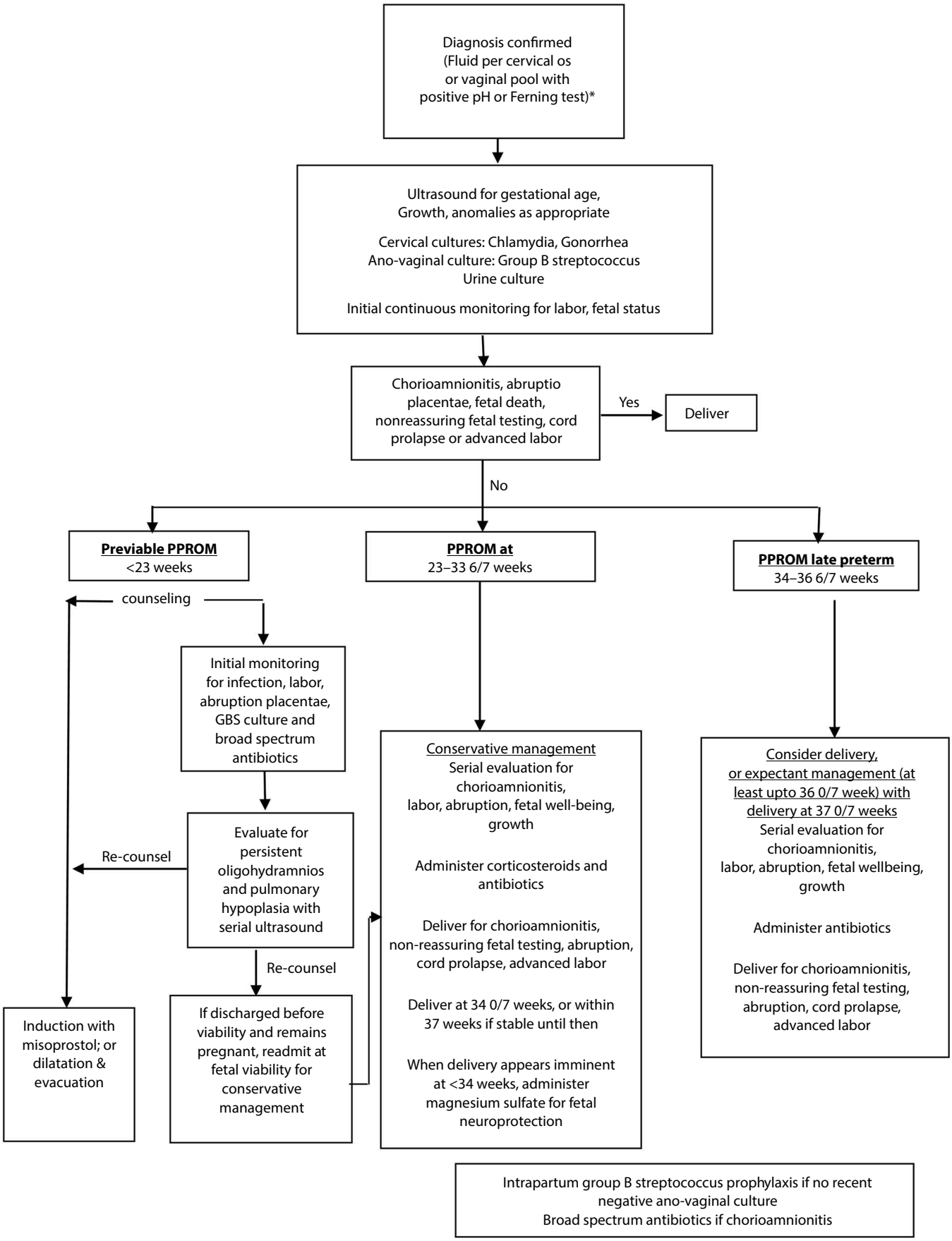


FIGURE 20.1 Management of PPROM. (Adapted from Refs. 1–5, 11–56.) *See also text and Table 20.1.

TABLE 20.1: Predictive Accuracy of PROM Diagnostic Tests

	Brief Description	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
Nitrazine test	Vaginal pH by a cervical-vaginal swab	85	39.7	49.3	79.3
Ferning test	Arborization on a slide of amniotic fluid	84	78.7	79.7	83.1
Placental alpha microglobulin test (PAMG-1)	Immune-chromatographic test on cervical-vaginal secretion detecting PAMG-1	92.7	100	100	95.2
Insulin-like growth factor binding protein (IGFBP)-1	Immune-chromatographic test on cervical-vaginal secretion detecting IGFBP-1	87.5	94.4	92.1	91.1
Diagnostic panty liner	Pad with a reactive strip to detect amniotic fluid	95.4	80	82.4	94.7
Fetal fibronectin (FFN)	Immune-chromatographic test on cervical-vaginal swab detecting FFN	94.5	89.1	89.7	94.2

Source: Adapted from Refs. [1–5].

to detect small concentrations of this glycoprotein in cervical-vaginal secretions (AmniSure PROM test). It is an easy, rapid (5–10 minutes), noninvasive test (speculum examination is not necessary). This test can be performed from 11 to 42 weeks of pregnancy. The result is not influenced by the presence of seminal fluid, urine, blood, or vaginal infections.

- **Insulin-like growth factor binding protein (IGFBP)-1** (PROM test): Immune-chromatographic test that detects amniotic fluid in the vaginal secretions. Monoclonal antibodies identify IGFBP-1, whose concentration is elevated in amniotic fluid (IGFBP-1 ≥10 µg/L: Positive test). The Actim PROM test is easy and rapid. The result is not influenced by the presence of urine or seminal fluid, although it can be altered by contamination with blood [2, 4].
- **Diagnostic panty-liner with polymer-embedded strip**: A pad with a reactive strip put in contact with external genitalia detects the presence of amniotic fluid.
- **Fetal fibronectin**: This test is sensitive but not specific for PROM—a negative result suggests the absence of PROM with high accuracy, while a positive result is not diagnostic for PROM. Fetal fibronectin test is not recommended in the case of PROM [1].

Transabdominal amnioinfusion of dye (indigo carmine, Evans blue, fluorescein) can be used as a confirmatory test in doubtful cases at low gestational ages. Methylene blue must be avoided, as it can cause fetal meta-hemoglobinemia [7].

Symptoms

Over 90% of women with PPROM report a history of a "gush of fluid."

Incidence

PPROM occurs in <1% at <24 weeks, about 1%–3% at 24–33 weeks, and 3%–5% at 34–36 weeks compared with about 8%–10% for PROM at term. PPROM is associated with about 25%–30% of all premature births (PTBs).

Etiology/Basic pathophysiology

Etiology is complex and multifactorial (see Chap. 18). Possible mechanisms leading to PPROM are choriodecidual infection, collagen degradation, decreased membrane collagen content, localized membrane defects, bleeding, uterine overdistention, and programmed amniotic cell death [6]. Evidence that supports a causal association between PPROM and infection is vast and includes the fact that microorganisms in the amniotic fluid are more frequently present and the rate of histologic chorioamnionitis is higher in PPROM than in intact membranes preterm delivery, and the frequency of PPROM is significantly higher in women with lower genital tract infections (e.g. group B streptococcus [GBS] and bacterial vaginosis). Microorganisms that colonize the lower genital tract produce phospholipases, which can stimulate the production of prostaglandins and lead to uterine contractions; the immune response in endocervix and/or fetal membranes leads to the production of multiple inflammatory mediators (particularly matrix metalloproteinases) that can weaken membranes and result in PPROM [8]. Invasive uterine procedures performed during pregnancy (such as amniocentesis, chorionic villus sampling, fetoscopy, and cervical cerclage) can damage the membranes, causing them to leak.

Classification

PPROM can be classified into **PPROM <23 weeks** (usually 16–$22^{6/7}$ weeks, also called previable or mid-trimester or very early PPROM—see also end of this chapter) and PPROM at $23^{0/7}$–$36^{6/7}$ weeks. PPROM at 23–36 weeks can be further subdivided into **PPROM at 23–$33^{6/7}$ weeks** (early PPROM) and **PPROM at 34–$36^{6/7}$** weeks (late-preterm PPROM—for management, see also Chap. 21). In 50% of PPROM, labor occurs within 24 hours, and in 80%–90% within 7 days. Median latency to delivery after PPROM is similar from 24 to 28 weeks' gestation (about 9 days) and shortens with PPROM ≥29 weeks [9]. The latency with PPROM >30 weeks is usually only 2–4 days.

Risk factors

The main risk factors for spontaneous PPROM are listed in Table 20.2 [10]. However, most cases of preterm PROM occur in otherwise healthy women without identifiable risk factors. See also Chap. 18.

TABLE 20.2: Selected Risk Factors for Spontaneous Preterm Prelabor Rupture of Membranes

Maternal Factors

- Preterm prelabor rupture of membranes (PPROM) in a prior pregnancy (recurrence risk is 16%–32% as compared with 4% in women with a prior uncomplicated term delivery)
- Antepartum vaginal bleeding
- Chronic steroid therapy
- Collagen vascular disorders (such as Ehlers–Danlos syndrome, systemic lupus erythematosus)
- Direct abdominal trauma
- Preterm labor
- Exposure to infections
- Cigarette smoking
- Illicit drugs (cocaine)
- Anemia
- Low body mass index (BMI 19.8 kg/m^2)
- Inadequate maternal weight gain
- Nutritional deficiencies of copper and ascorbic acid
- Low socioeconomic status
- Unmarried status
- Young or advanced maternal age
- Occupational factors (strenuous working conditions, long weekly work hours)
- Psychological factors

Uteroplacental Factors

- Uterine anomalies (such as uterine septum)
- Placental abruption (may account for 10%–15% of PPROM)
- Advanced cervical dilatation (cervical insufficiency)
- Prior cervical conization
- Cervical shortening in the second trimester (<2.5 cm)
- Uterine overdistension (polyhydramnios, multiple pregnancy)
- Intra-amniotic infection (chorioamnionitis)
- Multiple bimanual vaginal examinations (but not sterile speculum or transvaginal ultrasound examinations)

Fetal Factors

- Multiple pregnancy (PPROM complicates 7%–10% of twin pregnancies)
- Fetal anomalies (malformations, aneuploidies)

Source: Adapted from Ref. [10].

Complications

Complications are inversely correlated with gestational age (GA) at PPROM and at delivery. Fetal/neonatal and maternal PPROM-related morbidity are shown in Table 20.3 [11].

TABLE 20.3: PPROM Complications

PPROM Complications	Fetal/Neonatal and Maternal Complications
Preterm birth	Neonatal RDS, IVH, PVL, NEC, ROP, perinatal death, long-term infant morbidities
Intrauterine infection/ inflammation	Neonatal or maternal sepsis Childhood neurodevelopmental problems Chorioamnionitis, endometritis
Umbilical cord compression or prolapse Abruptio placentae	Fetal asphyxia CD
Oligohydramnios	Pulmonary hypoplasia and limb deformities (more frequent in the setting of severe oligohydramnios in the early-to-mid second trimester) Umbilical cord compression
Fetal malpresentation	Umbilical cord prolapse CD

Source: Adapted from Ref. [11].

Management (Figure. 20.1)

Prevention

See Chap. 18.

Preconception counseling

See Chaps. 1 and 18. Women with prior PPROM have a 20%–30% chance of PTB, including a 15%–20% chance of recurrent PPROM in the next pregnancy. Recurrence is higher in black women. These incidences are inversely related with GA at PPROM (the earlier the GA at PPROM, the higher the recurrence rate) and interpregnancy interval (shorter than 6 months is particularly associated with higher recurrence).

Counseling should also review *all* risk factors for PTB (Table 20.2). Several risk factors, such as smoking; low body mass index (BMI 19.8 kg/m^2); inadequate maternal weight gain; exposure to infections; illicit drug use; nutritional deficiencies of copper, ascorbic acid, and vitamin D; young or advanced maternal age; anemia; occupational factors such as prolonged walking or standing; strenuous working conditions; and long weekly work hours, in addition to psychological factors such as depression, anxiety, and chronic stress, can be modified and best addressed preconception (Table 20.2; see also Chap. 18). The woman with a history of PPROM should also be made aware that interventions in pregnancy, such as progesterone and cerclage, can further decrease her chance of recurrence (see later).

Prenatal counseling

Counseling regarding prognosis, possible complications, management, and expectations for neonatal outcome should be provided, preferably with reference to local/national data. Prognosis depends mostly on GA at PPROM and GA at delivery. Latency is inversely related with GA at PPROM (Table 20.4) [12] and can be prolonged by some interventions (see Antibiotics). Fetal maturity depends on GA and is probably not enhanced or delayed by PPROM.

Workup (Figure 20.1)

The current gold standard for the **diagnosis** of PROM is based on three traditional tests: Visual pooling of clear fluid in the

TABLE 20.4: Approximate Latency Depending on Gestational Age at PPROM

GA at		Delivery		
PPROM (weeks)	Mean Latency	<48 Hours	<7 Days	<14 Days
<24	7 days	20%	40%–50%	70%
24–33$^{6/7}$	3–6 days	50%	70%–80%	90%
34–36$^{6/7}$	24 hours	70%–80%	90%	>95%

Source: Adapted from Ref. [12].

posterior fornix of the vagina or leakage of fluid from the cervical os at speculum examination, ferning test, and pH test. Such tests become progressively less accurate when more than 1 hour has elapsed after the membranes have ruptured. We still perform these tests initially, with no need for additional tests in diagnosis in about 99% of women with possible PPROM. **Alternative tests can be used in equivocal cases, but caution is needed** due to the possible misleading results if used without a clinical assessment (see earlier). See Table 20.1 for the accuracy of diagnosis of PPROM with different tests [5].

Tests for **gonorrhea and chlamydia infection** are indicated in high-risk groups beyond the usual serologic third-trimester screening. **GBS** culture should be sent from anorectal and vaginal areas. Consider that **the proposed antibiotic prophylactic therapy (see later) covers GBS and *Mycoplasma***. **Avoid manual/digital examination of the cervix** in any woman with suspected PPROM and also after PPROM is diagnosed by speculum examination. Digital examination is associated with shorter latency and higher incidences of infection [13].

Ultrasound

Periodic ultrasound evaluation for presentation, growth, and amniotic fluid is suggested. **Oligohydramnios** per se is not an indication for delivery at the lowest GA. Fifty to seventy percent of PPROM cases have low amniotic fluid volume on initial sonography, and low amniotic fluid volume is associated with an increased risk of shorter latency (**the lower the amniotic fluid index, the shorter the latency between PROM and delivery**) and umbilical cord compression [14, 15]. Patients with **nonvertex presentations** have a higher risk for prolapsed umbilical cord and of an unintended vaginal delivery when compared with vertex presentations. PPROM may also interfere with **fetal growth**; thus Doppler surveillance is recommended in the case of fetal growth restriction [FGR], with the consequent management (see Chap. 47 in *Maternal Fetal Evidence Based Guidelines*). In a recent meta-analysis evaluating the impact of oligohydramnios following PPROM, the risk of delivery within the first 2 days and the rate of neonatal death and respiratory distress syndrome were increased, whereas the risk of placental abruption was not significant [16]. In a recent prospective study, the presence of hyperechoic membranes at ultrasound assessment was associated with a higher incidence of spontaneous onset of labor within 72 hours independently from the gestational age at PPROM [17]. See also Chap. 18.

Infection precautions

In women with PROM with recurrent active herpes simplex virus (HSV) or human immunodeficiency virus (HIV) infection, expectant management is usually recommended before $34^{0/7}$ weeks of gestation. Antiviral therapy is indicated during expectant management. If active HSV disease is present at the time of delivery, cesarean birth is recommended. In the case of primary HSV infection, the risk of vertical transmission is increased and the management of PPROM is less clear. Antiviral therapy is indicated, and if there is active HSV infection at the time of delivery, cesarean birth is recommended [5]. See Chap. 52 in *Maternal-Fetal Evidence Based Guidelines.*

Some data on the management of women with **PPROM and HIV** suggest that the **latency-to-delivery interval is not correlated with risk of vertical transmission in patients who receive antiretroviral therapy, have a low (e.g. undetectable) viral load, and receive antepartum and intrapartum zidovudine** [18]. The management should be individualized, taking into account GA, antiretroviral therapy, and viral load. The patient should be adequately counseled and involved in the clinical choices. See Chap. 34 in *Maternal-Fetal Evidence Based Guidelines.*

Amniocentesis

Amniocentesis is seldom, if ever, used clinically in the management of PROM. It can be of use in rare cases for evaluation of the following:

- **Diagnosis**: If the diagnosis is in doubt, 1 mL of indigo carmine (not currently available in the United States; alternatives are Evans blue, or fluorescein) in 9 mL of normal saline can be injected into the amniotic cavity under continuous ultrasound guidance. Presence of blue on a pad worn on the perineum for 2–4 hours confirms the diagnosis.
- **Eventual intraamniotic infection**: Send amniotic fluid glucose (<15 mg/dL associated with positive culture), Gram stain, and culture. Leukocyte esterase, white blood cell count, and interleukin-6 (IL-6), where available, can also be used. The role of amniocentesis to rule out intraamniotic infection is controversial, and it is not routinely performed.
- **Fetal lung maturity (FLM)**: Assessment of fetal maturity can be obtained from amniotic fluid by amniocentesis or from the vaginal pool [21]. The predictive value of lung maturity tests is not modified by PPROM. Phosphatidylglycerol (PG) and lamellar body counts (LBC) are accurate when tested in the vaginal pool. PG is not accurate in the presence of meconium or blood, LBC is not accurate in the presence of meconium, while the TDx/FLM is accurate with blood and/or meconium in the vaginal pool, yielding results similar to those observed with samples obtained with amniocentesis. Demonstration of a mature fetal lung index by antenatal testing does not improve neonatal outcomes [19]. **FLM testing is not clinically useful, and it is no longer recommended** [20].

Meconium

Meconium-stained amniotic fluid is associated with higher frequencies of clinical chorioamnionitis and positive amniotic fluid cultures when compared to clear amniotic fluid. In the absence of chorioamnionitis, meconium alone is not an indication for intervention; however, its presence is an exclusion criterion from most randomized studies regarding expectancy. See Chap. 25.

Hospitalization

There is **insufficient evidence** to compare hospital versus home management for PPROM.

A Cochrane review [21] including only two small trials shows no significant differences between home management and hospitalization in PPROM. Outpatient management can be offered only to reliable patients in these conditions: Absence of infection, an easy way to the hospital, evaluation in hospital before discharge, vertex presentation, vertical pocket of amniotic fluid >2 cm, recording of temperature and pulse every 6 hours, fetal movement count, twice-weekly nonstress tests (NSTs), and weekly ultrasound. **Only 18% of patients with PPROM meet these criteria**; thus **most of them are managed in the hospital**. A randomized controlled trial (RCT) reported 11% of women with PPROM managed at home delivered unexpectedly at other hospitals [22]. Women were **monitored for 48–72 hours** before randomization to hospitalization versus no hospitalization in the two RCTs on this subject [21]. **Compared to hospitalization,**

outpatient management was associated with similar incidences of perinatal mortality (relative risk [RR] 1.93, 95% confidence interval [CI] 0.19–20.05), serious neonatal morbidity, chorioamnionitis, GA at delivery, birth weight, and admission to neonatal intensive care unit, as well as cesarean delivery (CD) (RR 0.28, 95% CI 0.07–1.15). There was no information on serious maternal morbidity or mortality. Mothers randomized to care at home spent approximately 10 fewer days as inpatients and were more satisfied with their care. Furthermore, home care was associated with reduced costs [21]. **Evidence on the role of bed rest or activity restriction on latency and perinatal outcomes is poor; these interventions are not recommended** [23, 24].

Maternal surveillance

All women with PPROM should be **monitored for infection** by assessment of clinical parameters (e.g. fever, maternal/fetal tachycardia, uterine tenderness, and purulent vaginal discharge). A diagnosis of chorioamnionitis is usually made by the presence of two or more of these criteria. The value of the novel definition of "Triple I" is not well defined in the context of PPROM [25]. The presence of fever of unknown origin in the presence of PPROM is highly suspicious for chorioamnionitis. The higher the incidence of chorioamnionitis, the shorter the latency period. See Chap. 24.

There is no clear evidence to support the use of C-reactive protein (CRP) or procalcitonin (PCT) for the early diagnosis of chorioamnionitis. CRP shows better sensitivity (0.71; 95% CI 0.53–0.84) and better specificity (0.75; 95% CI 0.55–0.88) compared with PCT (sensitivity 0.50; 95% CI 0.28–0.73 and specificity 0.72; 95% CI 0.51–0.87) in diagnosing clinical or histologic chorioamnionitis. Maternal leukocytosis at admission is associated with higher adverse infant neurodevelopmental outcomes at 2 years of age in a study [26, 27].

Fetal surveillance (antepartum testing)

Fetal surveillance is based mainly on NST and biophysical profile score (BPS). Abnormalities of these tests can be somewhat predictive of fetal infection or umbilical cord compression related to oligohydramnios. There is **insufficient evidence to assess the optimal test or frequency of testing**. NST or BPS performed daily has poor sensitivity (39% and 25%, respectively) and similar predictive values for predicting infection [28]. **No improvement in perinatal outcome has been reported in one trial** [29]. Given the lower cost, **NST is usually suggested for daily** (e.g. continuously for the first 24 hours, then three times per day for about 30–60 minutes) **to twice-a-week fetal surveillance**. Monitoring may be more frequent with oligohydramnios, because it is associated with an increased risk of umbilical cord compression and shorter latency, with a preference for BPS as a backup if the NST is nonreassuring. One non-RCT study supports **continuous fetal monitoring** (CFM) in the management of PPROM [30], but there is insufficient evidence for a recommendation, and most practitioners and patients adopt **intermittent (e.g. 1 hour every 8–12 hours) fetal monitoring for inpatient management of PPROM**. Moreover, continuous prolonged fetal monitoring may not be practically feasible [31] and is associated with higher rates of intervention and CD compared with periodic NST, with no effect on perinatal mortality [32]. See previous paragraph on **Ultrasound**.

Amnioinfusion for prolonging latency after viability

Transabdominal amnioinfusion is associated with a **reduction in neonatal death** (RR 0.30), **neonatal sepsis** (RR 0.26), **pulmonary hypoplasia** (RR 0.22), **puerperal sepsis** (RR 0.20), and **less likelihood to deliver within 7 days** of membrane rupture (RR 0.18) [33]. These results are encouraging but limited by the sparse data and low methodological robustness [33]. Transcervical amnioinfusion to prevent NRFHT is discussed later, under the section "Delivery."

Corticosteroids for fetal/Neonatal maturation and benefit

A **single course of corticosteroids is recommended for pregnant women between $24^{0/7}$ weeks and $34^{0/7}$ weeks of gestation who are at risk of PTB** [34]. Antenatal corticosteroid therapy in cases of intact or ruptured membranes or PPROM is associated with **lower combined fetal and neonatal death** (RR 0.72, 95% CI 0.58–0.89), **respiratory distress syndrome (RDS)** (RR 0.66, 95% CI 0.56–0.77), **fewer intracranial hemorrhages** (RR 0.55, 95% CI 0.40–0.76), and **necrotizing enterocolitis (NEC)** (RR 0.50, 95% CI 0.32–0.78). There is no evidence that membrane status leads to differences in maternal death, chorioamnionitis, puerperal sepsis, or perinatal death [35]. A course of antenatal steroid therapy (**24 mg of betamethasone—12 mg IM every 24 hours**—or 24 mg of dexamethasone—6 mg IM every 12 hours) should not be repeated in patients with PPROM, since weekly courses do improve severe RDS, resulting in less composite neonatal morbidity among neonates delivered at 24–27 weeks, but are associated with shorter latency, higher risks of chorioamnionitis and neonatal sepsis, and no improvement in overall composite neonatal morbidity [34, 35].

A single **rescue course** of antenatal corticosteroids may be considered **if the antecedent treatment was given more than 2 weeks prior, the GA is less than $32^{6/7}$ weeks, and the woman is judged to be likely to give birth within the next week** [36, 37]. If the initial course was given at less than 26 weeks of gestation, a single repeated course may be considered if the delivery is expected within 1 week. A single rescue corticosteroid course in PPROM is not associated with an increased rate of neonatal sepsis [38], maternal chorioamnionitis, or neonatal morbidity (see also Chap. 18) [39].

Prior to 23 weeks' gestation there is a **paucity of data** on the efficacy of corticosteroids in women with PPROM; moreover, at low GAs there are only a few primitive alveoli on which the drug can exert an effect to improve lung tissue, but the beneficial effect could be related to the maturation of other organ function. A large study from the United States observed a reduction of death, intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), and NEC in neonates exposed to steroids at 23–25 weeks [40].

At 23 weeks it is reasonable to administer corticosteroids **if delivery in the next 7 days and active intensive care are anticipated** [21, 22, 41]. The decision should be always discussed.

A recent randomized study of steroids for fetal maturity including 620 cases of late PPROM at **34 and 36 + 6 weeks** showed a reduction of respiratory complications (RR 0.67, % CI 0.53–0.84) and an increase of hypoglycemia (RR 1.6, 95% CI 1.37–1.87). PPROM data were not analyzed separately (See Chap. 21) [42].

Antibiotics for prolongation of latency and fetal/Neonatal benefit

Administration of broad-spectrum antibiotics is indicated, as it prolongs pregnancy and reduces maternal and neonatal infections and GA-dependent morbidity. A systematic review of placebo-controlled randomized trials involving over 6800 women evaluated the use of antibiotics following PPROM before 37 weeks of

gestation. Compared with placebo, antibiotics for women with PPROM are associated with short-term **benefits** for both women and neonates [43, 44], in particular:

- Maternal: 34% less **chorioamnionitis**
- Fetal/Neonatal:
  - 29% reduction in **PTB within 48 hours**
  - 21% reduction in **PTB within 7 days**
  - 33% reduction in **neonatal infection**
  - 21% reduction in positive neonatal **blood culture**
  - 17% reduction in use of **surfactant**
  - 12% reduction in use of **oxygen therapy**
  - 19% reduction in **abnormal cerebral ultrasound scans** (including IVH) prior to discharge from hospital
  - 5 fewer days in neonatal **intensive care unit** (5.05 [–9.77, –0.33])
  - 10% **prolongation of pregnancy**
  - Decreasing trend in **perinatal mortality** (RR 0.93, 95% CI 0.76–1.14)
  - Decreased rates of **RDS and NEC** with ampicillin and erythromycin treatment (see later) [45]

A meta-analysis limited to PPROM before 34 weeks showed similar results [46]. The ORACLE study evaluated children's health at **7 years** and found no difference in any functional impairment after prescription of erythromycin, with or without co-amoxiclav, compared with those born to mothers who received no erythromycin or after prescription of co-amoxiclav, with or without erythromycin, compared with those born to mothers who received no co-amoxiclav. **Long-term adverse effects** of antepartum prophylactic antibiotics for PPROM have **not been observed** in children followed to age 7 years [47]. This finding is in contrast to the observation from the same authors that in patients with spontaneous preterm labor (PTL) and intact membranes, the rate of cerebral palsy was increased in children with in utero exposure to antibiotics [48]. These results suggest that further caution should be used when considering the routine treatment of women with antibiotics if there is uncertainty about the diagnosis of PROM.

Benefits in short-term outcomes (prolongation of pregnancy, infection, need for respiratory therapy, less abnormal cerebral ultrasound before discharge from hospital, etc.) should be balanced against a lack of evidence of benefit for other outcomes, especially long-term outcomes, such as the effect of in utero exposure to antibiotics on the child's gut microbiota and on maturation from the infant to the adult microbiome.

Antibiotic type

Multiple regimens have demonstrated benefit, but there is insufficient evidence on the optimal antibiotic type (and regimen) in women with PPROM. Frequently used antibiotics are penicillins or macrolides. Antibiotic regimens may consist of an initial parenteral phase, followed by an oral phase. A **7-day course** of therapy of latency antibiotics with a combination of intravenous **ampicillin** and **erythromycin** followed by oral **amoxicillin** and **erythromycin** is recommended during expectant management of women with PPROM [5, 45, 47–50]. In patients allergic to beta-lactam antibiotics, macrolide antibiotics should be used alone [43, 45, 46, 51, 52] or another agent effective against GBS can be considered. Since there are no evidence-based alternatives, the choice of antibiotic type should be based on the severity of the reported allergic reaction and antibiotic susceptibility results of the GBS culture, if available [5].

Azithromycin can be used instead of erythromycin [5, 53]. A retrospective comparison between azithromycin and erythromycin in addition to ampicillin in PPROM showed no differences in latency or maternal/fetal outcomes [54]. Another retrospective cohort study comparing erythromycin and azithromycin similarly found no difference in latency to delivery [55]. A cost-effectiveness analysis demonstrated cost benefits for azithromycin [56]. A prospective cohort study demonstrated that azithromycin instead of erythromycin was associated with lower rates and decreased risk of clinical chorioamnionitis, neonatal sepsis, and postpartum endometritis with no difference in pregnancy latency [57].

Azithromycin can be administrated as a **single oral dose of 1 g** [55, 57], even if there are several commonly used doses and there is no standard dosing regimen. A retrospective cohort study comparing different dosing regimens of azithromycin versus erythromycin in PPROM reported no difference in latency to delivery, incidence of chorioamnionitis, or neonatal outcomes. An extended course of azithromycin beyond the single-day dosing suggested by some authors [53] is considered insufficient by others to maintain an inhibitory concentration in the amniotic fluid [58, 59].

The mechanism of action of single antibiotic drugs should also be considered. Macrolides diffuse slowly in the tissues and act mainly on gram-positive microorganisms and *Chlamydia*; moreover, the microorganism disruption in the phagocyte prevents prostaglandin release and the consequent inflammatory cascade activation. Compared with erythromycin, azithromycin has an increased pharmacokinetic distribution, a longer half-life, and a slower elimination rate.

Azithromycin is easy to administer, has decreased dosing frequency, fewer side effects, and decreased cost [60, 61].

Cephalosporins have few side effects and a broad-spectrum antibacterial effect [62]. A randomized trial comparing cefazolin plus macrolide (erythromycin or clarithromycin) versus cefazolin alone in PPROM showed no difference among the three antibiotic regimens in terms of newborn outcome [49]. In a large trial, amoxicillin/clavulanate was associated with an increased risk of neonatal NEC, although there is no consistent trend toward a positive or negative effect of broad-spectrum antibiotics for NEC in the literature [45, 47]. According to a Cochrane review, **co-amoxiclav should be avoided** in women at risk of PTB due to an increased risk of neonatal NEC (RR 4.72, 95% CI 1.57–14.23). Possible antibiotic regimens are listed in Table 20.5. Our preference is ampicillin

TABLE 20.5: Possible Antibiotic Regimens

Ref.	Antibiotic	Dose
[55, 57]	**Ampicillin** **Azithromycin** **Amoxicillin**	**2 g IV, then 1 g IV every 6 hours and** **1000 mg PO single dose; or 500 mg PO single dose every 24 hours for 3 days followed by** **500 mg PO every 8 hours for 4 days**
[54]	Ampicillin Erythromycin Amoxicillin Erythromycin	2 g IV every 6 hours and 250 mg IV every 6 hours for 48 hours followed by 250 mg PO every 8 hours and 333 mg PO every 8 hours for 5 days
[52]	Erythromycin	250 mg PO every 6 hours for a maximum of 10 days
[49]	Cefazolin Erythromycin	1 g IV every 6 hours and 250 mg PO every 6 hours for 7 days

Source: Adapted from Refs. [47–62].

2 g IV, then 1 g every 6 hours and azithromycin 1000 mg PO single dose, or 500 mg PO single dose every 24 hours for 3 days, followed by amoxicillin 500 mg PO every 8 hours for 4 days.

Women with PPROM should be screened for GBS [5]. Patients with PPROM in whom intrapartum GBS prophylaxis is indicated should receive intrapartum antibiotic prophylaxis regardless of previous antibiotic treatments [63]. See Chap. 39 of *Maternal-Fetal Evidence Based Guidelines*.

Detection of specific cervicovaginal pathogens should be appropriately treated (see Chaps. 34–38 of *Maternal-Fetal Evidence Based Guidelines*) even if routine cervicovaginal swab analysis, except for GBS, is not indicated. Women with PPROM screened for urinary tract infections should be treated with appropriate antibiotics if positive.

Clinical chorioamnionitis requires therapeutic antibiotics (see Chap. 24). For example, ampicillin (2 g IV every 6 hours) or cefazolin (1 g IV every 6 hours), plus gentamicin (3–5 mg/kg single dose IV every 24 hours). In case of CD, an additional single dose of antibiotic therapy is suggested (or more doses based on the clinical course), and further prophylactic antibiotics for anaerobe coverage is indicated (clindamycin 900 mg IV or metronidazole 500 mg IV) (see also Chap. 14). Intrapartum GBS prophylaxis should be given until culture results are available and to carriers. There are insufficient data to assess the need for this intervention in women with PPROM in whom GBS is sensitive to antibiotics—like ampicillin—already given for PPROM. The suggested regimen is penicillin (5 million units IV and then 2.5 million units every 4 hours) or (if unavailable) ampicillin (2 g IV, then 1 g every 4 hours).

Tocolysis for prolongation of latency and fetal/Neonatal benefit

In a Cochrane review, tocolysis was associated with **longer latency** (mean difference [MD] 73.12 hours; 95% CI 20.21–126.03) and **fewer births within 48 hours** (average RR 0.55; 95% CI 0.32–0.95). However, tocolysis was associated with **increased incidence of 5-minute Apgar of less than 7** (RR 6.05; 95% CI 1.65–22.23) and **increased need for ventilation of the neonate** (RR 2.46; 95% CI 1.14–5.34), while it was not associated with a significant effect on perinatal mortality. For women with PPROM before 34 weeks, there was a **significantly increased risk of chorioamnionitis**; neonatal outcomes were not significantly different. Therefore, **there is insufficient evidence to support tocolytic therapy for women with PPROM**, and in fact there is **evidence to recommend against this intervention, as there was an increase in maternal chorioamnionitis without significant benefits to the infant**. However, the included studies did not consistently administer antibiotics and corticosteroids, both of which are now considered standard of care [64]. A recent large retrospective study with 90% use of antibiotic and corticosteroids shows no differences in the prolongation of pregnancy and histologic chorioamnionitis, confirming no neonatal benefits of this practice [65].

Long-term tocolysis >48 hours is associated with a nonsignificant prolongation of pregnancy and no differences in neonatal complications, but increased rate of chorioamnionitis and postpartum endometritis. It **should** therefore **be avoided** [66]. In agreement, a recent trial that was stopped before ending the recruitment did not show a beneficial effect [67].

Magnesium sulfate for fetal neuroprotection

A protective role of magnesium sulfate against the risk of cerebral palsy in preterm infants born before 34 weeks has been demonstrated by randomized trials (cumulative absolute risk reduction of 1.7) [68–72]. Results in PPROM cases were not reported separately in any study, but constituted almost the 90% of the population in the largest study [72]. In the absence of evidence for an optimal dose of magnesium sulfate, scientific societies suggested adopting the minimum dosage used in the published trials and when delivery appears imminent at <34 weeks [73, 74]. Further, a recent guideline by the Society of Obstetricians and Gynecologists of Canada (SOGC) stated that maintenance infusion is not necessarily required and that administration of magnesium sulfate should not influence decisions about neonatal resuscitation [75]. We administer magnesium sulfate 2–4 g load over 20 minutes, followed by 1 g/hour predelivery (see Chap. 19).

Progesterone

Progesterone (17P) or rectal progesterone is **not associated with increased latency**, and administration should not be commenced once a patient has experienced PPROM [76]. Vaginal progesterone administration could increase the risk of ascending infection and should be discontinued in the absence of evidence of benefit [77].

Vitamin supplementation

There is **insufficient evidence** to assess the effect of vitamin supplementation in women with PPROM [78]. Vitamin D and vitamin C may have potential benefits, but it has not been proved yet [79]. In one small trial, compared with placebo, vitamin C 500 mg and vitamin E 400 IU daily in women with PPROM at 26–34 weeks were associated with 7-day prolongation in latency, but no other effects on maternal or neonatal morbidity and mortality [80]. In a recent RCT, the use of vitamins C 1000 mg and E 400 IU in women with PPROM was associated with a longer latency period before delivery. Adverse neonatal and maternal outcomes, which are often associated with prolonged latency periods, were similar between groups [81]. Deficiency in vitamin D has been associated with several adverse pregnancy outcomes, including PTB [82, 83]. In a study of asymptomatic women who developed PPROM later in pregnancy, Vitamin D-binding protein (VDBP) was significantly elevated. VDBP concentrations increase in pregnancy and thus influence the biologically active form of vitamin D, free vitamin D. In this research VDBP and other proteins are responsible for some processes underlying membrane rupture [84].

Cerclage removal

PPROM occurs in about 38% of women with cerclage in place [85]. The benefit of a retained cerclage to prolong latency and decrease complications related to prematurity has to be weighed against the risk of adverse maternal and neonatal outcomes [86, 87]. **Leaving the cerclage in place >24 hours is associated with a longer latency >48 hours** (94% vs. 51%; odds ratio [OR] 16.1, 95% CI 3.7–71.3), but also **significantly increased maternal and fetal/neonatal infection risks, such as chorioamnionitis** (43% vs. 20%; OR 2.9, 95% CI 1.7–5.0) **and neonatal mortality from sepsis** (12% vs. 1%; OR 13.2, 95% CI 1.6–108.3) and **a trend for more neonatal sepsis** (13% vs. 6%; OR 2.4, 95% CI 0.9-6.0) and **neonatal mortality** (17% vs. 10%; OR 2.0, 95% CI 0.9–4.3) [37, 38, 85]. A recent small, randomized trial, stopped after an interim analysis, showed no differences between the two managements in terms of latency, infection, and composite neonatal outcomes. However, there was a **numerical trend in the direction of less infectious morbidity in case of immediate cerclage removal** [88]. In a recent meta-analysis, cerclage retention after PPROM did not significantly prolong the gestational latency period, but

it increased the rates of delivery after the first 48 hours. It did not significantly increase the rates of neonatal sepsis or neonatal death. Maternal chorioamnionitis was more prevalent among women with cerclage retention (OR 1.78) [89]. Therefore, **in most cases, cerclage should be removed in women upon diagnosis of PPROM, especially if corticosteroids have been previously administered and if GA is >32 weeks**.

Delivery

Timing

Once PPROM occurs, **the options for management include delivery versus expectant management** until later in pregnancy. In the absence of **clear indications for expeditious delivery, such as nonreassuring fetal status, clinical chorioamnionitis, abruptio placentae, or cord prolapse**, the optimal GA for delivery is less clear. A **longer latency is associated with a higher rate of chorioamnionitis, and a shorter latency with higher risks related to prematurity**.

A recent meta-analysis of 12 RCTs (3617 women) concluded that before 37 weeks' gestation, an expectant management with careful monitoring was associated with better outcomes for the mother and baby. GAs at birth were lower in those randomized to early birth than those randomized to expectant management (MD −0.48 weeks, 95% CI −0.57 to −0.39). In particular, no differences were observed between early birth and expectant management in neonatal sepsis (RR 0.93, 95% CI 0.66–1.30, 12 trials), proven neonatal infection with positive blood culture (RR 1.24, 95% CI 0.70–2.21), overall perinatal mortality (RR 1.76, 95% CI 0.89–3.50), or intrauterine deaths (RR 0.45, 95% CI 0.13–1.57). However, early birth was associated with a higher incidence of RDS (RR 1.26, 95% CI 1.05–1.53), a higher rate of neonatal death (RR 2.55, 95% CI 1.17–5.56), need for ventilation (RR 1.27, 95% CI 1.02–1.58), and admission to neonatal intensive care (RR 1.16, 95% CI 1.08–1.24, 4 trials). In assessing maternal outcomes, early birth was associated with a decreased rate of chorioamnionitis (RR 0.50, 95% CI 0.26–0.95), an increased rate of caesarean section (RR 1.26, 95% CI 1.11–1.44), endometritis (RR 1.61, 95% CI 1.00–2.59), and decreased total length of hospitalization (MD −1.75 days, 95% CI −2.45 to −1.05). Prophylactic antibiotics were shown to be effective in reducing maternal infections in women randomized to expectant management [90].

Delivery before 34 weeks is associated with severe neonatal complications, including death, and it is traditionally considered the cutoff age for expectancy. It is highly improbable that future RCTs will include these patients, although evidence is not strong, and, unfortunately, many old trials did not use steroids for fetal maturity or antibiotics [91–94]. A recent RCT was prematurely stopped for difficulty at recruitment [95]. **Women with PPROM before $34^{0/7}$ weeks should be managed expectantly if no maternal or fetal contraindications exist** [5].

Evidence on late PPROM (34–36 + 6 weeks) is based on more recent studies. An individual participant data meta-analysis of trials of PPROM from 34 + 0 to 36 + 6 weeks [96] showed that the two approaches resulted in similar rates of composite adverse neonatal outcome (neonatal sepsis, NEC, RDS, stillbirth, or neonatal death; RR 1.20, 95% CI 0.94–1.55). Concerning maternal morbidity, immediate delivery reduced the risk of antepartum hemorrhage (RR 0.57, 95% CI 0.34–0.95) and chorioamnionitis (RR 0.21, 95% CI 0.13–0.35), but slightly increased the risk of CD (RR 1.26, 95% CI 1.08–1.47). The rate of endometritis and the length of hospitalization (3.45 versus 3.39 days) were not statistically different between groups. Immediate delivery did reduce the risk of neonatal sepsis in the subgroup of patients with a positive vaginal culture at the time of randomization [96, 97].

At $34^{0/7}$–$36^{6/7}$ weeks either delivery or a cautious expectant management policy should be offered. Parent opinion, eventual vaginal colonization status, and GA at presentation after 34 weeks should be considered to balance the risk and benefit of conservative management (see Chap. 21).

Amnioinfusion for preventing NRFHT

There is **insufficient evidence** to assess the effect of routine amnioinfusion in all women with PPROM for prophylaxis either before labor or during labor. Compared with no amnioinfusion, **transcervical amnioinfusion** (warmed saline at 10 mL/min for 1 hour, then 3 mL/min—total volume infused mean 1160 mL) at the time of labor for women with PPROM at 26–35 weeks is associated with statistically similar but more favorable incidences of CD, low Apgar scores, and neonatal death in one small trial. In the amnioinfusion group, the number of severe fetal heart rate decelerations per hour during the first stage of labor was reduced by just about one in this small trial. Fetal umbilical artery pH at delivery was higher. These outcomes are consistent with the benefits found for amnioinfusion for cord compression. Transcervical amnioinfusion also reduced persistent variable decelerations during labor (RR 0.52) in a trial with 86 participants [98].

In conclusion, to date, **routine intrapartum amnioinfusion cannot be recommended for all women with PPROM** given the limited data (see Chap. 11).

Mode and site of delivery

Mode of delivery should not be chosen only on the basis of PPROM occurrence. Malpresentation is more common with PTB, being indirectly related to weeks of GA (see Chap. 26). Early preterm delivery should occur in a well-equipped facility, managed by skilled clinicians, providing all the necessary support to the mother and fetus/neonate born preterm. **Transferring women** at risk of very PTB to perinatal referral centers for delivery **decreases the neonatal mortality and morbidity rate considerably** [99, 100]. Predicting the time of delivery in PPROM is often impossible.

Anesthesia

No specific precautions.

Postpartum

See Chaps. 18 and 31. Women with PPROM are at high risk of recurrence in subsequent pregnancies, with an association between GA at the time of PPROM, latency period, and interval between pregnancies. Patients with a history of cervical insufficiency and fetal loss/miscarriage should be considered at increased risk of mid-trimester PPROM in the following pregnancy. See "Prevention" earlier.

Special considerations must be given when PPROM occurs before fetal viability, after invasive procedures, and in twin gestation.

PPROM <23 weeks

Definition

PROM <23 weeks, or "previable PPROM" (an arbitrary definition that varies among investigators and from year to year because of advances in neonatal intensive care) is a relevant and unique nosological entity because of its significant association with fetal and neonatal morbidity and mortality.

Incidence
The incidence is about 0.6% of pregnancies.

Etiology/Basic pathophysiology
There are two different categories: Spontaneous and iatrogenic. **Risk factors for spontaneous PPROM <23 weeks are similar to those for PTL and for PPROM later in pregnancy** (see Table 20.2 and Table 18.1 in Chap. 18). The major risk factors are a prior history of PPROM or PTB and intraamniotic infection. Fluid leakage or PPROM occurs in about 1% of second-trimester amniocenteses [88], 3%–5% of diagnostic fetoscopies, and 30%–40% of fetal surgery procedures [101].

Complications
Incidences of most complications are **inversely proportional to GA at PPROM, latency, residual amniotic fluid volume, and GA at delivery**.

Fetal/Neonatal

Neonatal death
Published data on **neonatal survival after early PPROM varies widely (20%–68%)** [102–106]. The mortality rates may be underestimated by selection bias due to the high rate of elective termination prior to viability and consequent inclusion of patients who chose to continue pregnancy or who have experienced initial latency. In 2012 an interesting study compared perinatal outcomes of two settings with different rates of elective termination of pregnancy (TOP) (assuming that patients with a poorer prognosis opted more frequently for TOP). Perinatal outcomes (mean GA at delivery, latency, birth weight, and survival) were better in the centers with a lower TOP rate; in particular, survival among live births was 95.8% in the center with lower TOP and 65% in the center with higher TOP [105]. A retrospective study on 58 women with prolonged PPROM at less than 24 weeks reported a survival rate in newborns of 90%, although pulmonary morbidities were common [98, 106]. Recent reports on perinatal survival in PROM <24 weeks involved patients routinely managed with antibiotics, antenatal steroids, postnatal surfactant, and high-frequency ventilation. A comparison between PPROM less than 25.0 weeks and 25.0–31.9 weeks showed a higher rate of severe composite neonatal morbidity and composite severe childhood morbidity in case of early PPROM. Neonatal death occurred in nearly 17% of early PPROM. Neonatal mortality is comparable to that in preterm deliveries matched for GA without PPROM.

Chorioamnionitis
Antenatal infection is the major complication limiting the latency interval. **If clinical infection occurs at any time during the latency period, delivery is indicated**. Chorioamnionitis complicates about 40% of cases of mid-trimester PPROM [107]. The occurrence of chorioamnionitis is higher early in the latency period; **more than 50% of cases occur within the first 7 days after rupture**, with the maximum clinical occurrence on 2–5 days [108]. After the first week of latency, the incidence falls, suggesting that subclinical uterine or chorioamniotic infections that weaken membranes and cause rupture were probably present before, whereas bacteria migration is a less important component. The risk of chorioamnionitis is inversely proportional to residual amniotic fluid volume [109].

Placental abruption
Abruptio placentae is more frequent in pregnancies with mid-trimester PPROM, occurring in up to **44%** of cases compared with 0.8% of the general obstetric population [101]. The risk is highest with lower GA at PPROM and with vaginal bleeding occurring prior to or after membrane rupture [110].

Cord prolapse
The incidence of prolapse is about **2%**. The risk is higher (11% in one study) in the setting of nonvertex fetal presentations [111].

Fetal death
Fetal demise is primarily related to abruption, cord prolapse and compression, or infection. The average risk of fetal death after mid-trimester PPROM is about **10%**, and it is difficult to determine which pregnancies will reach viability [112].

Pulmonary hypoplasia
Pulmonary hypoplasia (PH) is characterized by a decrease in the number of lung cells, airways, and alveoli, mainly due in the context of PPROM to alterations of normal amniotic fluid pressure and egress of lung fluid during the canalicular stage of lung development (ending at nearly 24 weeks) (Figure 20.2). The gold standard for the diagnosis of PH is lung weight by autopsy. The incidence of PH resulting from mid-trimester PPROM varies from **13% to 28%** [113, 114]. The mortality rate in neonates with this condition is 50%–95% [115]. The main independent reported risk factors for development of PH are as follows: (1) early GA at membrane rupture [114, 116]—a risk of 50%–60% was reported when PPROM occurs at 20 weeks or less—and (2) low residual amniotic fluid volume [117]. PH is more common among pregnancies with oligohydramnios (defined by maximum vertical pocket <2 or amniotic fetal index [AFI] <5), after controlling for GA at rupture. Incidences of PH with severe, moderate, and absent-to-mild oligohydramnios are 43%, 21%, and 7%, respectively [118].

Candidate tests to diagnose PH prenatally are the following: Ultrasound measurement of amniotic fluid, fetal breathing movements, fetal chest circumference, lung length, lung volume, fetal lung area to head circumference ratio (LHR), Doppler studies of pulmonary vessels, and O_2 tests. In general, the predictive accuracy is poor and may be improved by combining tests [116, 119, 120].

Fetal compression syndrome
In early PPROM, asymmetric intrauterine pressure and restriction in fetal movement can lead to limb position deformities and craniofacial defects of variable severity, originally described in the context of renal agenesis. The mean frequency of skeletal deformities is **7%**. Prolonged latency and severity of oligohydramnios independently increase the risk of skeletal abnormalities and act synergistically [121]. The GA at PPROM is not a significant determinant due to the progressive and continuous development of the axial skeleton.

Increased likelihood of skeletal deformities observed among infants diagnosed with PH suggests that the two disorders share common risk factors. Surgical correction is not generally required, as they resolve with postnatal growth and physiotherapy.

Other morbidities
Other neonatal morbidities are similar to that in PTB and are related to GA at PPROM. These include **RDS, bronchopulmonary dysplasia (BPD), IVH, NEC, sepsis, and retinopathy of prematurity**. The incidence of neonatal IVH and cystic PVL increases in cases complicated by clinical chorioamnionitis [122]. Since mid-trimester PPROM is associated with early delivery and infections, it constitutes a potential risk factor for long-term neurologic morbidities. There may be a higher risk of PVL in infants

Gestational Age (weeks)	Stage of lung development	Description
4 to 6	EMBRIONIC	Lung bud arises
7 to 16	PSEUDOGLANDULAR	Non respiratory bronchi and bronchioles develop
17 to 24	CANALICULAR	First gas exchanging acini and pulmonary capillaries are forming
25 to 37	TERMINAL SAC	Subsaccules and alveoli develop with extensive capillary invasion and expansion of the alveolar blood barrier surface area
38 to age 3 years	ALVEOLAR	Subsaccules become alveoli

FIGURE 20.2 Phases of lung development.

born after prolonged PPROM compared with other types of prematurity. Prolonged latency in mid-trimester PROM patients is not associated with an increasing frequency of abnormal neonatal cranial ultrasound examination [108].

Long-term morbidities

About 63%–84% of survivors after mid-trimester PPROM will be neurologically intact [113]. **Cerebral palsy** rate in a group of 275 pregnancies complicated by early PPROM was **9.8%** [106].

Maternal

Cesarean delivery

Higher CD rates are mainly due to common fetal heart rate abnormalities (related to oligohydramnios and chorioamnionitis), malpresentation, and abruptio. A traditional uterine incision may be required to reduce fetal trauma at early GA (oligohydramnios, fetal malpresentation, and lower uterine segment characteristics constitute risk factors). In general, **CD should be avoided before 22 weeks**, if possible, and neonates should receive palliative care. Because most newborns at 24–25 weeks of gestation will survive if resuscitated, efforts to prolong pregnancy, intrapartum interventions for fetal benefit, and neonatal resuscitation should generally be offered, if appropriate. Special consideration is needed if the newborn is at 22–23 weeks of gestation: Management decisions will need to be made based on whether the fetus is considered potentially viable on individual clinical circumstances and whether the family desires aggressive measures to improve the potential for newborn survival after birth. In general, those born at 23 weeks of gestation should be considered potentially viable, as survival with resuscitation is 26%–28% or more. Those considered nonviable at 22–23 weeks of gestation can be treated similarly to pregnancies at 20–21 weeks of gestation, while those considered potentially viable should be treated consistent with similar pregnancies at 24–25 weeks of gestation. If feasible, delivery of potentially viable infants should be undertaken in settings in which resources are available to care for extremely small and immature infants. This approach has the potential to increase the opportunity for survival and reduce morbidities among survivors (See Chap. 18) [41].

Retained placenta

The risk of undergoing either uterine exploration or curettage is **9%–18%** and more likely if rupture occurs prior to 20 weeks of gestation.

Postpartum endometritis

This condition occurs in about **13%** of cases. Postpartum maternal **sepsis** (about 0.8%) and **death** (about 1/1000) are uncommon. The risk of maternal infection is inversely proportional to the latency period.

Management

Counseling

Parents should be counseled regarding the prognosis, complications, and management of PPROM <23 weeks. The **options** are **expectant management** or **delivery**. The impact of immediate delivery on neonatal outcome and the potential benefits and risks of conservative management should be reviewed. PPROM related to genetic amniocentesis is associated with favorable outcomes even with expectant management (91%–99% perinatal survival), which is very different than the prognosis with spontaneous PPROM <23 weeks.

Incidences of most complications are inversely proportional to **GA at PPROM, latency, residual amniotic fluid volume**, and **GA at delivery**.

The **latency** period between membrane rupture and delivery is critical in determining perinatal outcome.

Latency is indirectly correlated with GA at PPROM (Table 20.4) [12]. While the mean latency is about 7 days, the median latency may be up to about 10–21 days. **Up to 14%** of women with mid-trimester PPROM **stop amniotic fluid loss**, presumably due to resealing of membranes. This subgroup of cases has similar outcomes to uncomplicated pregnancies. In 10%–20% of patients, amniotic fluid loss continues, but a partial reaccumulation during expectant management is observed [114].

Oligohydramnios (AFI <5 or mean vertical pocket [MVP] <2 cm) on admission, during the latency period, or at the last ultrasonographic examination is **associated with shorter latency and higher occurrences of PH, chorioamnionitis, and perinatal mortality** [123]. Conversely, adequate residual amniotic fluid volume identifies cases with elevated odds of perinatal survival (85%–93%) and better long-term neurologic outcomes [123].

In a retrospective cohort of 92 cases of PPROM under 24 weeks, the overall neonatal survival rate at discharge was 85%; the survival rate was lower and the developmental delay more frequent in patients with persistent oligohydramnios compared to those with normal amniotic fluid volume [124].

Workup

See earlier.

Therapy

See Figure 20.1.

Delivery in previable PPROM is **indicated in** the presence of:

- **Intrauterine death**
- Spontaneous onset of **labor**
- Evidence of **maternal and/or or fetal infections**
- Any other **obstetric or medical condition necessitating delivery** (e.g. abruptio placentae, cord prolapse, and preeclampsia)
- **Pregnancy termination request**

Delivery (termination) can be carried out usually by induction or by dilatation and extraction (D&X) by experienced operators, with no trials comparing these two modalities.

For management of women who elect **expectant management**, recent data [125, 126] give a direction, taking into account that deciding upon a threshold of viability is challenging.

Tocolysis

Tocolytic therapy in previable PROM is **not recommended** [125, 126]. In summary, prophylactic tocolysis may be associated with a longer latency but an increased risk of chorioamnionitis, without significant maternal or neonatal improved outcomes.

Antenatal corticosteroids

Antenatal corticosteroids are **not recommended before 22 weeks**. The latest joint workshop on periviable management by the American Academy of Pediatrics and ACOG stated that a single course offered in the mid-22nd week is **reasonable** if delivery at 23 weeks is anticipated and the family agrees on aggressive neonatal intervention after counseling [41]. NICE Guidelines 2019 [125] stated that **it may be considered from $23^{0/7}$ weeks after discussion of the potential benefits and risks**. If the pregnancy is not delivered within 7 days, it is not recommended to offer routine repeat courses, but GA should be taken into account, along with the interval since the end of the last course and the likelihood of delivery within 48 hours.

Magnesium sulfate neuroprotection

Magnesium sulfate for neuroprotection **is not recommended before 23 weeks** [41, 125, 126]. **Between 23+0 and 23+6 weeks, neuroprotection should be discussed** with the woman and her family **in the context of her individual circumstances** [125].

GBS culture and prophylaxis

In a previable PROM, a rectovaginal GBS culture should be obtained. Antibiotics for GBS carrier or unknown carrier status should be started from **23 weeks**.

Antibiotics

In 2016, ACOG [126] stated that most studies on antibiotic prophylaxis with preterm PROM enrolled patients only after $24^{0/7}$ weeks of gestation; thus there are no adequate data to assess the risks and benefits of such treatment at earlier GAs. However, **it is reasonable to offer a course of antibiotics for pregnancy prolongation to patients with previable PROM** (usually ≥20 weeks) **who choose expectant management** [41].

Transabdominal amnioinfusion before viability

Serial amnioinfusion in the second trimester is a procedure used in an attempt to increase amniotic fluid, reduce PH, prolong pregnancy and improve neonatal outcomes. Data are mostly derived from prospective nonrandomized or retrospective studies. Three meta-analyses have been published, two of which report an improvement in mortality after amnioinfusion [127, 128], while a Cochrane review on the argument [129] did not identify any randomized studies focused on PROM management before 26 weeks.

Regarding the use of this clinical practice in nonviability contexts, a multicenter randomized controlled study (PPROMEXIL III) concluded that **this procedure does not lead to a reduction in perinatal mortality** [130]. Long-term follow-up of these small cohorts at 5 years of age revealed that **amnioinfusion did not improve neurodevelopmental outcomes**; of note, 71% of survivors did not report neurodevelopmental delay [131]. A European randomized multicenter study (AMIPROM) is ongoing. Transabdominal amnioinfusion can be considered in a research context.

Outpatient-inpatient management and timing of hospitalization (see Figure. 20.1)

In women desiring expectant management with PPROM <23 weeks, **avoid vaginal examination until labor or delivery**. During expectant management, monitor on an outpatient basis for the onset of infectious complications, observing temperature, maternal or fetal tachycardia, uterine contractions or tenderness, or purulent vaginal discharge. As an outpatient, instruct to avoid intercourse, check temperature, and refer to hospital for vaginal bleeding and contractions. **At 23–24 weeks, consider (re)admission to the hospital**, taking into account whether or not families and clinicians agree on aggressive neonatal intervention after counseling.

PPROM following invasive procedures (iatrogenic PPROM) and strategies to repair

Iatrogenic PPROM (iPPROM) and spontaneous PPROM have different characteristics. In iPPROM, the hole, which subsequently fails to close, is created by the instrument (needle or fetoscope, as an example).

Although the introduction of increasingly sophisticated screening techniques for chromosomal abnormalities led to less invasive testing based on maternal age, advancing skills in ultrasound screening have meant that there is an increased need for invasive prenatal testing via chorionic villus sampling in the first trimester or amniocentesis in the second trimester [132]. A risk of approximately 1%–3% for subsequent amniotic fluid leakage

is reported [132]. Subclinical leakage after amniocentesis may occur more frequently than initially thought [133]. In these cases, outcomes are better than after spontaneous PPROM, and reaccumulation of normal amniotic fluid volume is more probable [134].

Parameters that have been suggested to affect iPPROM rates are the diameter of the surgical instrument and the number of entries to the uterine cavity [135]. Other possible risk factors are duration and difficulty of the procedure, operator experience, membrane friction due to instrument manipulation, type of anesthesia, GA at intervention, number of interventions, and placental location. In one review the maximum diameter of the instrument predicted iPPROM rate, GA at birth, and fetal survival [136].

In a retrospective study of 1092 cases of Twin-to-twin transfusion syndrome (TTTS) operated by fetal laser coagulation between 2000 and 2016 [137], both survival and PPROM rates rose; in particular, PPROM <32 weeks increased from 15% to 40% along with an overall improvement of perinatal outcomes: Dual survival rose from 42% to 66%, whereas dual losses dropped twofold, from 19% to 9%. GA at surgery at <17 weeks was a significant risk factor for PPROM, with an additional risk of 10% within the first week of surgery. Although early PPROM at <20 weeks carried a 56% risk of miscarriage, the occurrence of PPROM at >20 weeks did not affect survival, despite an increase in PTB at <32 weeks. Surgical technique is probably the most prominent factor. Substantial changes were introduced throughout the study period: First, a gradual improvement in the selectivity of the procedure between 2000 and 2008 and secondly, the introduction of the "Solomon" technique, which consists of a continuous chorionic coagulation along the vascular equator. Recent reports [138] stated that the **Solomon technique could improve perinatal survival**, but there are concerns that the amount of coagulation required to complete the procedure could lead to significant placental damage, **increasing the occurrence of PPROM and preterm birth**.

Several techniques have been developed in an **attempt to artificially reseal the fetal membranes** and prevent leakage of amniotic fluid. These include intraamniotic injection of platelets and cryoprecipitate (amniopatch), sealing the cervical canal [139]. Compared to spontaneous PPROM, iPPROM is not only a different entity etiologically but also has a better response to therapeutic measures. One report demonstrated successful membrane sealing for persistent oligohydramnios after amniocentesis and fetoscopy in seven women, using intraamniotic injection of platelets and cryoprecipitate through a 22-gauge needle [140].

According to a review of cases of iPPROM, amniopatch effectively seals the fetal membranes in over two-thirds of cases [141]. A retrospective analysis of 24 amniopatch procedures performed for PPROM after a needle-based procedure or after fetoscopic intervention reported a success rate of 58% [142].

A Cochrane review of 2016 [143] included two studies (involving 141 women, with data from 124 women), both considered being at high risk of bias. Meta-analysis was not possible because the included studies examined different interventions (both in comparison with standard care) and reported on few, but different, outcomes. One study compared cervical adapter (mechanical sealing), and the other study examined an immunologic membrane sealant. Neither of the included studies reported on this review's primary outcome of interest—perinatal mortality. Similarly, data were not reported for the majority of this review's secondary infant and maternal outcomes. Concerning **cervical adapter (mechanical sealing) versus standard care (one study, data from 35 participants)**, there was no clear difference between the mechanical sealing group and the standard care control in relation to the incidence of **neonatal sepsis** (RR 1.19, 95% CI 0.28–5.09 [*very low-quality evidence*]) or **chorioamnionitis** (RR 1.19, 95% CI 0.28–5.09 [*very low-quality evidence*]). Concerning **oral immunologic membrane sealant versus standard care (one study, data from 94 participants)**, no data were available for perinatal mortality (this review's primary outcome) or for the majority of this review's infant and maternal secondary outcomes. Compared to standard care, the immunologic membrane sealant was associated with a reduction in **PTB less than 37 weeks** (RR 0.48, 95% CI 0.34–0.68 [*very low-quality evidence*]) and a reduction in **neonatal death** (RR 0.38, 95% CI 0.19–0.75 [*very low-quality evidence*]). However, there was no clear difference between groups in terms of **neonatal sepsis** (RR 0.64, 95% CI 0.28–1.46 [*very low-quality evidence*]) or **respiratory distress syndrome** (RR 0.64, 95% CI 0.28–1.46 [*very low-quality evidence*]). In conclusion there is **insufficient evidence to recommend sealing procedures for PPROM**.

There was limited evidence to suggest that an immunologic membrane sealant was associated with a reduction in PTB at less than 37 weeks and neonatal death, but these results should be interpreted with caution, as this is based on one small study, with a high risk of bias, and the intervention has not been tested in other studies.

Even if such practices have not yet been incorporated into clinical practice, current experience suggests that in cases of fluid leakage following an invasive fetal procedure, the use of sealing techniques is a therapeutic option that should be researched further.

PPROM in twin gestations

Overall, PPROM complicates 7%–8% of twin pregnancies at a mean GA of 30–32 weeks (see also Chap. 46, in *Maternal-Fetal Evidence Based Guidelines*). PPROM occurs at an earlier GA among multiple gestations, with 36% of twin PPROM cases occurring at less than 28 weeks. PPROM in singleton pregnancies is related mainly to infection/inflammation, while PPROM in twin gestation may probably be more related to uterine overdistension. **The latency period seems to be shorter in twins** compared with singleton pregnancies [144].

Most studies report a median latency of less than 24 hours with only 16%–50% of twin pregnancies remaining undelivered at 48 hours, decreasing to 7%–22% at 7 days. Latency tends to be longer when PPROM occurs before 30 weeks of gestation [145]. The membrane rupture usually occurs in the **lower sac (90% of cases)** [146].

Most studies comparing **obstetric outcome between singleton and twin pregnancies with PPROM reported no difference in neonatal outcome** [147]. A retrospective cohort of 23 multifetal pregnancies complicated by PPROM before $26^{0/7}$ weeks showed a median latency of 11 days with expectant management. Of the 46 newborns, 20 (43%) survived to hospital discharge. Of these, 12 (60%) experienced severe neonatal morbidity. The multiple pregnancy cases with ruptured membranes were more likely to experience intrauterine fetal demise, but all other outcomes did not differ by membrane status [148]. In 48 multiple pregnancies complicated by PPROM and delivering at a median GA of 31 weeks, neonatal morbidity and mortality were not different between the presenting and nonpresenting twin, and no difference was found between fetuses with or without a ruptured sac. The outcomes were not affected by duration of the latency period [149].

A retrospective study of twin pregnancies compared the latency period from PPROM to delivery and subsequent neonatal outcomes resulting from rupture of the presenting versus nonpresenting sac. The mean latency-to-delivery periods were 10.1 days ($n = 7$) when the presenting sac ruptured and 41.3 days ($n = 10$) when the nonpresenting sac ruptured ($p < 0.05$). Neonatal death was higher with PPROM of the presenting than the nonpresenting sac (21.4% vs. 0%). The rates of neonatal adverse outcomes were similar between the two groups, except for retinopathy of prematurity (ROP) (more frequent if PROM occurred in the presenting sac, 57% vs. 19%) and for persistent PH of the newborn (less frequent if PROM occurred in the presenting sac, 0% vs. 25%) [150].

The incidence of both clinical and subclinical chorioamnionitis has been reported as significantly higher in singleton pregnancies compared to twin pregnancies complicated by PPROM [133, 138]. In a retrospective study of 698 women with twin and singleton pregnancies complicated by PPROM between 24 and 34 weeks of gestation, the rate of clinical chorioamnionitis or placental abruption following PPROM was lower in twins compared with singletons (15.8% vs. 26.0%, $p = 0.03$) [144]. A study evaluating neonatal and infant outcomes in 151 twin gestations with PPROM at 24–31 weeks reported a neonatal mortality rate of 9.0% and an overall cerebral palsy rate of 7.3% [151]. These data suggest that **rupture of membranes per se probably does not worsen the outcomes and supports a conservative management of twin pregnancies with PPROM <34 weeks**.

The management of PPROM in twin pregnancies does not differ significantly from that of singletons. **Antenatal steroids, antibiotics to prolong latency, and magnesium sulfate for neuroprotection** with delivery no later than $34^{0/7}$ weeks of gestation are all recommended in twins with PPROM.

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21

PRELABOR RUPTURE OF MEMBRANES AT OR NEAR TERM

Teodora Kolarova and Kimberly Ma

Key points

- **The diagnosis** of prelabor rupture of membranes (PROM) at term is based on **pooling, ferning**, and **nitrazine tests** on speculum exam. Rapid bedside immunoassays such as placental alpha-microglobulin-1 or others may be helpful in cases in which the diagnosis of rupture of membranes (ROM) is suspected but cannot be confirmed with pooling, ferning, and/or nitrazine tests. Initial digital examinations should be avoided and subsequent such exams kept to an absolute minimum, as they are associated with a higher risk of infection.
- The main **complication** of PROM is **intrauterine infection**; this incidence increases with the duration of PROM, and with longer latency, the risk of **neonatal infection** also increases.
- Women with PROM at term should be **hospitalized** and **induced** with **oxytocin** within 6–12 hours of PROM, or earlier as feasible. **Most women with PROM at term, if given a choice, prefer induction**. **Oxytocin induction is safe, effective, and cost-effective**, and is therefore the preferred **first-line agent** for induction after PROM. Misoprostol induction is an alternative, with limited data suggesting safety and noninferiority to oxytocin. Foley catheter ripening is not superior to other methods of induction and has been associated with increased risk for intrauterine infection.
- Antibiotics are recommended if the patient is group B streptococcus (GBS) positive or complications (chorioamnionitis) develop during labor. In women expected to have a latency from PROM to delivery of over 12 hours, antibiotics are associated with significantly decreased chorioamnionitis and endometritis.
- **PROM at $34^{0/7}$ and $36^{6/7}$** can be managed expectantly if infection is not present, or delivered immediately. Decision should be made after sufficient counseling and through shared decision-making. Corticosteroid administration for fetal maturity should be offered if not received previously. If expectant management is chosen, latency antibiotics should be administered per institutional protocol for PROM <34 weeks.

Definition

Prelabor rupture of membranes is rupture of fetal membranes prior to the onset of labor [1]. Preterm prelabor rupture of membranes (PPROM) is prelabor rupture of fetal membranes ≤37 weeks [1]. This chapter includes guidance for late-preterm ($34^{0/7}$–$36^{6/7}$ weeks), as well as term (≥37 weeks) prerupture of membranes (PROM). For PPROM <34 weeks, see Chap. 20.

Diagnosis

The diagnosis of PROM and PPROM is based on history and physical examination findings (see also Chap. 20). A maternal history suggestive of PROM includes a gush of fluid soaking clothes or a constant trickle of fluid that does not stop. Physical exam for PROM starts with a **sterile speculum** examination [1–3]. **Visualization of amniotic fluid passing from the cervical canal is diagnostic** of this condition [1–3].

Another helpful test is the **nitrazine test**. The pH of the vagina is usually 4.5–6.0, whereas amniotic fluid has a pH 7.0–7.7; nitrazine paper turns blue with pH >6.5 [1, 2]. A false-positive nitrazine test can be caused from blood, semen, alkaline antiseptic, or bacterial vaginosis. A false-negative nitrazine test can be caused by prolonged leaking of amniotic fluid or minimal residual fluid. The sensitivity of nitrazine is 90.2% (81.3%–100%), and the specificity is 79.3% (16%–100%) [2].

A third helpful test is called "**ferning**." A swab of vaginal fluid from the posterior fornix is placed on a slide and allowed to air dry. Arborization (ferning) under microscopic visualization suggests rupture of membranes. Cervical mucus can cause a false-positive result. Ferning has a sensitivity of 90.8% (62.0%–98.5%) and a specificity of 95.3% (88.2%–100%) [2].

The combination of vaginal pool of fluid, nitrazine, and ferning has a sensitivity of 90.8% and a specificity of 95.6% [2]. These tests are more accurate when patients present in labor and less accurate when nonlaboring [3]. If these tests are equivocal, an ultrasound can be performed to evaluate for amniotic fluid, but oligohydramnios is not diagnostic of PROM, since it can be associated with other etiologies, such as placental insufficiency.

Placental alpha-microglobulin-1 is a 34-kDa glycoprotein abundant in amniotic fluid (2000–25,000 ng/mL); there is a negligible amount of this glycoprotein in vaginal fluid with intact fetal membranes (0.05–2.0 ng/mL) [2, 4, 5]. AmniSure is a bedside immunoassay that uses the delta in concentration of placental alpha-microglobulin-1 for diagnostic accuracy. AmniSure has a sensitivity of 98.7%–98.9% and a specificity of 87.5%–100% [4, 5].

Insulin-like growth factor binding protein 1 (IGFBP-1) has a high concentration in amniotic fluid compared to other body fluids such as vaginal secretions, urine, or semen [6]. An immunochromatography dipstick method (Actim PROM) is available to diagnose rupture of membranes. The test is more popular in Europe compared to the United States and is most accurate when the timing of the test is close to the timing of rupture of membranes. The sensitivity of the test is 95%–100% with a specificity of 93%–98% [7–10].

A negative fetal fibronectin can be helpful in ruling out rupture of membranes; however, a positive test cannot distinguish between intact and ruptured membranes [11]. Alpha-fetoprotein levels are higher in amniotic fluid compared to urine, semen, or normal vaginal discharge. A recent study showed a 96.2% sensitivity and 100% specificity; however, it may be falsely positive if a vaginal infection is present and requires further study in a larger cohort [12]. Further studies are needed to assess reliability, with special attention paid to time of presumed membrane rupture [2, 3]. **Placental alpha-microglobulin-1, IGFBP-1, and these other tests have limited clinical applicability** currently, given the high accuracy of pooling, ferning, and nitrazine tests. Nonetheless, they **can be helpful**

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in cases in which the diagnosis of ROM is suspected but cannot be confirmed with pooling, ferning, and/or nitrazine tests.

Incidence

PROM occurs in approximately 8% of all term deliveries [1].

Etiology

The etiology of PROM without signs of infection or bleeding is often unknown, and this should be considered a physiologic, not pathologic, event.

Risk factors

The risk factors associated with rupture of fetal membranes include low socioeconomic status, low body mass index (BMI) <19.8 kg/m^2, nutritional deficiencies of ascorbic acid and copper, connective tissue disorders, smoking, cold knife cone biopsy, cervical cerclage, pulmonary disease, uterine overdistension, and amniocentesis [1]. In addition, pregnant women with a previous preterm birth, midtrimester short cervix, and preterm labor are at increased risk for PROM; however, the majority of cases have no identifiable cause [1].

Complications

The most common complications of PROM are **chorioamnionitis, endometritis, and postpartum hemorrhage**. With increasing time interval from ROM, there is a significant increase in these complications: About 12 hours for chorioamnionitis, 16 hours for endometritis, and 8 hours for postpartum hemorrhage [13]. As the latency from ROM to delivery increases, so does the risk for neonatal infection. Maternal group B streptococcus (GBS) colonization also increases the risk for neonatal infection. Incidence of cesarean delivery is not affected by management with either induction or expectant management, but depends on other risk factors (e.g. nulliparity) [14].

Management

Initial evaluation

Initial evaluation of PROM involves confirmation of the diagnosis. **Digital examination** can increase the risk of infection and as a result **should be avoided** [14]. The cervix can be visually assessed for dilation and effacement [15]. Fetal presentation should be confirmed by ultrasound. Fetal well-being and the presence of uterine contractions should be assessed by external monitoring.

Counseling

Risk factors, complications, and management of PROM should be reviewed with the patient. About 50% of women with PROM at term deliver within 6–12 hours, and 95% of women will deliver within 28 hours of membrane rupture [1, 14]. Principles of management can be reviewed (Table 21.1).

Hospitalization

Compared with management in the hospital, expectant management of PROM at term at **home** is associated with a 52% increase in the **need for maternal antibiotics** for nulliparas and 97% more **neonatal infections** [16]. **PROM at term should be managed in hospital**.

TABLE 21.1: Management of PROM at ≥37 Weeks

- Deliver (e.g. start induction <6–12 hours after PROM)
- Manage in hospital
- Oxytocin is the induction agent with the best safety and effectiveness
- Antibiotics are recommended if the patient is GBS positive or complications (chorioamnionitis) develop during labor. In women expected to have a latency from PROM to delivery of over 12 hours, antibiotics are associated with significantly decreased chorioamnionitis and endometritis

Abbreviations: PROM, prelabor rupture of membranes; GBS, group B streptococcus.

Delivery versus expectant management

Women with PROM ≥37 weeks should be delivered. Induction of labor with **oxytocin** has been shown to **decrease the rate of maternal chorioamnionitis and postpartum fevers** without significantly affecting the rate of cesarean delivery, compared with expectant management, and is the **preferred method of induction with PROM** [14]. In most randomized controlled trials (RCTs), induction was with oxytocin or prostaglandins, with one trial using homeopathic *Caulophyllum* and another acupuncture. Overall, no differences were detected for mode of birth between induced and expectant groups: **Cesarean (relative risk [RR] 0.84**, 95% confidence interval [CI] 0.69–1.04) or operative vaginal birth (RR 1.03, 95% CI 0.67–1.59). Significantly fewer women in the induced compared with expectant management groups developed chorioamnionitis and/or endometritis (RR 0.49 95% CI 0.33–0.72). Infants of those who were induced experienced less probable or definitive early-onset sepsis (RR 0.73, 95% CI 0.58–0.92). Further, fewer infants under induced management went to the neonatal intensive unit or special care nursery compared with expectant management (RR 0.75 95% CI 0.66–0.85) [17]. In subgroup analysis, parity did not have an effect on cesarean delivery rates or maternal or neonatal infections [17].

Compared with expectant management, induction of labor by **oxytocin** is associated with a 42% **decrease** in the risk of **maternal infection** and 36% in definitive or probable **neonatal infection** [17]. Based on one trial, women were more likely to view their care positively if labor was induced with oxytocin [14]. Cesarean delivery rates are similar between groups if induced with oxytocin. Perinatal mortality rates are low and not significantly different between groups, although the **trend** is toward **fewer perinatal deaths** with induction of labor by oxytocin [17].

Studies utilizing prostaglandins as the initial mode of induction of labor are varied in the type, formulation, dosage, and duration of use [17]. No clear differences were observed in neonatal infections using prostaglandins compared to placebo or no treatment. Subgroup analysis suggests a differential treatment effect for maternal infectious morbidity (RR 0.21, 95% CI 0.12–0.36) and cesarean section (RR 0.54, 95% CI 0.45–0.66) when sublingual misoprostol (prostaglandin E1) is used compared to expectant management, but this was based on a single clinical trial [17]. There is insufficient data to make meaningful comparisons of the different prostaglandin formulations in clinical use.

Medications for induction

Immediate induction of labor with intravenous **oxytocin** has been shown to decrease the rate of maternal and neonatal infection without increasing the rate of cesarean section [14, 17].

Misoprostol (PGE1) and dinoprostone (PGE2) have not been shown to be superior to intravenous oxytocin even in women with an unfavorable cervix [17, 18]. However, when misoprostol is compared to PGE2, length of labor is shorter but there is increased uterine tachysystole [18]. **Cost is less with oxytocin induction**. Vaginal or oral misoprostol appears to be an effective means of labor induction comparable to oxytocin, but the studies reviewed were not large enough to exclude the possibility of serious adverse events with misoprostol [19–23]. There is insufficient evidence to assess if the combination of PGE2 together with oxytocin is superior to oxytocin alone [24].

The efficacy of **Foley bulb** or other mechanical means of induction in women with PROM has been evaluated, and Foley does not shorten time to delivery when compared to oxytocin alone in PROM [25, 26]. Foley is also not superior to prostaglandins for induction of labor in women with term PROM [27]. Regarding its safety, **induction with Foley bulb has been associated with increased risk for clinical chorioamnionitis** in one RCT where women received antibiotic prophylaxis per American College of Obstetricians and Gynecologists (ACOG) guidelines [25].

In summary, in patients with PROM at term, once the diagnosis has been confirmed, **induction of labor is recommended**. Induction should probably occur at least **within 6–12 hours of PROM, or earlier if feasible**. If expectant management is performed, there is a significant increase in chorioamnionitis and neonatal infection as duration increases [28–30]. **Oxytocin is the recommended induction medication, as it is safe, effective, and cost-effective.** Foley bulb (or other balloon) is not superior to oxytocin or prostaglandins and confers an increased risk for chorioamnionitis [25–27, 31]. Vaginal and oral misoprostol are also safe and effective but have not been proven to be superior to oxytocin when appropriate doses (e.g., 25 mcg for vaginal misoprostol) are used [18]. With increasing latency from PROM to delivery, there is an increased risk for chorioamnionitis, endometritis, and postpartum hemorrhage [13]. **Women should be counseled to initiate induction of labor as soon as amenable after PROM** in order to decrease the risk of these complications.

Antibiotics

GBS positive: In women with a positive GBS culture, antibiotics should be administered according to the Centers for Disease Control and Prevention (CDC) and ACOG guidelines [32, 33] (see Chap. 39 in *Maternal-Fetal Evidence Based Guidelines).* **Women who are GBS positive with PROM at ≥34 weeks are treated with penicillin in labor**. Ampicillin is a reasonable alternative. If the patient is penicillin-allergic but not at high risk for anaphylaxis, cefazolin is the agent of choice. For women at high risk for anaphylaxis, GBS isolate should be tested for susceptibility to clindamycin and erythromycin. Vancomycin is recommended if the isolate is resistant to either clindamycin or erythromycin. Intrapartum treatment for chorioamnionitis is recommended regardless of GBS maternal status.

In these revised recommendations, 4 hours of intravenous antibiotics are considered adequate treatment for a neonate; however, no medically necessary obstetric procedure should be delayed to achieve 4 hours of intravenous antibiotic therapy [32]. If a patient presents with PROM at term, antibiotics can be administered and induction of labor can begin concurrently. In addition, if a woman is scheduled for a repeat cesarean section and presents with PROM, GBS antibiotic prophylaxis should be administered while arranging for the repeat cesarean section [32].

GBS negative: Although ACOG guidelines recommend against routine antibiotic prophylaxis in patients with documented GBS-negative status, there is evidence that women with PROM and latency >12 hours have a reduced risk of infectious morbidity with administration of antibiotics. A meta-analysis and Cochrane review evaluated the efficacy of antibiotic prophylaxis in women with term or late-preterm prelabor rupture of membranes and concluded that routine antibiotic prophylaxis was not associated with maternal or neonatal benefits, although for women with latency greater than 12 hours, **prophylactic antibiotics were associated with significantly lower rates of chorioamnionitis** (2.9% versus 6.1%, RR, 0.49, 95% CI, 0.27–0.91) **and endometritis** (0% versus 2.2%; RR, 0.12, 95% CI, 0.02–0.62) in the meta-analysis, and a similar trend was observed in the Cochrane review [34, 35]. Thus, in women with latency over 12 hours, prophylactic antibiotics can reduce the risk of maternal infectious morbidity.

GBS status unknown: Per ACOG and CDC guidelines, if the patient has no risk factors (previous infant with GBS sepsis, <37 weeks, rupture of membranes >18 hours, chorioamnionitis, GBS presence in previous pregnancy), routine antibiotic use should be avoided [32, 33, 35]. As referenced earlier, however, there is evidence of benefit when antibiotics are administered with rupture of membranes >12 hours and can be considered sooner than 18 hours as suggested by ACOG [34, 35]. Alternatively**, in PPROM $34^{0/7}$–$36^{6/7}$ weeks, if the patient has no GBS culture from the previous 5 weeks, antibiotics should be administered** per protocol, or a rapid GBS test can be performed. If the rapid GBS result is negative, antibiotics can be withheld unless other risk factors develop (chorioamnionitis or rupture of fetal membranes greater than 12–18 hours) [32].

In summary, for PROM at ≥37 weeks, antibiotics should be given if the woman is GBS positive or clinical chorioamnionitis develops during labor and should be considered for all women with expected latency from PROM to delivery >12 hours [33–35]. **In PPROM between $34^{0/7}$ and $36^{6/7}$ weeks, antibiotics should be administered if GBS status is positive or unknown** [33, 34].

Special considerations for PPROM at 34–36 weeks' gestation

Delivery versus expectant management

Based on newer evidence reviewed next, the ACOG Practice Bulletin suggests that in patients with **PROM between $34^{0/7}$ and $36^{6/7}$ weeks of gestation, either expectant management or immediate delivery is a reasonable option; the balance between benefit and risk from both a maternal and neonatal perspective should be carefully considered** (Table 21.3). If expectant management is continued beyond $34^{0/7}$ weeks of gestation, it should not extend beyond $37^{0/7}$ weeks of gestation [1].

The original research determining the best antenatal approach to PPROM, including the late preterm period, studied patients with documented fetal maturity [36, 37]. Overall, these studies found that expectant management in late preterm PPROM produced longer latencies; however, there was a significant increase in maternal infection without demonstrated neonatal benefit [36–40].

Recent studies have called attention to the neonatal complications of late preterm birth, which include respiratory complications, sepsis evaluations, hyperbilirubinemia requiring phototherapy, and death. This combination of potential complications has led to an increase in neonatal intensive care unit (NICU) admissions, increasing length of stay, urgent hospital visits, and hospital readmissions [41–48]. The effort to decrease late-preterm birth in the United States has been successful, with a decrease from 9.15% in 2006 to 7.99% in 2013 (a 13% decrease) [49].

More contemporary research addressing the management of late preterm PROM has included two international RCTs (PPROMEXIL and PPROMEXIL-2) and a third multicenter RCT (PPROMT study) [50–52]. **An individual participant meta-analysis of these three trials showed no difference in their primary outcome, a composite of neonatal adverse events, in the immediate delivery versus the expectant management group** (RR 1.20, 95% CI 0.94–1.55) [53]. Specifically, there was **no difference in neonatal sepsis** between the groups (RR 0.74, 95% CI 0.47–1.15). However, **neonates in the immediate group were more likely to be diagnosed with respiratory distress syndrome** (RR 1.47, 95% CI 1.10–1.97) **and hyperbilirubinemia and to be admitted to the NICU or special care nursery** (RR 1.17, 95% CI 1.11–1.23), leading to longer hospital stays [53]. **In a subgroup analysis of patients with a positive vaginal culture (included 14 different pathogens), immediate delivery did reduce the risk of neonatal sepsis** (see Table 21.2). In regard to maternal outcomes, those who were **delivered immediately experienced less antepartum hemorrhage** (RR 0.57, 95% CI 0.34–0.95) and **less chorioamnionitis** (RR 0.21, 95% CI 0.13–0.35), but were more likely to require cesarean delivery (RR 1.26, 95% CI 1.09–1.47) [53]. Most women received antibiotics (76% in the immediate delivery group and 78% in the expectant management group, but the rates varied in each trial) [53]. In the subgroup analysis for positive GBS, antepartum tocolysis, corticosteroid administration, and administration of latency antibiotics showed no difference in treatment effect for the composite adverse neonatal outcome or any of its components [53].

With the additional information from this meta-analysis, ACOG now recommends that **either expectant management or immediate delivery is a reasonable option for rupture of membranes between $34^{0/7}$ and $36^{6/7}$ weeks after sufficient counseling** [1]. **Care should be individualized through shared decision-making. Women with vaginal infections should be induced at $34^{0/7}$ weeks (see Tables 21.2 and 21.3).**

TABLE 21.2: Management of PPROM at $34^{0/7}$–$36^{6/7}$ Weeks

- Deliver if infection present[a]
- If no infection present, deliver OR expectantly manage until 37 weeks 0 days. Shared decision-making weighing risks and benefits (see Table 21.3)
- Manage in hospital
- Single course of corticosteroids for fetal maturity, if steroids not previously given (if no contraindications exist and delivery not expected in less than 24 hours or greater than 7 days)
- Antibiotics are recommended if the patient is GBS positive, GBS unknown, or expectant management is chosen

[a] Infections include clinical chorioamnionitis or any of the following on vaginal culture: *Bacterial vaginosis, Candida albicans, Candida glabrata, Candida tropicalis, Chlamydia,* coagulase-negative *Staphylococcus, Enterococcus, Escherichia coli,* group B streptococcus, *Hemophilus influenza, Staphylococcus aureus, Staphylococcus agalactiae, Trichomoniasis,* and *Ureaplasma urealyticum.*

Abbreviations: PPROM, preterm prelabor rupture of membranes; GBS, group B streptococcus.

TABLE 21.3: Risks and Benefits of Expectant Management versus Immediate Delivery in Late-Preterm (between $34^{0/7}$ and $36^{6/7}$ weeks) PROM

Benefits of Expectant Management	Benefits of Immediate Delivery
Less neonatal respiratory distress syndrome	Less antepartum hemorrhage
Less hyperbilirubinemia	Less chorioamnionitis
Less NICU or SCN admission	In women with positive vaginal culture, decreased neonatal sepsis[a]
Shorter NICU stays	
Shorter neonatal hospital stays	
Decreased risk of cesarean delivery	

[a] See Table 21.2 for details.

Abbreviations: PROM, premature rupture of membranes; NICU, neonatal intensive care unit; SCN, special care nursery.

Steroids for fetal maturity

Regarding corticosteroid administration for fetal maturity, evidence suggests that steroids are associated with neonatal benefit in the late preterm period. The largest of these trials (the ALPS trial) demonstrated a decrease in multiple neonatal respiratory morbidities with steroid administration, but also an increased risk of neonatal hypoglycemia [54]. A meta-analysis of six RCTs with three of these trials including women at $34^{0/7}$–$36^{6/7}$ weeks at risk for imminent premature delivery confirmed these findings [55]. Neonates who received antenatal corticosteroids ≥34 weeks had a significantly lower incidence tachypnea of the newborn (RR 0.72, 95% CI 0.56–0.92), severe respiratory distress syndrome (RDS) (RR 0.60, 95% CI 0.33–0.94), and any RDS (RR 0.74, 95% CI 0.61–0.91) [55]. **Steroids should be considered for decreasing respiratory morbidities and other neonatal outcomes in women $34^{0/7}$–$36^{6/7}$ weeks** [55]. It should be noted that although evidence supports short-term benefit, long-term benefits of antenatal corticosteroids in the late preterm period are unknown. See Chap. 20 for other details on management for women with PPROM <34 weeks [48].

Antibiotics

ACOG currently does not recommend the administration of latency antibiotics in those patients who elect for expectant management in late-preterm PPROM [1]. However, most patients in the individual participant meta-analysis on late-preterm PPROM received antibiotics [53]. A Cochrane review on antibiotic use for patients with PPROM <37 weeks also demonstrates that antibiotics decrease the risk for chorioamnionitis and neonatal infection and prolong latency [56]. It is unclear what antibiotics are best, because different regimens were used in the late-preterm PPROM trials. **If PROM occurs at $34^{0/7}$–$36^{6/7}$ weeks and expectant management is elected, it is recommended that the patient receive the same institutional latency antibiotic regimen utilized in patients who experience PPROM <34 weeks** [56] (see Chap. 20).

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22

MANAGEMENT OF THE UNCOMPLICATED TERM PREGNANCY

Rebecca Jackson

Key points

- **Postterm pregnancy** is defined as a pregnancy that has lasted until ≥**42 weeks, or ≥294 days**. **Late-term pregnancy** is defined as a pregnancy that has lasted **41$^{0/7}$ to 41$^{6/7}$ weeks of gestation**.
- **Late-term and postterm pregnancies have a twofold increase in the risk of macrosomia and subsequent increase in labor dystocia, operative vaginal delivery, cesarean delivery, perineal injury, and shoulder dystocia**.
- **Postterm neonates are at increased risk for seizures, meconium aspiration, 5-minute Apgar scores less than 4, and admission to the neonatal intensive care unit. Postterm pregnancies are also at increased risk for intrauterine infection, oligohydramnios, nonreassuring fetal heart rate tracing (NRFHT), low umbilical artery pH,** and **perinatal mortality**.
- **Pregnancies with risk factors** such as maternal (e.g. hypertension and diabetes) and fetal (growth restriction, etc.) diseases should be delivered at term or as described in Chap. 23.
- **Prevention** of postterm pregnancy can be achieved with accurate dating by **routine first-trimester ultrasound** and with serial membrane stripping starting at 38 weeks.
- There is insufficient evidence to assess the efficacy of antepartum testing for pregnancies after their due date. Twice-weekly fetal testing with nonstress test (NST), or NST and maximum vertical pocket (MVP) of amniotic fluid volume (AFV), or biophysical profile (BPP), has been proposed, starting at 41 weeks.
- **All women should be offered induction of labor for 39 weeks' gestation** (preferred name of this indication for induction), as it has been shown to **decrease the risks of cesarean delivery; of hypertensive disorders of pregnancy; and of adverse perinatal outcomes, including stillbirth, admission to the neonatal intensive care nursery, and need for respiratory support**, compared to expectant management up to 40 weeks 5 days. These benefits are similar for all race/ethnic groups, ages, Bishop scores, and body mass indexes (BMIs). **Induction for 39 weeks' gestation is also associated with decreased pain in labor and higher maternal satisfaction and sense of control compared to expectant management**. Most women do want to be induced at 39 weeks when offered the option. **Induction for 39 weeks' gestation is also associated with less costs and other health care system benefits**.

Diagnosis/Definition

Postterm pregnancy is defined as pregnancy that has lasted until **≥42 weeks**, or ≥294 days, or ≥14 days after the due date (estimated date of confinement [EDC]) [1]. **Late-term pregnancy** can be defined as a pregnancy that has lasted until **≥41 weeks**, or ≥287 days, or ≥7 days after the due date (EDC) [1]. The term "postdates" can signify a pregnancy that lasted until ≥40 weeks, or ≥280 days, but is often defined differently in the literature and should be avoided [1]. All these definitions may have slightly different meanings in the literature, so it is important to be clear when using these terms. These definitions and this guideline pertain to **singleton gestations**. For multiple gestations, please refer to Chap. 46 in *Maternal-Fetal Evidence Based Guidelines.*

Epidemiology/Incidence

In 2018, in the United States, the **incidence** of late-term pregnancy was 5.90% and of postterm pregnancy was 0.30% [2]. These incidences have significantly decreased in the last few years.

Etiology/Basic pathophysiology

The most frequent cause of postterm pregnancy is an **error in dating** [1, 3]. See Chap. 4 for accurate dating criteria and their benefits, as well as the following sections.

Risk factors/Associations

Poor (wrong) dating; prior postterm pregnancy, obesity, nulliparity, long (>28 days) cycles without early ultrasound, placental sulfatase deficiency, anencephaly, and male fetus. Obesity appears to be one preconceptionally modifiable risk factor for postterm pregnancy [4].

Complications

Perinatal

Many epidemiologic studies have shown that fetal and neonatal complications increase with gestational age after 41 weeks. **Meconium aspiration, intrauterine infection, oligohydramnios, macrosomia, nonreassuring fetal heart rate tracing (NRFHT), low umbilical artery pH,** and **low 5-minute Apgar score** have all been associated with postterm pregnancy. **Perinatal mortality** (fetal and neonatal deaths) is twice as high at ≥42 weeks and 6 times as high at ≥43 weeks compared with the rate for pregnancies delivered between 39 and 40 weeks [1, 5].

Two markers of **immediate neonatal morbidity**, umbilical artery pH <7 and base excess ≥12, have been shown to increase in a continuous manner in pregnancies beyond 40 weeks and increase by odds ratio (OR) 1.65 for pH <7 for pregnancies between 41 and 42 weeks [6].

Neonatal mortality of normal-weight infants appears to be higher for infants born between 41 and 0 days and 41 weeks and 6 days compared with infants born between 38 weeks and 40 weeks and 6 days (OR 1.37, 95% confidence interval [CI] 1.08–1.73) [7].

However, these data are mixed and may vary based on whether risk factors such as fetal growth restriction (FGR) are included

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in the analysis. In a review of epidemiologic studies published between 1990 and 2004, 7 out of 11 studies demonstrated an increased stillbirth risk with postterm pregnancies, and 4 suggested that other issues such as FGR or fetal anomalies had a greater contribution to the stillbirth rate than did prolonged pregnancy [8].

Postmaturity syndrome is present in about 10%–20% of neonates born postterm. These fetuses have decreased subcutaneous fat and lack of vernix and lanugo. Postmature neonates are also more likely to have meconium staining of the amniotic fluid, skin, membranes, and umbilical cord [1].

Maternal

Women giving birth late-term and postterm are at increased risk of **perineal injury, infection, postpartum hemorrhage, and cesarean delivery** [1].

Pregnancy considerations

Every woman should be counseled early in pregnancy that up to 50% of gestations, especially in nulliparous women, last until past the due date. This is physiologic and natural for humans. The incidence of fetal death is significantly higher than that of neonatal death at ≥283 days (≥40 weeks and 3 days) [9]. In a large series, delivery at 38 weeks is associated with the lowest risk of perinatal death, but this risk is low at <1 to 2/1000 up to 41 weeks and 6 days [10]. **It is important to identify maternal (e.g. hypertension and diabetes) and fetal (e.g. growth restriction) risk factors that would necessitate special management**, as described in the specific chapters in *Maternal-Fetal Evidence Based Guidelines.* The OR for stillbirths and neonatal mortality increases in gestations from 40 weeks onward, and this increase is compounded sevenfold to tenfold when the fetus is growth restricted [11].

Management (Figure 22.1)

Preconception counseling

Women with prior postterm pregnancy are at increased risk for recurrent postterm pregnancy. **Prevention strategies, including weight loss for obese women, appropriate weight gain during the pregnancy, early initiation of prenatal care, early ultrasound screening, and stripping of membranes starting at 37–38, weeks should be discussed** [3].

Prevention

Routine early ultrasound to reduce postterm pregnancies

Accurate assessment of gestational age is extremely important in improving perinatal morbidity and mortality. **First-trimester ultrasound** is the most accurate for pregnancy dating. Early ultrasound also reduces the number of postterm inductions.

Over 40% of women randomized to undergo first-trimester screening had their gestational age adjusted based on the ultrasound measurement of crown–rump length, whereas the corresponding number was only 10.9% for women assigned to second-trimester ultrasound. Furthermore, 4.8% in the first-trimester screening group compared with 13% in the second-trimester ultrasound group had labor induced for a postterm pregnancy (relative risk [RR] 0.37, 95% CI 0.14–0.96), which is a **63% reduction in the induction rate for postterm pregnancy** [11, 12]. Compared with no routine early ultrasound, **routine early pregnancy (<20 weeks) ultrasound reduces by 32%–39% the incidence of postterm pregnancy and of induction for postterm pregnancy** [4, 12, 13] (see also Chap. 4).

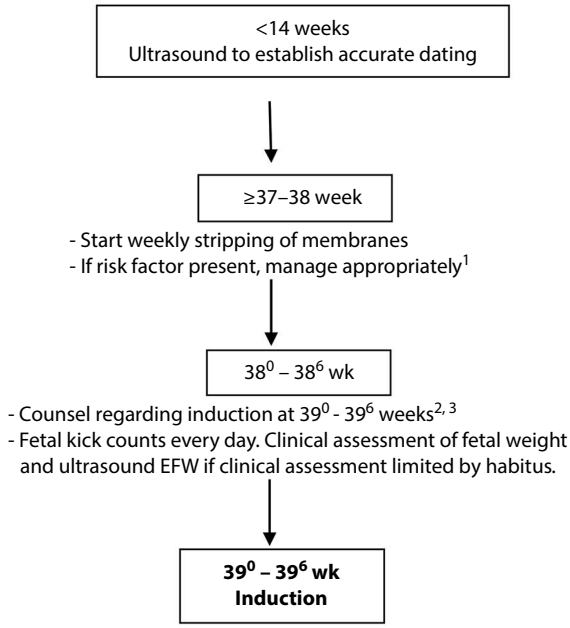


FIGURE 22.1 Management of term pregnancy. 1 – Risk factor examples include hypertension, diabetes mellitus, FGR, multiple gestation, etc. Please see guideline pertinent to specific risk factor for management. 2 – Strongly suggest induction for all women between 39⁰ and 39⁶ weeks. 3 – See Chap. 23 for effective induction management. *Abbreviation:* EFW, estimated fetal weight.

Stripping/Sweeping of membranes

Compared with no sweeping, **sweeping of the membranes**, performed weekly as a general policy in women at term (e.g. **weekly starting at 37–38 weeks**), **is associated with reduced duration of pregnancy** and **reduced frequency of pregnancy continuing beyond 41 and 42 weeks** [14, 15]. To avoid one formal induction of labor, sweeping of membranes must be performed in eight women. **Risk of cesarean section, maternal, or neonatal infection is similar**. Serial sweeping of membranes starting at 41 weeks every 48 hours also decreases the risk of postterm pregnancy from 41% to 23%, with efficacy both in nulliparous and multiparous women [16]. Discomfort during vaginal examination and other adverse effects (bleeding and irregular contractions) are more frequently reported by women allocated to sweeping, but its safety has been confirmed in multiple studies [14–17] (see also Chap. 23).

Breast and nipple stimulation to reduce postterm pregnancies

Breast and nipple stimulation daily starting at 39 weeks has not been sufficiently studied to ascertain safety, but it does appear to reduce the incidence of postterm pregnancy by 48% [18, 19].

Antepartum testing

If a woman with an uncomplicated pregnancy accepts induction at 39 weeks, there is no need for earlier antepartum testing. If she declined induction, there are insufficient data to assess the best mode of fetal monitoring after the due date, as there are **no trials** to assess the effect of antepartum testing on these pregnancies compared with no testing. Since fetal death rates incrementally

increase after the due date, it seems reasonable to test fetuses to assure well-being, especially at ≥41 weeks [1, 4, 9]. The most used options include nonstress testing (NST) (also called cardiotocography or CTG), biophysical profile (BPP), and modified BPP. Modified BPP includes NST and ultrasound measurement of maximum vertical pocket (MVP) of amniotic fluid volume (AFV). Others have been described, but with even less evidence for efficacy. Doppler of any vessel, including the umbilical artery, is not effective in the management of postterm pregnancy. Compared with fetal monitoring using NST and AFV, BPP (computerized CTG, MVP, fetal breathing, fetal tone, and fetal body movements) is associated with increased incidence of inductions and similar outcomes in a small trial in women ≥42 weeks [20]. At ≥41 weeks, **twice-weekly testing** (e.g. with NST and MVP) is recommended [1], but not based on trials (see also Chap. 58 in *Maternal-Fetal Evidence Based Guidelines).* In addition, an effort should be made to **assess fetal weight**, either clinically or, if this assessment is limited, by ultrasound, as the known increase in fetal and neonatal mortality in pregnancies beyond their due date is even higher in FGR fetuses [11, 21].

Interventions

Induction of labor for ≥39 weeks

When compared to expectant management up to 40 weeks and 5 days, **induction of labor at 39 weeks (39–$39^{4/7}$)** in low-risk nulliparous women has been shown to **decrease the frequency of cesarean delivery** by 16%, of **hypertensive disorders** of pregnancy by 36%, of **adverse perinatal outcomes** by 20%, and of **neonatal respiratory support** by 29% [22].

The percentage of women undergoing cesarean delivery was significantly lower in the induction group (18.6% vs. 22.2%; RR 0.84; 95% CI 0.76–0.93). This was true regardless of whether or not the cervix was favorable. Women undergoing induction also had a lower risk of developing hypertensive disorders of pregnancy (9.1% vs. 14.1%, RR 0.64, 95% CI 0.56–0.74) [22]. The primary perinatal outcome occurred 4.3% in the induction group and 5.4% in the expectant group (p-value 0.049; RR 0.80, 95% CI 0.64–1.0) [22]. These **results were similar for all race/ethnic groups, ages, Bishop scores, and body mass indexes (BMIs)** [22]. Moreover, pain in labor was significantly decreased in the induction group and **maternal satisfaction and sense of control significantly higher** in the induction group [22]. Most women do want to be induced at 39 weeks when offered the option [23]. **Induction for 39 weeks' gestation (as it should be called)** [24] is also associated with **less costs**, as it is associated with fewer prenatal visits, fewer unanticipated or urgent visits, less antepartum hospitalization, fewer tests and treatments prior to delivery, and shorter hospital stay, and with only a slightly longer time in labor and delivery (20 vs. 14 hours) [22]. Induction for 39 weeks' gestation is also associated with 883 fewer stillbirths per year if implemented in the United States alone [25].

Induction of labor at ≥40 weeks

If induction for 39 weeks' gestation is declined, induction should occur soon after the due date, and certainly by 40 weeks 5 days, or 41 weeks 0 days maximum. A policy of labor induction at 41 completed weeks (41–$41^{6/7}$) or beyond is associated with significantly fewer perinatal deaths (1/2814 vs. 9/2785; RR 0.30, 95% CI 0.09–0.99) compared with expectant management, with induction not before 42 weeks [21]. If deaths due to congenital abnormality are excluded, no deaths remain in the labor induction group and 11 deaths remain in the no-induction group. There were fewer cesarean sections in the induction group (RR 0.89, 95% CI 0.81–0.97). Labor induction at 41 weeks also significantly reduces the risk of perinatal meconium aspiration syndrome compared with expectant management (RR 0.50, 95% CI 0.34–0.73). Other maternal and perinatal outcomes are similar between the groups. It is important to recognize, however, that in general the outcomes are very good with both expectant management and induction, with the absolute perinatal death rate per 1000 ongoing pregnancies no higher than 1.2/1000 at 42 weeks, increasing up to 6/1000 ongoing pregnancies at 43 weeks [23]. About 410 inductions (95% CI 322–1492) would need to be done at 41 weeks in order to prevent one perinatal death [21].

Routine induction is more cost-effective than expectant management [26]. Several studies have shown that **patient satisfaction is higher with induction of labor** [21, 26, 27]. Iatrogenic prematurity should be avoided by careful assessment of gestational age. This risk should be minimal with the advent of widespread early ultrasound use to confirm pregnancy dating. Planned induction without medical indications at $39^{0/7}$–$40^{6/7}$ weeks has been shown not to be associated with an increase with cesarean delivery [28]. See also Chap. 23 for other induction risks and benefits, as well as management of induction. For women with a prior cesarean delivery, see Chap. 15.

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23

INDUCTION OF LABOR

Corina N. Schoen

Key points

- **An early (e.g. <20 weeks) ultrasound examination** helps determine accurate gestational age and is associated with a **reduction in the rates of induction of labor for postterm pregnancy**.
- Gestational age should be documented accurately before considering induction.
- **Possible indications** for induction of labor and the suggested best gestational age for induction are listed in Table 23.1. **Induction for 39 weeks' gestation** is associated with a decrease in hypertensive disorders of pregnancy, cesarean delivery (CD), and perinatal morbidity and mortality, compared to expectant management up to 40 weeks 5 days.
- **Without indications, induction before 39 weeks should be avoided**.
- **Contraindications** to induction of labor include malpresentation, umbilical cord prolapse, previous classical uterine incision or transfundal uterine surgery (e.g. from myomectomy), placenta or vasa previa, active genital herpes infection, and any contraindications to vaginal delivery, or indication for CD (Table 23.2).
- Compared to expectant management, induction of labor can be complicated by a **prolonged first stage of labor**.
- **Misoprostol should not be used for cervical ripening or labor induction in women with prior uterine incisions, given the >5% risk of uterine rupture**. In women with prior uterine incisions, **prostaglandin E2 (PGE2)** for cervical ripening is associated with an approximately **1.4%–2.5% risk of rupture; oxytocin has a 1.1% risk**. **Cervical ripening with the Foley catheter does not appear to be associated with any additional risk of uterine rupture in patients undergoing a trial of labor after cesarean section**.
- In women with an **unfavorable** (Bishop score <5, or even <9) **cervical exam**:
  - **Sweeping of membranes** starting at 37–38 weeks weekly doubles the rate of onset of labor **in the next 48 hours** and decreases the incidence of no spontaneous labor by the due date.
  - Induction in these women should be done by **two agents**, such as **Foley balloon (single balloon, inflated to 60–80 mL, with traction) and misoprostol (e.g. 25 µg every 2–4 hours)**. **If misoprostol is contraindicated, combine Foley with oxytocin IV infusion**.
  - **The Foley balloon** is associated with **less hyperstimulation accompanied by fetal heart rate (FHR) changes and increased use of oxytocin**, but results in the same number of vaginal deliveries and the same number of women delivered within 24 hours as all of the locally applied prostaglandins (prostaglandin E1 and E2 [PGE1 and PGE2]). It is therefore **one of the preferred methods for labor induction** when the cervix is <3 cm dilated.
  - **Vaginal misoprostol 25 mg every 2–4 hours** is the preferred safe dosage and is as effective as PGE2 or any other method; this is also a preferred method of labor induction.
  - PGE2 tablet, gel, and insert appear to be as safe and efficacious as each other in terms of tachysystole, CD rates, and neonatal outcomes.
- Other cervical ripening or induction agents are either not sufficiently studied, unsafe, or not as effective as the agents already mentioned.
- Oxytocin IV infusion is recommended with **favorable** cervical exam.
- Oxytocin IV infusion is recommended for **prelabor rupture of membranes (PROM)** and should be started within 12 hours, or as soon as feasible, after term PROM.
- There are insufficient safety data for **outpatient use** of pharmacologic cervical ripening or induction agents. However, there is emerging evidence that the **Foley catheter may be an effective and safe method for outpatient cervical ripening**.
- Contraction pressures of **≥200 Montevideo units** should be targeted in induction or augmentation of laboring patients to achieve **adequate labor**.
- While the definition of a failed induction of labor is elusive, a **failed induction** should not be diagnosed until after **18–24 hours of oxytocin after membrane rupture in the active phase (usually ≥6 cm in nulliparous women)**, assuming reassuring fetal heart pattern.
- **Induced labor should be managed, in general, as spontaneous labor**.

Definitions

Induction of labor is the stimulation of uterine contractions prior to spontaneous labor in order to achieve childbirth. **Cervical ripening** is a process that occurs prior to labor in which the cervix is softened, thinned, and dilated.

Incidence/Epidemiology

In 2017, there were 3.86 million births in the United States, of which **25.7%** were induced [1]. There is evidence for a decreasing rate of indicated preterm births (17% decline from 2005 through 2012) [2].

Basic pathophysiology

The cervix functions as the gatekeeper to parturition, maintaining a fine balance between the integrity of the pregnancy and delivery. Histologically, the cervix is composed of mostly

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TABLE 23.1: Indications for Induction of Labor with Suggested Timing of Delivery

Condition	Gestational Age at Induction (weeks^{days})	Quality of Evidence [135]	Strength of Recommendation [135]
Obstetric			
Intrauterine infection (e.g. chorioamnionitis)	At detection	Moderate	Strong
Abruptio placenta	At detection	Moderate	Strong
39 weeks gestation	39^0–39^6	High	Strong
Maternal			
Chronic hypertension – no medications	38^0–39^6	High	Strong
Chronic hypertension – controlled on medications	37^0–39^6	High	Strong
Chronic hypertension – difficult to control (requiring frequent medication adjustments)	36^0–37^6	Moderate	Weak
Gestational hypertension	37^0–37^6, at diagnosis thereafter	High	Strong
Preeclampsia – no severe features	37^0–37^6, at diagnosis thereafter	High	Strong
Preeclampsia – severe features	34^0, at diagnosis thereafter	High	Strong
Eclampsia	At detection	Moderate	Strong
Diabetes – pregestational, well-controlled	39^0–39^6	Moderate	Strong
Diabetes – pregestational, poorly controlled	34^0–38^{6a}	Low	Weak
Diabetes – gestational, well-controlled on diet	39^0–39^6	Moderate	Strong
Diabetes – gestational, well-controlled on medication	39^0–39^6	Moderate	Strong
Diabetes – gestational, poorly controlled on medication	34^0–39^{6a}	Low	Weak
Intrahepatic cholestasis of pregnancy with bile acids ≥100	36^0–37^6	Low	Weak
Intrahepatic cholestasis of pregnancy with bile acids <100	37^0–39^6	Low	Weak
Prior stillbirth	39^0–39^6	Low	Weak
PPROM	34^0–36^6	High	Strong
Fetal			
FGR – singleton, otherwise uncomplicated, normal umbilical artery Doppler	38^0–39^6	Moderate	Weak
FGR – singleton, decreased but present diastolic flow in umbilical artery Doppler	37^0–37^6	Moderate	Weak
FGR – singleton, absent diastolic flow in umbilical artery Doppler	33^0–34^6	Moderate	Weak
FGR – singleton, reversed diastolic flow in umbilical artery Doppler	31^0–32^6	Moderate	Weak
FGR – twin gestation, dichorionic-diamniotic twins with isolated FGR with normal umbilical artery Doppler	35^0–36^6	Low	Weak
FGR – twin gestation, monochorionic-diamniotic twins with isolated FGR with normal umbilical artery Doppler	32^0–34^6	Low	Weak
Macrosomia (e.g. EFW >4000 g, or larger for gestational age >95% percentile)	38^0–38^6	High	Weak
Twin gestation: dichorionic/diamniotic, uncomplicated	37^0–37^6	Moderate	Weak
Twin gestation: monochorionic/diamniotic, uncomplicated	36^0–36^6	Low	Weak
Twin gestation: monochorionic/monoamniotic, uncomplicated	32^0–34^6	Low	Weak
Oligohydramnios (MVP <2 cm) – isolated but persistent	37^0–37^6	Low	Weak
Nonreassuring fetal heart tracing (e.g. category III)	At detection	Low	Strong
Fetal death	At detection	Low	Weak

Source: From Berghella V, Bellussi F, Schoen C. Evidence-based labor management: induction of labor (part 2). Am J Obstet Gynecol MFM. 2020:1–9. [III, Review] Ref. [134], with permission.

Abbreviation: EFW, estimated fetal weight; FGR, fetal growth restriction.

collagen, with some smooth muscle; the stability of these components and the ability to become dynamic when stressed on a physical and molecular level are what changes the cervical status. This cervical status prior to induction is predictive of induction success, as described later [3].

Risk factors/Associations

Factors that may increase the risk for complications associated with induction are nulliparity, no prior vaginal delivery, unfavorable cervical exam, postterm, obesity, and a large fetus.

TABLE 23.2: Contraindications to Induction of Labor[a]

Condition	Usual Gestational Age at Cesarean (weeks^{days})
Obstetrical	
Transverse or oblique fetal lie (malpresentation)	39^0–39^6
More than two prior low-transverse cesarean deliveries	38^0–39^6
Placenta previa	36^0–37^6
Placenta accreta/increta/percreta	34^0–35^6
Vasa previa	34^0–36^6
Maternal	
Prior classical cesarean delivery	36^0–37^6
Prior myomectomy requiring cesarean delivery	37^0–37^6
Prior uterine rupture	36^0–37^6
Active genital herpes infection	39^0–39^6
HIV with viral load >1000 copies/mL	38^0–38^6
Fetal	
Nonreassuring fetal testing precluding fetal tolerance to labor	At diagnosis (individualize for periviable)
Umbilical cord prolapse	At diagnosis
Other	
Any other contraindications to vaginal delivery	Depending on diagnosis

Source: From Berghella V, Bellussi F, Schoen C. Evidence-based labor management: induction of labor (part 2). Am J Obstet Gynecol MFM. 2020:1–9. [III, Review] Ref. [134], with permission.

[a] Perform cesarean if/when delivery is indicated.

Complications

Complications of inductions include prolonged first stage of labor, especially in the latent phase [4], leading to increased risk of postpartum hemorrhage, intraamniotic infection, and endometritis [5, 6]. Cesarean delivery (CD) risk is not increased with induction of labor compared to expectant management [7, 8]. Preterm (<37 weeks) induction is associated with prematurity risks and should only be performed for appropriate maternal or fetal indications. The safety of the induced patient can be enhanced through the use of safety checklists available through the American College of Obstetricians and Gynecologists (ACOG) [9].

Pregnancy considerations

The risks and complications of induction of labor should be weighed against the potential benefits. A **successful induction** has been defined in many ways, but usually is one that achieves an uncomplicated vaginal delivery within 24 hours. If the active phase is not achieved within 24 hours, this is not a reason per se for CD. Compared with a shorter induction-to-delivery interval, an induction lasting greater than 24 hours is associated with a higher risk for adverse outcomes, with a higher (e.g. 50%) risk of CD [10]. Neonatal outcomes, including ICU admission, Apgar <7, and arterial cord pH <7, do not appear to increase with a prolonged latent stage as long as fetal status is reassuring [5, 6]. **A minimum of 18–24 hours should be allowed *after* cervical ripening *and* oxytocin administration (optimally with membranes ruptured) prior to diagnosing a failed induction** [10, 11]. After appropriate counseling, this period may be extended, assuming a reassuring fetal status.

Prevention

A routine **early ultrasound** examination (e.g. before 20 weeks) is associated with a 39% reduction in the incidence of postterm pregnancies and rates of induction of labor for postterm pregnancy by allowing a more precise estimation of exact gestational age. An ultrasound performed in the first trimester (6–14 weeks) provides the best estimate of gestational age and the most benefit in terms of avoiding induction for postterm pregnancy (see also Chap. 4) [12]. **Membrane sweeping** can also reduce the need of a labor induction by about 25% [13] and should be routinely offered to women who do not have a contraindication to vaginal delivery starting at 37 weeks (Figure 23.1).

Criteria for induction

Workup/Counseling

Gestational age should be **documented accurately** before considering induction to avoid inadvertent postterm and preterm deliveries. Indications and contraindications need to be carefully reviewed. Counseling with the patient should include discussion of specific indications, risks (possible complications), and benefits of induction.

Indications

Once a term gestation has been confirmed, possible indications for induction and suggested best timing are shown in Table 23.1 [14, 15].

For more details on the indications, see each specific guideline (e.g., Chaps. 15 and 20 in this volume and Chaps. 4, 5, 10, 46, and 48 in *Maternal-Fetal Evidence Based Guidelines*).

Gestational age of induction

The gestational age at which the induction is being considered is very important. There are some indications for induction before 39 weeks (Table 23.1), but **without indications induction before 39 weeks should be avoided** [14, 16]. In this chapter, induction and ripening in the third trimester, usually at or near term, is reviewed. For second-trimester induction and ripening, see Chap. 57 in *Maternal-Fetal Evidence Based Guidelines*.

Induction at 39 weeks' gestation without medical indication

The ARRIVE trial was completed in the United States in 2018, which randomized 6,106 low-risk nulliparous women to **induction at $39^{0/7}$–$39^{4/7}$ weeks** versus expectant management until at least $40^{5/7}$ weeks [17]. Although the **20% decrease in** the primary outcome of **perinatal morbidity and mortality** was not statistically significant, induction was associated with a significant **reduction in the risk of CD, maternal hypertensive disease, and respiratory distress in the newborn, and maternal satisfaction was significantly increased and pain significantly decreased** [17]. In a meta-analysis of 34 studies including over 21,000 women, there was a clear reduction (70%) in perinatal mortality when induction of labor occurred beyond 37 weeks when compared to expectant management [18]. NICU admission and Apgar score <7 at 5 minutes were also decreased in this population, by 12% and 27%, respectively [18]. Maternal benefits seen in the ARRIVE trial were also confirmed in the meta-analysis data. With 21,030 participants included in mode of delivery outcome, there was a 10% reduction in the risk of CD for induction compared with expectant management (relative risk [RR] 0.9, 95% confidence interval

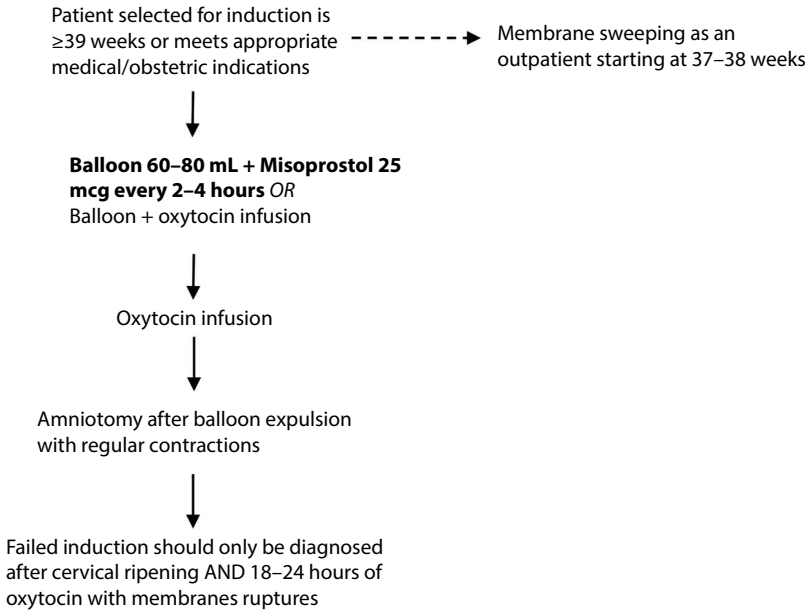


FIGURE 23.1 Induction algorithm to reduce the risk of cesarean delivery and time to delivery.

[CI] 0.85–0.95) [18]. **These data indicate women who are low risk should be given the opportunity to be induced primarily for the indications of 39 weeks' gestation**.

Contraindications

Induction of labor is **contraindicated** in the situations shown in Table 23.2 [16]. The supervising physician should use their discretion in the event of multifetal pregnancy, maternal heart disease, prior low-transverse CD, severe hypertension, and abnormal fetal heart rate (FHR) patterns not necessitating emergent delivery.

Induction of labor after cesarean

The **risk of uterine rupture** after induction in **women with a prior CD** deserves special attention (see Chap. 15). Misoprostol induction in women with a prior CD was associated with a 5.6% risk of uterine rupture in one of the largest series [19]. **Therefore, misoprostol should not be used for cervical ripening or labor induction in women with prior uterine incisions except under very unusual circumstances or management of stillbirth in the second trimester** (see Chap. 57 in *Maternal-Fetal Evidence Based Guidelines).* According to retrospective studies, using prostaglandin E2 (PGE2) for cervical ripening in women who have a history of previous cesarean also increases the risk of uterine rupture [20–23]. Risk of uterine rupture is approximately **1.4–2.5% with PGE2** use (with or without oxytocin) [22, 23] and about **1.1% with oxytocin alone** [23]. Alternatively, **cervical ripening with the Foley catheter is not associated with any additional risk of uterine rupture in patients undergoing a trial of labor after cesarean** section [24]. Mifepristone 400 mg orally may outperform Foley to induce labor in a prior cesarean due to its lack of uterine stimulation, but currently is understudied [25]. A patient who has a prior CD, no previous vaginal delivery, and an unfavorable Bishop score up to 39–40 weeks has more risks (e.g. septicemia, uterine rupture, and hysterectomy) from induction of labor; these women may elect for repeat CD after counseling (Chap. 15) [20–23]. However, in a prospective observational trial of 12,676 women undergoing either induction of labor or expectant management after a prior CD, induction at 39 weeks remained associated with a significantly higher chance of vaginal birth after cesarean (VBAC), as well as uterine rupture (odds ratio [OR] 1.31, 95% CI 1.03–1.67 and OR 2.73, 95% CI 1.22–6.12, respectively) [26]. Uterine rupture was not statistically different in those women induced at 40 completed weeks compared to expectantly managed women; however, there was also no increase in VBAC odds [26].

Time of day for induction

Spontaneous labor has been shown to have a circadian rhythm with a higher occurrence at night due to a higher concentration of myometrial oxytocin receptors and maternal oxytocin concentrations. A meta-analysis of three randomized controlled trials (RCTs) was performed; however, results were not pooled secondary to substantial heterogeneity between studies [27]. One RCT comparing morning and evening oxytocin inductions showed no difference in outcomes for women induced in the morning versus the evening, except for slightly increased neonatal admission to the maternity ward, medium care neonatal unit, or ICU (RR 1.48, 95% CI 1.02–2.14) in the morning group, though the authors could not explain a reason for this effect [28]. The remaining two RCTs compared prostaglandin induction timing and showed no differences in neonatal outcomes or CD but higher maternal satisfaction in morning inductions [27]. Inductions should be timed to best accommodate the staffing needs of the labor unit and patient preference, given the lack of clear benefit for morning or night inductions.

Prediction of successful induction

Maternal characteristics

Certain maternal characteristics have been shown to favorably predict successful induction of labor. A secondary analysis of a study investigating vaginal misoprostol versus vaginal dinoprostone showed that prior vaginal delivery, lower maternal body

TABLE 23.3: Bishop Score for Cervical Favorability

Score	Dilation (cm)	Effacement (%)	Station	Cervical Consistency	Position of Cervix
0	Closed	0–3	–3	Firm	Posterior
1	1–2	40–50	–2	Medium	Midposition
2	3–4	60–70	–1, 0	Soft	Anterior
3	5–6	80	+1, +2	–	–

Source: Modified from Ref. [3].

mass index (BMI), tall maternal stature, and neonatal birth weight <4000 g were associated with a higher likelihood of a vaginal delivery, independent of method. [29].

Bishop score

In 1964, Bishop reported that his pelvic score (Table 23.3) is inversely proportional to the time from examination to the time at which spontaneous labor begins [3]. **Unfavorable (<5) Bishop scores at admission for induction of labor are associated with twofold to threefold increased risk of CD** when compared to spontaneous onset of labor [3, 4, 30]. Data show a score of ≥9 to predict a short time until onset of spontaneous labor and therefore indicate favorability for induction [29]. A simplified Bishop score might also be considered [31]. In a meta-analysis of mostly cohort studies aimed primarily to assess Bishop score as a predictor of cesarean, scores of 4, 5, or 6 were not predictive. A Bishop score of 8 or 9 had a negative predictive value of 96% for cesarean [32]. In an additional meta-analysis that included a larger sample of studies and randomized trials, higher Bishop scores were associated with a higher rate of vaginal delivery. A Bishop score of 4 had an OR of 2 for vaginal delivery, whereas a Bishop score of 8 increased the odds of vaginal delivery by 5.5 [33]. A Bishop score of **≥9** is usually associated with a **probability of vaginal delivery** after labor induction **similar to that after spontaneous labor** [16].

Transvaginal cervical length

In a systematic review of mostly observational studies, a cervical length (CL) of <30 mm did not predict vaginal delivery; a CL >30 mm did not predict cesarean section [34]. When compared with Bishop score, there was no significant difference in the prediction of successful labor induction, mode of delivery, vaginal delivery within 24 hours of starting induction, or achievement of the active stage of labor [35, 36]. In nulliparas, a CL cutoff of 30 mm had a sensitivity of 70% and specificity of 74% for predicting cesarean [36].

Fetal fibronectin

Of five prospective observational trials [37–41], only one showed an association with positive fetal fibronectin and successful induction [37]. As such, **fetal fibronectin is not recommended to predict which patient's labor induction will result in a successful vaginal delivery.**

Induction/Ripening methods

Induction of labor is one of the most-studied interventions in obstetrics, with hundreds of trials reported. Cervical ripening/induction agents can be functionally divided into two methods: **mechanical** and **pharmacologic**. Mechanical methods have been utilized since the days of Hippocrates, 460–360 B.C. Many methods have been compared not only to placebo or no treatment but also among themselves in different populations and clinical settings, making for an extensive experience.

Combination methods

Compared with prostaglandin alone, the **addition of a Foley** catheter to locally applied prostaglandins (PGE1 and PGE2) increases the likelihood of vaginal delivery within 24 hours in three trials, with a lower likelihood of observing no cervical change when a balloon catheter is used [42, 45]. There was no difference in CD between the groups in a network meta-analysis of 30 trials [42].

Compared to Foley alone, Foley with oxytocin reduced the total time to delivery, increased delivery within 24 hours, and had no effect on mode of delivery in a network meta-analysis of eight trials [42]. Either Foley with misoprostol or Foley with oxytocin can be used to significantly reduce total time to delivery [42].

For parturients undergoing an inpatient induction, the combination of cervical ripening and induction methods has been shown to reduce the time to delivery and should be considered if there are no other contraindications. Individual methods are described later. **In summary, Foley catheter combined with either misoprostol or oxytocin is the preferred method of inpatient labor induction for pregnancies without other contraindications to receive two agents**.

Mechanical methods

Mechanical methods include the following: hygroscopic dilators (laminaria, Lamicel, or Dilapan), balloon (Foley catheter, double-balloon catheters), and balloon with extra-amniotic infusion. Other methods reviewed under this category are membrane stripping and amniotomy.

Hygroscopic (osmotic) dilators (Laminaria, Lamicel, or Dilapan)

Hygroscopic devices are made either from synthetic or organic material. ***Laminaria*** are used as organic hygroscopic devices, which are made from cold-water seaweed. Under direct visualization facilitated by a vaginal speculum, *Laminaria* are placed in the cervical canal. Once in the cervix, the device absorbs water from surrounding tissues, causing it to slowly swell, dilating the cervix. Generally, the *Laminaria* are left in place for 6–12 hours but less than 24 hours. Sterility cannot be reliable ensured in the organic product. Polyvinyl alcohol polymer–magnesium sulfate (Lamicel) and polyacrylonitrile (Dilapan) were developed as synthetic hygroscopic devices to avoid this issue and allow sterile insertion into the cervix.

Currently, **no evidence exists to support using *Laminaria* to decrease either the interval from induction to delivery or the rate of CD when compared to vaginal PGE2, intracervical PGE2, oxytocin, or amniotomy** [43]. *Laminaria* were associated

with less uterine hyperstimulation compared to vaginal PGE2, but other secondary outcomes were uncertain based on an meta-analysis of >22,000 women (endometritis, meconium staining, NICU admission, etc.) [43].

Compared to 60 mL intracervical Foley, Dilapan-S was noninferior in achieving vaginal delivery with similar maternal infectious morbidity. Women reported higher satisfaction with Dilapan-S in one trial [44].

Balloon catheter

In 1853, Kraus first described a balloon device for preinduction cervical ripening. A vaginal speculum is often utilized to insert the Foley catheter in the cervical os, but placement via a digital examination is also common. The Foley catheter affects cervical ripening in two ways: (1) gradual mechanical dilation and (2) separation of the decidua from the amnion, stimulating prostaglandin release. Many studies have demonstrated the Foley catheter to be an effective tool for achieving a favorable cervix [45].

Technique

Optimally, the catheter is placed at a level above the internal cervical os, sometimes with the assistance of forceps or a clamp to guide the catheter. Placement may be done with the aid of a stylette if preferred, but it has not been shown to reduce the rate of failed insertion [46]. Rather, reduced insertion failure is associated with increased cervical dilation and experience of the practitioner [46]. **Placement should be attempted digitally without a speculum first**, as this is associated with lower pain score. However, compared to placement with a speculum, both digital and speculum methods had a high satisfaction score with women [47].

Once placed above the internal os, the operator uses sterile saline or water to inflate the catheter's balloon. Various sizes and balloon capacities have been investigated and used; these include a range from 25 to 80 mL balloons with 14–18 F catheters. **Compared to balloons filled with 30 mL, filling a balloon to 80 mL resulted in an average decreased time to delivery of 2 hours in a meta-analysis of seven studies** [48]. Correct placement is verified by gentle traction on the catheter until the inflated balloon meets the resistance of the internal os. Vaginal exam of the posterior fornix should be performed to palpate the balloon above the level of the internal os. Once the location is verified, gentle traction is applied by taping the distal end of the catheter to the patient's inner thigh. Adding weighted traction has not been shown to increase vaginal delivery overall, vaginal delivery within 24 hours, or decrease the CD rate [49]. **If the Foley is not expulsed within 12 hours, consideration should be given to removing it and starting the induction with oxytocin**, as leaving it in 24 hours is associated with longer inductions but no reduction in rate of CD [50].

Efficacy

Compared with no treatment, one trial reported Foley catheters to have no effect on the risk of CD [45].

Compared with all locally applied prostaglandins (LAPGs), including PGE2 and misoprostol, the rate of CDs is the same in a meta-analysis of 21 studies ($n = 3202$) [45]. There was no significant difference in vaginal delivery in 24 hours in the Foley catheter group [45]. LAPGs were associated with a higher rate of excessive uterine activity, and the Foley catheter was associated with an increased need for oxytocin augmentation in labor according to a meta-analysis of nine trials [45].

Compared with vaginal misoprostol, transcervical Foley catheter has been demonstrated to be **equivalent** for cervical ripening. There is a **similar risk of CD, chorioamnionitis and other maternal and perinatal outcomes, except a higher incidence of tachysystole associated with misoprostol** (RR 2.9, 95% CI 1.39–5.81) [51–54]. Foley was associated with a longer time from induction to delivery in two meta-analyses [53, 55]. In a network meta-analyses of 51 RCTs, vaginal misoprostol reduced the risk of not achieving a vaginal delivery in 24 hours (RR 0.43, CI 95% 0.35–0.67) and cesarean section (RR 0.84, 95% CI 0.0.71–0.99), but Foley catheter reduced the risk of hyperstimulation (RR 0.15, 95% CI 0.07–0.3) [55].

Compared with dinoprostone (intracervical and vaginal), Foley catheter had similar rates of not achieving a vaginal delivery within 24 hours and CD. Foley catheter was significantly less likely to cause hyperstimulation than vaginal dinoprostone (RR 0.27, 95% CI 0.12–0.52), but not intracervical dinoprostone [55].

Compared with use with oxytocin for cervical ripening, Foley use without oxytocin was associated with a lower rate of CD (RR 0.57, 95% CI 0.38–0.88) [45]. There was no difference in tachysystole with or without FHR changes between groups [45].

Theoretical risks associated with Foley catheter use include bleeding, fever, displacement of the presenting part, and premature rupture of membranes (PROM) (Figure 23.2). However, **no randomized trial has shown an increase in these complications** in comparison to other methods. Foley should not be used in women with low-lying placentas. Overall, **the Foley catheter is an inexpensive, safe, well-tolerated, and easy tool for cervical dilation** [56]. In a review of over 1200 low-risk women who received the intracervical Foley catheter for cervical ripening, there were no adverse events necessitating delivery in the preinduction ripening period [57]. In a meta-analysis of 26 trials including 5563 women, there was no increased risk of infectious morbidity with Foley catheter use [56]. **Foley is as effective as other methods, including misoprostol, and possibly safer than pharmaceutical methods and should be considered as first line in all inductions** (see Chap. 21).

Sequential ripening

There is no evidence the Foley catheter after pharmacologic ripening will reduce time to delivery or CD rate in those women who

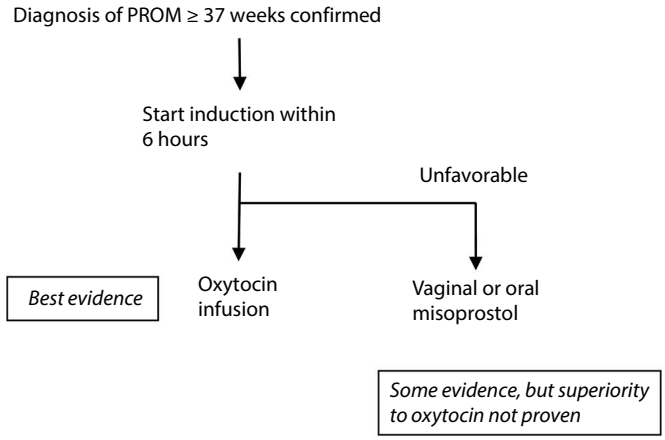


FIGURE 23.2 Induction for prelabor rupture of membranes (see Chap. 21).

have not achieved a favorable Bishop score after the initial ripening method [58]. Serial ripening with repeated doses of dinoprostone similarly have shown increased time to delivery without affecting the CD rate [59]. **Using cervical ripening in sequence (as opposed to simultaneous) does not improve obstetric outcome and should be avoided**. Oxytocin is recommended after the initial cervical ripening course is completed.

Extra-amniotic saline infusion

Extra-amniotic saline infusion (EASI) involves, as the term states, infusing usually saline through the cervix by a Foley balloon. For information on infusion of PGE2, see the section "Extra-amniotic Prostaglandins."

Compared with LAPG, EASI showed no difference in risk to delivery >24 hours, CD, or tachysystole (six studies, $n = 747$) [45].

Compared with PGE2, EASI with an intracervical Foley balloon is associated with **shorter time intervals to yield a favorable Bishop score** and similar incidence of CD [45, 60–62].

Compared with vaginal misoprostol, EASI with an intracervical Foley balloon and oxytocin is associated with a shorter induction-to-delivery interval in one trial, but no difference in another [63, 64]. There was similar incidence of CD in both trials [63, 64].

Compared with *Laminaria*, EASI with an intracervical Foley balloon is associated with **a shorter induction-to-delivery interval** and fewer **CDs for failed induction** in one trial [64].

Compared with Foley only, EASI with Foley catheters has been associated with a shorter induction-to-delivery interval in one RCT [65] but not in another larger RCT [66].

In summary, **there is insufficient evidence to use EASI instead of Foley balloon for cervical ripening**.

Double-balloon Foley catheters

Double-balloon Foley catheters (Cook Catheter or Atad catheters) have become more frequently used for mechanical labor induction. The catheter is designed specifically for labor induction, providing an intracervical and vaginal balloon to compress the cervix in addition to membrane separation to ripen the cervix. Both balloons in the Cook catheter are approved to fill to a volume of 80 mL in each balloon.

Compared to PGE2, no difference in CD rates were reported in five RCTs [67–71]; one RCT of 126 women found a higher rate of CD in the dinoprostone group [72]. Time to vaginal delivery was shorter in the double-balloon group in two out of four RCTs reporting on the outcome [68, 69, 71, 72], and delivery within 24 hours was increased for the double-balloon group in two of three trials reporting the outcome [69, 71, 72]. Overall maternal and neonatal morbidity was similar in both groups, except tachysystole was more common with PGE2 [72]. **There is insufficient evidence to support the use of a double-balloon catheter over PGE2 for labor induction**.

Compared to a single-balloon Foley catheter, there was no difference in time to delivery, CD, or intrapartum fever in two meta-analyses of four trials [67, 73]. Additionally, there was a higher rate of patient discomfort with the double-balloon catheter compared to single-balloon Foley [73]. Time from induction to delivery was longer in the double-balloon group in one trial [68]. There is also a significant cost difference between the catheters: single-balloon Foley catheters may cost up to $12–$14 (US) for large balloon catheters (75 mL), but are cheaper when 30 mL balloons are used. The double-balloon catheter costs labor and delivery units over $200 (US) per unit. **There is currently insufficient evidence to support the use of double-balloon catheters over single-balloon catheters for the induction of labor. Until further information is available, a Foley catheter should be used over a double-balloon catheter for both efficacy and economic concerns**.

Membrane stripping (or sweeping)

Membrane stripping is the practice of inserting a finger through the internal os and sweeping to separate the membranes from the lower uterine segment. This technique stimulates prostaglandin release, as plasma prostaglandin levels have been observed to increase post-stripping. Sweeping the membranes promotes the onset of labor and is found acceptable to a vast majority of women [13].

Compared with no sweeping or a sham procedure, sweeping of the membranes at term (i.e. weekly starting at 38 weeks) is associated with a slight **increase in spontaneous labor** (RR 1.21, 95% CI 1.08–1.34) and **reduced frequency of labor induction** (RR 0.73, 95% CI 0.56–0.94), although certainty on these outcomes was low due to heterogeneity and multiple biases [13]. To avoid one formal induction of labor, sweeping of membranes must be performed in eight women. **Rates of CD and maternal and neonatal morbidity are similar**. Discomfort during vaginal examination and other adverse effects (bleeding and irregular contractions) are more frequently reported by women allocated to sweeping, but are not associated with complications.

Studies comparing sweeping with prostaglandin administration (vaginal or intracervical) did not show a difference in induction of labor, spontaneous vaginal delivery, cesarean, or spontaneous labor. Sweeping more than once weekly did not increase the vaginal delivery rate or decrease the need for labor induction. Membrane sweeping also was not more effective than amniotomy and oxytocin for promoting spontaneous labor, induction of labor, or cesarean [13].

When used as a means for induction of labor, the woman should be counseled that her chance of going to spontaneous labor after one sweeping at term is about 36% in the next 48 hours versus 17% without sweeping (so doubling the rate of onset of labor) [74]. Possible complications such as bleeding, infection, and ruptured membranes are not found to be increased with stripping [74]. **In nulliparas being induced with PGE2 and oxytocin**, the **addition of membrane sweeping** is associated with a **shorter induction-to-delivery interval and increased vaginal delivery rates** in one trial [75]. No differences were noted in nulliparas with favorable cervices or in multiparas.

In women attempting trial of labor after cesarean (TOLAC), weekly membrane sweeping had no effect on spontaneous labor or vaginal delivery rate [76]. Membrane stripping was also found to be safe in group B streptococcus (GBS) carriers, without any cases of neonatal sepsis, death, or serious neonatal morbidity in a trial of 542 women [77]. There was also no increase in neonatal composite morbidity.

Amniotomy

Amniotomy—artificial rupture of the membranes—is another technique used in labor induction. There is **insufficient evidence** to assess the effectiveness of amniotomy alone [78]. No trials compared amniotomy alone with intracervical prostaglandins. If performed without cervical ripening or achieving a favorable cervix, amniotomy may be followed by long intervals before onset of labor. **In induced patients, early amniotomy is associated with a shorter duration of labor and no increase in CD in a meta-analysis of four trials** [79]. The rate of intrapartum fever is mixed in RCTs and warrants additional research [79].

Pharmacologic methods

Pharmacologic methods include the prostaglandins—E1: misoprostol; E2: dinoprostone; and F2a—as well as mifepristone, estrogen, relaxin, oxytocin, etc.

Misoprostol

Misoprostol (Cytotec; PGE1) is an endogenously produced hormone that acts locally on surrounding tissues. Through complex molecular actions, PGE1 stimulates uterine contractions and cervical dilation in a manner akin to the onset of spontaneous labor. More specifically, PGE1 potentiates calcium ion transport across the cellular membrane and regulates cyclic adenosine monophosphate (AMP) within the uterine smooth muscle cells to trigger contractions. PGE1 facilitates cervical ripening by stimulating the pathway leading to activation of collagenases. Collagenases, in turn, break down the structural collagen network of the cervix, yielding a softer, thinner cervix.

Although it is currently on the market as a 100-mg tablet to prevent peptic ulcers, misoprostol is available and widely used in an "off-label" form for preinduction cervical ripening and induction. **Misoprostol should not be used for cervical ripening or labor induction in women with prior uterine incisions** (e.g. prior CD) **after 28 weeks** [16, 19]. For use of misoprostol for induction in the second trimester, see Chap. 57 in *Maternal-Fetal Evidence Based Guidelines.* Misoprostol can be administered vaginally, orally, buccally, or sublingually.

Vaginal misoprostol

Vaginal misoprostol is most commonly administered by placing a tablet in the posterior fornix of the vagina. Several studies have focused on the dose administered. **Vaginal misoprostol in doses above 25 μg every 4 hours is more effective** (higher success rate for vaginal delivery within 24 hours of induction, decreased need for oxytocin, and decreased induction-to-delivery intervals) **than conventional methods of labor induction, but with more uterine hyperstimulation**. **Lower doses (25 μg) are like conventional methods in terms of effectiveness and risks**. Lower doses of misoprostol compared with higher doses were associated with more need for oxytocin augmentation and less uterine tachysystole, with and without FHR changes, and less meconium aspiration and less CD for nonreassuring fetal heart rate tracing (NRFHT) [80, 81]. Therefore, **25 μg of misoprostol** (one-quarter of a 100-μg tablet) **given not more frequently than every 3–6 hours has been recommended** by the ACOG [16].

Compared with placebo, misoprostol is associated with reduced failure to achieve vaginal delivery within 24 hours (RR 0.51, 95% CI 0.37–0.71) and with increased uterine tachysystole without FHR changes (RR 3.52, 95% CI 1.78–6.99) [80, 81].

Compared with vaginal PGE2, vaginal misoprostol is associated with a higher rate of vaginal delivery in 12 or 24 hours and similar cesarean and hyperstimulation risk in a meta-analysis of 11 studies [82]. There was a reduced need for oxytocin augmentation with misoprostol compared to vaginal dinoprostone [80]. These results remain unchanged when a separate meta-analysis by Liu et al. analyzed only singleton pregnancies [83]. A later network meta-analysis of 92 studies confirmed the shorter time to delivery with vaginal misoprostol compared to vaginal PGE2, although it did also show higher rates of hyperstimulation in vaginal misoprostol, unlike the prior meta-analysis [55]. However, the risk of hyperstimulation is primarily dose dependent. Vaginal misoprostol <50 μg has an OR of uterine hyperstimulation of 2.75 (95% CI 1.36–5.04) compared to placebo [81]. Vaginal misoprostol >50 μg has an OR of 4.40 (95% CI 2.22–7.94) compared to placebo. When compared to dinoprostone, the CIs cross, but are higher for high-dose vaginal misoprostol and slow-release vaginal PGE2 pessary (Cervidil) (OR 2.97, 95% CI 1.36–5.73) [81]. Additionally, the cost of a 50-μg pill of misoprostol is approximately $2 compared to the dinoprostone vaginal insert at approximately $168 [82].

Compared with intracervical PGE2, vaginal misoprostol showed a reduction in the number of failed vaginal deliveries in 24 hours and reduced risk of CD [55]. There is a slightly lower risk of hyperstimulation compared to both high-dose and low-dose vaginal misoprostol [55, 81].

Compared with oral misoprostol solution and all formulations of PGE2, a network meta-analysis including over 48,000 women showed that oral misoprostol solution had a higher vaginal delivery rate in 24 hours and reduced risk of CD. High-dose vaginal misoprostol, then low-dose misoprostol, followed as the most effective treatments [81].

In summary, **vaginal misoprostol less than or equal to 50 μg every 2 (25 μg) to 6 hours is a safe, effective means for cervical ripening and more effective than PGE2**.

Vaginal misoprostol insert

A 100-μg vaginal insert (which is equivalent to a 25-μg tablet fragment being inserted every 6 hours) had a similar time to vaginal delivery as a 10-mg dinoprostone vaginal insert in a randomized trial and similar CD rate [84]. Misoprostol inserts of 50, 100, and 200 μg have similar rates of vaginal delivery within 24 hours, but higher rates of NRFHT requiring CD and tachysystole in the 200-μg group [85]. Although 100 μg of vaginal misoprostol insert has a shorter time to delivery and similar CD rate compared to vaginal dinoprostone, the rate of tachysystole was much higher [86]. There was a higher rate of NRFHT and CD secondary to NRFHT in the high-dose misoprostol insert groups [86, 87]. In summary, **there is still insufficient evidence for clinical use of the misoprostol vaginal insert**.

Oral misoprostol

Compared with placebo in women with PROM, women who received oral misoprostol had a higher likelihood to deliver vaginally within 24 hours (RR 0.16, 95% CI 0.05–0.49), needed less oxytocin (RR 0.42, 95% CI 0.37–0.49), and had a lower cesarean section rate (RR 0.72, 95% CI 0.54–0.95) (see Chap. 21) [88].

Compared with vaginal PGE2, low-dose oral misoprostol (e.g. 20 μg) administered every 2 hours had the same rate of vaginal delivery in 24 hours and a significantly lower rate of CD [88, 89]. Women given oral misoprostol were also less likely to need a cesarean section (RR 0.88, 95% CI 0.78–0.99). There was some evidence that they had slower inductions, but there were no other significant differences [88].

Compared with oxytocin, oral misoprostol was associated with an increase in meconium-stained liquor in women with ruptured membranes (RR 1.65, 95% CI 1.04–2.6) but lower CD rate (RR 0.77, 95% CI 1.04 – 2.6) [88].

Compared with vaginal misoprostol, oral misoprostol had similar outcomes for vaginal delivery in 24 hours and CD in a meta-analysis of 37 RCTs [88]. There were fewer babies with low Apgar score or postpartum hemorrhage in the oral misoprostol group, but higher rate of meconium-stained fluid [88]. A network meta-analysis, which allows for ranking treatments across studies through indirect comparisons, found that vaginal misoprostol had the highest probability of performing best among all prostaglandins to achieve vaginal delivery in 24 hours, but oral

misoprostol avoided the most CDs [90]. When the informal analysis of both achieving vaginal delivery in 24 hours and avoiding CD was combined, low-dose (<50 µg) oral misoprostol performed best, followed by high-dose, then low-dose vaginal misoprostol [90]. A later network meta-analysis showed that vaginal misoprostol avoided failed vaginal delivery in 24 hours the most, but was not different from oral misoprostol for reduced chance of CD [55]. Compared with vaginal misoprostol, **low-dose titrated oral misoprostol (20–25 µg) given every 2 hours** was shown to cause fewer incidences of uterine tachysystole with FHR changes and a higher rate of vaginal delivery in 24 hours [89]. Studies that examine patient satisfaction have shown a definite preference toward oral administration [86, 87].

Sublingual misoprostol

Based on only three small trials, **sublingual** misoprostol appears to be at least as effective as when the same dose is administered orally [91].

Compared to vaginal misoprostol, a meta-analysis of five trials found no difference in vaginal delivery within 24 hours, tachysystole (when grouped according to dose), or CD for sublingual dosing [92]. There is **inadequate data** to assess safety, optimal dose, and side effects.

Prostaglandin E2 (dinoprostone)

PGE2 is an endogenously produced hormone that acts locally on surrounding tissues. Such effect is manifested in the smooth muscle of the uterus and gastrointestinal tract. PGE2 can be used for induction of labor via different routes of administration, such as vaginal, extra-amniotic, oral, and intravenous. The vaginal route is the most common route of administration of PGE2 for labor induction. It can be given in different forms, such as tablet, gel, and insert.

PGE2 vaginal gel

Dinoprostone gel (Prepidil) is packaged as a 0.5-mg dose in a 2.5-mL syringe. A shielded catheter is added to the syringe end to facilitate safe injection, usually intracervically. Under direct visualization using a speculum, the syringe contents should be injected into the endocervical canal using sterile technique. The patient should remain supine for 30 minutes to minimize leakage from the canal. An alternative method for administering the gel is to inject it into the posterior fornix or intravaginal administration. Until achieving a favorable cervix, dinoprostone 0.5 mg may be repeated every 6 hours up to a maximum dose of 1.5 mg in a 24-hour period. Once the cervix is favorable, oxytocin may be initiated for induction 6 hours after the last dose.

Compared with placebo, intracervical PGE2 is associated with a decreased risk of not achieving vaginal delivery within 24 hours (RR 0.61, 95% CI 0.47–0.79). There was a small, nonsignificant reduction of the risk of cesarean section when PGE2 was used (RR 0.88, 95% CI 0.77–1.0). The finding was statistically significant in a subgroup of women with intact membranes and unfavorable cervix (RR 0.82, 95% CI 0.68–0.98). The risk of tachysystole with FHR changes was not significantly increased (RR 1.21, 95% CI 0.72–2.05). However, the risk of tachysystole without FHR changes was significantly increased (RR 1.59, 95% CI 1.09–2.33) [93, 94].

Compared with PGE2 tablets, PGE2 gel has a similar rate of vaginal delivery not achieved in 24 hours, CD, hyperstimulation causing FHR changes, and oxytocin use [93].

PGE2 vaginal insert

The PGE2 vaginal insert (Cervidil) (also called a slow-release pessary) is a thin, vaginal insert containing 10 mg of dinoprostone and delivers roughly 0.3 mg of dinoprostone each hour over a 24-hour period. The insert is placed in the posterior fornix of the vagina and left in place until the desired ripening has occurred, when the insert is removed. Removal should occur at least 30 minutes prior to starting oxytocin.

Compared with PGE2 gel, a PGE2 insert is associated with an increased risk of not achieving a vaginal delivery within 24 hours (RR 1.26, 95% CI 1.12–1.41). There was no change in the risk of cesarean section (RR 1.07, 95% CI 0.93–1.22). The risks of tachysystole with FHR changes (RR 0.76, 95% CI 0.39–1.49) and without FHR changes (RR 0.80, 95% CI 0.56–1.15) were not different with the two methods of PGE2 administration. The use of sustained-release PGE2 inserts is associated with a reduction in instrumental vaginal delivery rates (RR 0.47, 95% CI 0.32–0.68) when compared to vaginal PGE2 gel or tablet. Compared with intracervical PGE2 low dose, intracervical PGE2 high dose has a higher rate of hyperstimulation with FHR changes but no change in CD rate [93].

Compared with dinoprostone insert followed by oxytocin, dinoprostone insert started concurrently with oxytocin is associated with a shorter induction-to-delivery interval and higher incidence of vaginal deliveries within 24 hours in one small trial [95].

Extra-amniotic prostaglandins

There is **insufficient evidence** to fully assess the effectiveness of extra-amniotic prostaglandins for induction of labor, with enough evidence to discourage its use compared with other methods (see also the section "Extra-Amniotic Saline Infusion"). Extra-amniotic placement of prostaglandins was first undertaken in the early 1970s and has been largely replaced with cervical or vaginal placement. Most of the studies used PGE2 (the minority prostaglandin F2α) and gel preparations. Of the primary outcomes, there were significantly fewer women delivered vaginally within 24 hours among those induced with extra-amniotic prostaglandin F2α (PGF2α) compared with vaginal misoprostol (RR 2.43, 95% CI 1.42–4.15). Oxytocin was used to initiate or augment labor more frequently when compared with vaginal misoprostol (RR 1.73, 95% CI 1.20–2.49). When extra-amniotic PGE2 was compared with Foley catheter only, the only difference between the groups was that there were fewer cases of unfavorable cervix at 12–24 hours following treatment (RR 0.59, 95% CI 0.41–0.86). There were no other significant differences when extra-amniotic prostaglandins were compared with other methods of cervical ripening or induction of labor. Although this could suggest that extra-amniotic prostaglandins are as effective as other agents, the findings are difficult to interpret because they are based on very small numbers and may lack the power to show a real difference [96].

Oral PGE2

All oxytocin treatments were more likely to achieve vaginal delivery in 24 hours compared to oral PGE2 [97]. Oral prostaglandin was associated with vomiting across all comparison groups. There are no clear advantages to oral prostaglandin over other methods of induction of labor [97].

Intravenous prostaglandins

IV prostaglandins **should not be used** for induction or cervical ripening. They are no more effective than IV oxytocin or

vaginal/cervical PGE2 for the induction of labor, but their use is associated with higher rates of maternal side effects (e.g. gastrointestinal, thrombophlebitis, pyrexia) and uterine tachysystole [98]. No significant differences emerged from subgroup analysis or from the trials comparing combination oxytocin/PGF2α and oxytocin or extra-amniotic versus IV PGE2 [98].

Oxytocin

In 1948, the posterior pituitary extract oxytocin was first used for labor induction via IV drip. Oxytocin was then synthesized by du Vigneaud and associates in 1953; this accomplishment won the Nobel Prize in Chemistry in 1955. Oxytocin is routinely utilized, as it is the drug of choice also for augmentation of labor. While induction of labor is the stimulation of contractions before the spontaneous onset of labor, augmentation is the stimulation of contractions in the face of inadequate contractions following the spontaneous onset of labor.

By increasing intracellular calcium concentration, oxytocin stimulates the smooth muscle cells of the breast, vessels, and, moreover, the uterus. Receptors for oxytocin are expressed in cells of the endometrium, liver, pancreas, and breast tissue. After the 13th week of gestation, myometrial cells express oxytocin receptors as well. Peak expression by the myometrium and endometrium occurs at term. Oxytocin increases both the amplitude and frequency of contractions, making labor effective. When continuously administered IV, oxytocin affects uterine response within 1 minute. Steady-state plasma concentrations are obtained within 40 minutes.

Overall, comparison of oxytocin with either intravaginal or intracervical PGE2 reveals that the **prostaglandin agents probably increase the chances of achieving vaginal birth within 24 hours** [99]. Compared with expectant management, oxytocin-alone inductions are associated with fewer women failing to deliver vaginally within 24 hours (8% vs. 54%; RR 0.16, 95% CI 0.10–0.25), but with the CD rate slightly increased (RR 1.17, 95% CI 1.01–1.35). There is a significant increase in the number of women requiring epidural analgesia (RR 1.10, 95% CI 1.04–1.17) [99]. **Compared with vaginal prostaglandins**, oxytocin alone is associated with an **increase in unsuccessful vaginal delivery within 24 hours** (70% vs. 21%; RR 3.33, 95% CI 1.61–6.89), irrespective of membrane status, but there was no difference in cesarean section rates [99].

Compared with intracervical PGE2 prostaglandins, oxytocin alone is associated with an **increase in unsuccessful vaginal delivery within 24 hours** (50% vs. 35%; RR 1.47, 95% CI 1.10–1.96). For all women with an unfavorable cervix regardless of membrane status, the cesarean section rate is also increased (19% vs. 13%; RR 1.37, 95% CI 1.08–1.74) [99].

Compared to vaginal prostaglandin F2α, there was no difference in CD rate (RR 1.19, 95% CI 0.65–2.18). The outcome of failing to delivery vaginally in 24 hours was not reported in any of the three RCTs included in the meta-analysis [99].

Oxytocin seems to be as effective as prostaglandins in women with PROM (see Chap. 21) [99].

Compared to low-dose oxytocin regimens (<100 mU in the first 40 minutes and <600 mU in the first 2 hours), there were no differences in rates of vaginal delivery not achieved within 24 hours (RR 0.94, 95% CI 0.78–1.14) or CD (RR 0.96, 95% CI 0.81–1.14). There was no difference in serious maternal or neonatal morbidity. No trials reported on the number of women who had uterine hyperstimulation with FHR changes. When high-bias studies were removed from the meta-analysis, there was a significant reduction of the induction to delivery interval and an increase in hyperstimulation without specifying FHR changes. Table 23.4 shows examples of each regimen (see also Chap. 7). **There is insufficient evidence to support the use of high-dose oxytocin over low-dose protocols** [100].

TABLE 23.4: Labor Stimulation with Oxytocin: Examples of Low- and High-Dose Oxytocin Protocols

Regimen	Starting Dose	Incremental Increase (mU/minute)	Dosage Interval (minute)
Low dose	0.5–1	1	30–40
	1–2	2	15
High dose	~6	~6	15
	6	6[a], 3, 1	20–40

[a] The incremental increase is reduced to 3 mU/minute in the presence of tachysystole and reduced to 1 mU/minute with recurrent tachysystole.

Prostaglandin F2α

Compared with placebo, vaginal PGF2α has a similar CD rate (RR 0.59, 95% CI 0.31–1.14). Vaginal delivery within 24 hours was not reported in the three trials included in a meta-analysis [93]. There were insufficient data to make meaningful conclusions for the comparison of vaginal PGE2 and PGF2α [93]. There are therefore **insufficient data** to assess the safety and efficacy of PGF2α for induction.

Mifepristone

Compared with placebo, mifepristone-treated women were more likely to be in labor or to have a favorable cervix at 48 hours (RR 2.41, 95% CI 1.70–3.42), were less likely to need augmentation with oxytocin (RR 0.80, 95% CI 0.66–0.97), and were less likely to undergo cesarean section (RR 0.74, 95% CI 0.60–0.92), but more likely to have an instrumental delivery (RR 1.43, 95% CI 1.04–1.96) and abnormal FHR pattern [101].

Compared to oxytocin, women treated with mifepristone for PROM after 36 weeks were less likely to have a vaginal delivery within 24 hours (RR 0.66, 95% CI 0.45–0.96) and their babies had an increased likelihood of neonatal adverse outcomes with more NICU admissions (RR 3.56, 95% CI 1.09–11.58) and abnormal FHR patterns (RR 4.36, 95% CI 1.02–18.66) in one trial [101]. Uterine hyperstimulation was not increased.

One poor-quality study comparing mifepristone to dinoprostone found no difference in cesarean rate but a smaller change in Bishop score for mifepristone [102]. **There is insufficient information available from clinical trials to support the use of mifepristone to induce labor**.

Estrogen

Several studies have shown that estradiol given via a variety of routes has the ability to achieve some degree of improved cervical ripening with minimal myometrial stimulation [103]. However, on the whole there were **insufficient data** to draw any conclusions regarding the efficacy of estrogen as an induction agent, given small, differing trials with different controls and different outcomes reported [103]. It also was not shown to improve Bishop score when compared to placebo in the outpatient setting [104].

Relaxin

There is **insufficient evidence** to assess the safety and efficacy of relaxin as an intervention for induction of labor. There are no reported cases of uterine tachysystole with NRFHT in any of the four

small trials [105]. Compared with placebo, relaxin is not associated with differences in CD [105]. In a phase 2 study, there was no difference in Bishop score between relaxin infusion and placebo [106].

Dehydroepiandrosterone sulfate

Dehydroepiandrosterone sulfate (DHEAS) is converted to estrogen by the fetoplacental unit, and it was investigated as a possible mechanism for cervical ripening without myometrial contractions. One trial of 84 women showed a 6-day difference to onset of labor and 4-hour shorter labor course for DHEAS compared to placebo, but this was only for nulliparous women ($n = 40$) [107]. Given twice-weekly infusions during the trial, there is **insufficient evidence** on its efficacy and would be quite cumbersome as a method of outpatient ripening, as one trial that investigated its use showed poor results when compared with placebo.

Dexamethasone sulfate

There is **insufficient evidence** to assess the safety and efficacy of steroids as induction agents. Compared with oxytocin alone, dexamethasone IM and oxytocin are not associated with significant effects in maternal and perinatal outcomes in one small RCT [108]. Compared to Foley catheter, Foley catheter plus extra-amniotic infusion of dexamethasone solution had a significantly shorter time from induction to delivery in one small RCT (11.9 ± 3 hours vs. 14.5 ± 4.8 hours, $p < 0.01$ [109].

Hyaluronidase

There is **insufficient evidence** to assess the safety and efficacy of intracervical injections of hyaluronidase for cervical ripening. It is not common practice, and it is an invasive procedure that women may find unacceptable in the presence of less invasive methods. In one RCT, when compared with placebo for cervical ripening, intracervical injections of hyaluronidase resulted in women receiving significantly fewer cesarean sections (RR 0.37, 95% CI 0.22–0.61), less need for oxytocin augmentation (10% vs. 47%; RR 0.20, 95% CI 0.10–0.41), and increased cervical favorability after 24 hours (60% vs. 98%; RR 0.62, 95% CI 0.52–0.74). No side effects for mother or baby were reported in this trial [110]. Compared to Foley catheter, hyaluronidase was associated with a higher CD rate and no difference in oxytocin use [111].

Nitric oxide donors

Nitric oxide (NO) donors **do not appear currently to be a useful tool** in the process of induction of labor. A meta-analysis including 23 studies compared NO donors with placebo, vaginal PGE2, intracervical PGE2, vaginal misoprostol, and intracervical catheter. There is no evidence of any difference between failed vaginal delivery within 24 hours, CD, or hyperstimulation [112]. There was an increase in nonserious maternal side effects (nausea, headache) [112].

Other methods

Acupuncture

There is insufficient and conflicting evidence to assess the efficacy of acupuncture for induction of labor. Compared with a sham procedure, **the use of acupuncture prior to a scheduled induction is not associated with any difference in the need for induction agents or CD, but had greater cervical change** [113].

Breast stimulation

Compared with no intervention, breast stimulation is associated with a significant **reduction in the number of women not in labor at 72 hours** (63% vs. 94%; RR 0.67, 95% CI 0.6–0.74). This result is not significant in women with an unfavorable cervix. The rate of postpartum hemorrhage is reduced (0.7% vs 6.0%, RR 0.16, 95% CI 0.03–0.87). There is no significant difference in the cesarean section rate, in the rate of meconium staining, or in uterine tachysystole. The three perinatal deaths were associated just with breast stimulation (1.8% vs. 0%; RR 8.17, 95% CI 0.45–147.77) [114].

Compared with oxytocin alone, breast stimulation had similar rates of women not in labor after 72 hours, cesarean section rates, and meconium staining. Three of the four perinatal deaths were in high-risk women in the breast stimulation group (17.6% vs. 5%; RR 3.53, 95% CI 0.40–30.88) [114]. Until **safety issues** have been fully evaluated, breast stimulation should not be used in high-risk women [114].

Castor oil

Castor oil **should not be used routinely for induction of labor, given the incidence of maternal side effects and insufficient evidence for efficacy** [115]. There was no evidence of a difference in caesarean section rate in the two trials reporting this outcome (RR 2.04, 95% CI 0.92–4.55). No data were presented on neonatal or maternal morbidity. All women who ingested castor oil felt nauseous [115]. One additional small trial ($n = 81$) found no difference in labor at 24, 36, and 48 hours after ingestion of castor oil compared to sunflower oil [116]. However, a sub-analysis of 37 women did show some benefit for onset of labor for multiparous women. Forty percent of women had an increase in bowel movement after ingestion, but there was no increase in meconium staining or abnormal FHR tracing [116].

Enemas and baths

There are no trials on enemas or baths for induction of labor.

Homeopathy

There is insufficient evidence to recommend the use of homeopathy (e.g. with *Caulophyllum*) as a method of induction. **No benefits** were seen in the two small, poor-quality trials [117].

Sexual intercourse

Women randomized to sexual intercourse had similar incidence of spontaneous labor compared to the control group (RR 1.02, 95% CI 0.98–1.07) [118]. **Intercourse is not effective to induce labor in women with low-risk term pregnancies**.

Summary

Most cases of inpatient inductions who require cervical ripening should be performed with **two agents**. Evidence supports the combination of **Foley catheter (single balloon, inflated to 60–80 mL, with or without traction) and misoprostol (e.g. 25 µg every 2–4 hours; or 25mcg followed by 50 mcg every 3–4 hours)**. If misoprostol is contraindicated, oxytocin IV infusion is recommended with Foley catheter. Once cervical ripening is completed (i.e. 12 hours of Foley catheter use, four to six doses of misoprostol), oxytocin infusion is recommended. Amniotomy should be performed once regular contractions are achieved, and usually after Foley expulsion and cervix is about >3–5 cm dilated, with the head engaged. If the Bishop score is ≥9 or there is rupture of membranes (ROM), oxytocin IV infusion is recommended.

Fetal testing during cervical ripening

Fetal heart monitoring during cervical ripening depends on the agent used. There are no trials to assess the effectiveness and best

modality for monitoring. In general, a nonstress test (NST) should be obtained before any induction or cervical ripening agent is used to assure fetal well-being. After administration of **PGE2 gel or tablet**, the fetal heart can be monitored continuously for about 0.5–2 hours, although the proper amount of time for monitoring is unclear. After administration of **PGE2 insert**, the fetal heart can be monitored continuously for the duration of the insertion [119]. After administration of **misoprostol**, the fetal heart should be monitored continuously, given the higher chance of contractions and uterine tachysystole with related NRFHT [120].

Outpatient versus inpatient

Induction of labor in outpatient settings appears feasible, but the evidence is still insufficient for routine use for most methods. Important adverse events are rare [121]. There is insufficient evidence to know which induction agents are most effective and safe to use in the outpatient setting. A meta-analysis of seven trials ($n = 1610$) had high heterogeneity for many outcomes, and many of the prespecified obstetric and safety outcomes were not reported, with high risk of bias and imprecision [121]. There **is limited evidence to assess the safety of outpatient misoprostol** for induction of labor. While effective in decreasing the length of gestation and induction-to-delivery interval, the safety of this approach, even at low (25 mg) doses, is still unproven in the three small trials [122–124]. There **are insufficient data to assess the safety of outpatient dinoprostone for induction of labor**. In an RCT including 827 women, the outpatient dinoprostone group had more NRFHT and were unable to be discharged home. Over half of the randomized women did not receive the allocated intervention secondary to labor or not requiring ripening [125]. **For this reason, prostaglandins are not recommended in the outpatient setting**.

Conversely, **there is a large body of evidence that supports the safety of inpatient Foley catheter use, with one of the lowest risks of hyperstimulation** [81]. Although outpatient trials in Foley catheter ripening are also not powered for safety, there is a lower risk that intervention will be required [57]. Likewise, in a meta-analysis of 26 studies of mostly inpatient women who were ripened with a Foley catheter, this incidence of adverse effects was 0.26%, most of which were reported as pain or discomfort [126]. In a trial of 126 nulliparous women undergoing outpatient ripening with Foley catheter, an average of 4 fewer hours were spent on the labor and delivery unit. There was no difference in cesarean or infectious morbidity between the outpatient and inpatient groups [127]. Inpatient time was not reduced for multiparous women who underwent outpatient Foley catheter ripening in a separate trial; however, this was compared to inpatient ripening with Foley and oxytocin [128]. That trial also did not show any difference in mode of delivery, low Apgar score, or NICU admission [128]. Reduction in inpatient time was shown in a third trial of 170 nulliparous and multiparous women [129]. **If outpatient ripening is desired, it should be performed with a Foley catheter until other agents are studied more thoroughly**.

In one cost analysis performed alongside a prospective RCT, inpatient prostaglandin gel did not have a significantly increased cost compared to outpatient Foley catheter, although outpatient Foley catheter was associated with fewer prelabor hours spent on the birthing unit [82]. A survey conducted along with an outpatient induction RCT found that women were willing to accept an extra 1.4 trips to the hospital (2.4 trips total) and a travel time of 30 minutes per trip to be able to return to their own home while waiting for the priming to work, and overall preferred outpatient priming when the option was to return to their own home [130].

Women who are offered outpatient ripening should be of a low-risk population with reliable transportation back to the hospital in case of labor, ROM, decreased fetal movement, or bleeding. The patient should be able to opt for inpatient ripening if desired, receive verbal and written instructions prior to discharge, and complete 1–2 hours of monitoring prior to discharge with a reassuring fetal tracing.

Labor management during induction

The patterns by which labor progresses in spontaneous labor and electively induced labor are significantly different [30]. **Latent and early active phases proceed slower than a spontaneous labor in induced labor** in which cervical ripening was necessary. Induction not requiring cervical ripening may be associated with a quicker labor course from 4 to 10 cm [30]. The risk of CD is increased during the first stage of labor of an induction needing cervical ripening, mainly because of dystocia. Induction without need for cervical ripening may have no or only a minor effect on the risk of cesarean [30]. Applying the same standards of spontaneous labor curves (e.g. Friedman's curve) to induced patients may lead to an increased cesarean section rate in induction (see Chaps. 8 and 9).

When administering oxytocin, the target is to stimulate uterine activity that is enough to effect cervical change as well as fetal descent without compromising the fetus. Minimal criteria for effective uterine activity are three contractions per 10 minutes averaging greater than 25 mmHg above baseline, with five contractions in 10 minutes. The Montevideo unit was created in 1957 to describe the summation of the amplitudes of all contractions in a 10-minute window. Uterine tachysystole is defined as more than five contractions in 10 minutes. During induction with oxytocin, 91% of patients delivered vaginally achieved 200 Montevideo units without neonatal morbidity in one retrospective study [131]. Contraction pressures of ≥200 Montevideo units should be targeted in induction or augmentation of laboring patients to achieve adequate labor [131, 132]. **Induced labor should be managed, in general, as spontaneous labor** (see Chaps. 8 and 9). If active phase is not achieved within 24 hours, this is not a reason per se for CD. A **failed induction** should not be diagnosed until after **18–24 hours of oxytocin after membrane rupture in the active phase** (usually 6 cm in a nulliparous patient), assuming reassuring fetal heart pattern [11, 133].

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24

INTRAAMNIOTIC INFECTION AND INFLAMMATION (TRIPLE I)

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Key points

- Intraamniotic infection and inflammation (triple I) is the infection and/or inflammation of any combination of the amniotic fluid, placenta, fetus, fetal membranes, or decidua.
- Triple I is diagnosed by **maternal fever** (single temperature of ≥39°C or two temperatures of 38–38.9°C that are at least 30 minutes apart) **and one or more other clinical criteria**: **Maternal leukocytosis** (white blood cell [WBC] count ≥15,000/mm^3), **purulent cervical drainage**, and/or **fetal tachycardia** (>160 beats per minute for ≥10 minutes) in the absence of other causes of fever.
- Rates of triple I increase with duration of labor and rupture of membranes (ROM) greater than 24 hours.
- Triple I is associated with increased maternal and neonatal morbidity.
- Rates of cesarean delivery are higher in women with a diagnosis of triple I.
- The clinical diagnosis of triple I may not correlate with histologic findings in the placenta, which has led to a shift in separating *suspected* intraamniotic infection based on clinical criteria from *confirmed* intraamniotic infection by Gram stain, glucose level, culture results, or placental pathology.
- **Antibiotics** (e.g. ampicillin and single-dose gentamycin) **should be given at the time of diagnosis of suspected intrapartum triple I**. Because isolated maternal fever is a common occurrence during labor, when it occurs, antipyretics should be given and a clinical suspicion for triple I should be raised. If the fever persists without other clinical signs of triple I, it is reasonable to start antibiotics.
- **Antibiotic treatment can generally be stopped after vaginal delivery. For cesarean, anaerobic coverage (clindamycin or metronidazole) should be added intrapartum, and one additional dose of triple I regimen given postpartum**.
- Neonates delivered after a triple I diagnosis should be evaluated and treated as per Centers for Disease Control and Prevention (CDC) and American Academy of Pediatrics (AAP) guidelines. In general, if a maternal fever occurs prior to the delivery of a **neonate <34 weeks, workup and antibiotic treatment are recommended. In neonates ≥34 weeks born to mothers with a diagnosis of *isolated maternal fever or suspected triple I,* workup and treatment with antibiotics are recommended only for ill-appearing babies**, while most can instead be closely observed in the nursery. Antibiotics are usually continued for 24–48 hours and stopped when culture results return as negative.
- There are several **preventive techniques** shown to decrease rates of triple I. Some of these include antibiotic prophylaxis in prelabor rupture of membranes (PROM), as well as limiting the length of labor—especially with ROM—and the number of vaginal examinations.

Definitions/Diagnosis

A wide range of terminology continues to be used in the literature to describe intrapartum infection. The term "**chorioamnionitis**" has traditionally been used to describe infection of the amniotic fluid, placenta, membranes, and/or umbilical cord; however, "**intraamniotic infection and inflammation**" (**triple I**) may be a more accurate representation of the clinical picture. As evidenced by decades of research and intellectual exchange, the ongoing clinical challenge of diagnosis and management of triple I is still disputed [1]. A 2016 National Institute of Child Health and Human Development (NICHD)–sponsored workshop of maternal and neonatal experts proposed separating triple I into three different categories: (1) isolated maternal fever, (2) suspected intraamniotic infection, and (3) confirmed intraamniotic infection [2]. For clinical purposes, the American College of Obstetrics and Gynecology (ACOG) recommends using the term "**intraamniotic infection**" alone because confirmation of intraamniotic infection will most commonly be after delivery.

The clinical and histologic presentation of triple I is heterogeneous, and its association with maternal and neonatal morbidity varies widely (Table 24.1). Maternal fever is the most important and identifiable sign [3]; however, isolated maternal fever may be from an extrauterine source or may not be infectious in etiology. Isolated maternal fever is defined as any temperature between **38 and 38.9°C** with no other clinical criteria to diagnose intraamniotic infection, with or without persistent temperature elevation. In line with the most recent ACOG Committee Opinion, **the definition of suspected intrapartum infection is maternal fever (≥100.4°F or 38–38.9°C) with at least one of the following criteria: Leukocytosis** (white blood cell [WBC] count ≥15,000/mm^3), **purulent cervical drainage, or fetal tachycardia (>160 beats per minute for 10 minutes) in the absence of other causes of fever** [4]. Intraamniotic infection can only be confirmed after delivery with histologic examination of the placenta or analysis of the amniotic fluid (such as Gram stain or culture) [4].

Ancillary signs of triple I have been identified and quantified in a number of studies [2]. The presence of maternal tachycardia is reported in 50%–80% of cases of triple I, and fetal tachycardia in 40%–70% of cases. Uterine tenderness and foul-smelling amniotic fluid are present in 70%–90% of cases, but tenderness may be masked by epidural anesthesia [5]. In fact, these clinical criteria for triple I diagnosis and ancillary signs correlate poorly with positive bacterial polymerase chain reaction (PCR) or culture by amniocentesis [6]. Furthermore, studies show that there is a poor relationship between clinical suspicion for triple I and histopathologic diagnosis postdelivery. Investigations particularly focusing on increasing latency in preterm labor have shown that other markers of inflammation—amniotic fluid WBC count, matrix metalloproteinase-8 (MMP-8), and interleukin-6—may lead to a more accurate diagnosis or better predict adverse outcomes [7, 8].

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TABLE 24.1: Definition/Diagnosis of Suspected Triple I

Maternal fever (single temperature of ≥39°C or two temperatures of 38–38.9°C that are at least 30 min apart) plus at least one of the following:
• Leukocytosis (WBC count ≥15,000/mm^3)
• Purulent cervical drainage
• Fetal tachycardia (≥160 beats per minute for ≥10 min)

Abbreviation: WBC, white blood cell; min, minutes.

Epidemiology

Triple I incidence ranges from 0.6%–19.7%, and a meta-analysis of high-quality studies showed a pooled incidence of 3.9% (95% confidence interval [CI] 1.8–6.8). This includes not only the United States but several other countries around the world [9]. This chapter focuses on triple I **at term** (≥37 weeks). The incidence of triple I in preterm births may be as high as 40% in deliveries under 27 weeks' gestation. The rate is higher in cesarean section, with as many as **12% of cesarean deliveries** having a clinical diagnosis of triple I [10].

In women with prelabor rupture of membranes (**PROM**), the reported incidence is higher. The Term PROM study showed a rate overall of **7%** in women with rupture of membranes prior to active labor [11]. In women with PROM greater than 24 hours, the rates of infection may be as high as 40% [12].

Pathophysiology

Triple I is largely considered to be an acute inflammation that is due to an ascending polymicrobial infection from the cervix after membrane rupture. Additional routes have been proposed, including hematologic dissemination from the gastrointestinal (GI) tract, retrograde spread from the peritoneal cavity via the fallopian tube, and iatrogenic spread through medical procedures [13]. In this setting, the most common bacteria implicated are *Ureaplasma*, *Urealyticum*, and *Mycoplasma*. Other bacteria often isolated in amniotic fluid cultures are *Gardnerella*, *Bacteroides*, group B streptococcus, and *Escherichia coli* [14]. Rarely, hematogenous spread is the source, as in the case of *Listeria* infection [15].

Triple I can be diagnosed histologically based on placental evaluation; however, a clinical diagnosis may not be confirmed by histologic studies. It has been reported that **up to one-third of clinical diagnoses may not have corresponding histologic findings** [16]. A number of grading systems have been proposed to describe the histologic severity of triple I, and they include depth and location of neutrophil infiltration of the placenta. A number of inflammatory markers may be associated with the clinical syndrome and histologic diagnosis of triple I, including cytokines such as interleukin (IL)-1-alpha, IL-1-beta, IL-6, and IL-8, among others. It is suggested that microorganisms invading the amniotic space stimulate these inflammatory cytokines, which favors the migration of neutrophils and ultimately produces the histologic diagnosis of triple I [17].

Risk factors

Risk factors for developing triple I include **longer duration of labor, prolonged rupture of membranes, meconium-stained amniotic fluid, use of internal fetal monitoring, group B streptococcus (GBS) colonization, nulliparity, bacterial vaginosis, delayed pushing in the second stage, and increased number of vaginal exams** [18–26]. For example, the International Multicentre Term Prelabor Rupture of Membranes Study (Term PROM) demonstrated that increasing the number of digital vaginal exams, longer duration of labor, and meconium-stained amniotic fluid were the most commonly identified risk factors for developing infection. There is some evidence that some of these previously identified risk factors are eliminated by controlling for confounders such as length of labor and prolonged rupture [4].

The increased risk of triple I in the setting of cervical catheter use for induction is controversial. A meta-analysis of several RCTs demonstrated that the use of **transcervical Foley catheters** for induction of labor was not associated with increased infectious morbidity [27]. In PROM alone, a recent multicenter randomized controlled trial (RCT) showed that a Foley catheter in addition to oxytocin does not shorten time to delivery; however, it does increase the incidence of triple I [28]. Furthermore, another multicenter RCT demonstrated that **delayed pushing** in the second stage results in higher rates of triple I compared to immediate pushing (6.7% vs. 9.1%; between-group difference, –2.5% [95% CI, –4.6% to –0.3%], $p = 0.005$) [25].

Complications

Maternal

Intrauterine infection is associated with increased risk of **cesarean delivery and endometritis, as well as postpartum hemorrhage, need for blood transfusion, intensive care unit (ICU) admission, and need for hysterectomy** (Table 24.2). The duration of triple I has been shown to be associated directly with blood transfusion and ICU admissions. Fortunately, infection rarely lasts greater than 24 hours after delivery, particularly when given a dose of antibiotics postpartum (see "Management" section). Treatment failure, defined as persistent fevers after receiving one postpartum dose of antibiotics, is reported to be from 2% to 6%. The patients likely to have treatment failures had either undergone cesarean delivery, had prolonged rupture of membranes, or were obese [29].

The risk of cesarean section is approximately twofold to threefold higher for a woman meeting clinical criteria for triple I [30, 31]. The increased risk is thought to be due to decreased uterine contractility and subsequent dysfunctional labor. Decreased

TABLE 24.2: Selected Possible Complications Associated with Triple I

Maternal
• Cesarean delivery
• Endometritis
• Postpartum hemorrhage
• Need for blood transfusion
• ICU admission
• Need for hysterectomy
Neonatal
• Pneumonia
• Meningitis
• Sepsis
• Risk of cerebral palsy or bronchopulmonary dysplasia
• Death

Abbreviation: ICU, intensive care unit.

uterine contractility may also lead to higher rates of postpartum hemorrhage due to atony; risk of postpartum hemorrhage after vaginal delivery may be up to 80% more likely, and 50% more likely after cesarean section [32]. The international multicenter **PPROMT trial** showed that with PPROM close to term—between 34 and 36.6 weeks—women who were managed expectantly had higher rates of hemorrhage (RR 0.6, 95% CI 0.4–0.9), intrapartum fever (RR 0.4, CI 0.2–0.9), use of postpartum antibiotics (RR 0.8, CI 0.7–1.0), and longer hospital stays (p <0.0001) compared with those who were delivered within 24 hours [33] (see Chap. 20).

Neonatal

Triple I is associated with increased rates of **bacteremia, sepsis, and mortality in neonates, as well as an increased risk of cerebral palsy** [34]. **A neonatal sepsis rate of 8% when born with triple I has been reported; the mortality rate of neonates born to mothers with triple I was 1.4/1000 as compared to 0.8/1000 of neonates born to mothers without infection** [35]. Intrapartum fever has been shown to increase transient neonatal adverse effects, including neonatal seizures and encephalopathy [36–39]. These risks are present in both term and preterm infants, though the relative risk is greater preterm. It is posited that the fetal inflammatory response is a contributing factor to cerebral palsy. Studies show that elevated levels of inflammatory cytokines were present in the amniotic fluid of mothers of children with cerebral palsy [40].

Recent studies emphasize that an *association* with cerebral palsy be differentiated from the *risk* of cerebral palsy when discussing triple I. One large meta-analysis delineated that *clinical* diagnosis of triple I was not a risk factor for cerebral palsy; however, an *association* was found. There was no association between *histologically* diagnosed triple I and cerebral palsy in preterm neonates, likely due to other factors related to preterm birth contributing to the neonate's outcome [41].

Complications from triple I have also been explored in children beyond the neonatal and infant years. Using NICHD data on magnesium for prevention of cerebral palsy in early preterm delivery, an observational cohort study demonstrated that there were no significant differences in Mental Developmental Index scores between children of mothers with or without triple I (19.1% versus 17%). This study did, however, show that neonates diagnosed with *sepsis* had decreased Mental Development Index scores at age 2 (absolute risk reduction [ARR] 1.36, CI 1.04–1.78). Therefore, though exposure to triple I does not result in measurable neurocognitive delays in children, a known complication of triple I, neonatal sepsis, was significantly associated with this outcome [42].

Management

Once triple I has been diagnosed at any gestational age, the recommended management is prompt delivery, with intrapartum antibiotics. Currently, expectant management without delivery for triple I is contraindicated, unless an amniocentesis is done and triple I is ruled out (e.g. amniotic fluid with glucose >15 mg/dL; negative Gram stain; negative culture).

Intrapartum

Initiation of antibiotics at the time of diagnosis is the standard of care for treatment of triple I (Table 24.3). This recommendation is supported by several studies demonstrating decreased maternal and fetal morbidity with administration of intrapartum antibiotics. These studies most consistently have shown decreased rates of neonatal bacteremia and sepsis, and also decreased rates of maternal febrile morbidity and length of postpartum stay [43, 44]. These data are exclusively from cohort studies; there still have been no RCTs to date comparing intrapartum antibiotics to no treatment/placebo for women with triple I. A recent analysis showed that the sensitivity and specificity of the NICHD criteria for suspected triple I to predict confirmed triple I were 71.4% (95% CI 61.4%–80.1%) and 40.5% (95% CI 33.6%–47.8%), respectively. Furthermore, the incidence of adverse clinical infectious outcomes was similar between the isolated maternal fever group and the suspected triple I group (11.8% in suspected triple I group, 9.5% in isolated fever group, $P = 0.5$), suggesting that febrile women not meeting criteria for suspected triple I are still at risk and may benefit from antibiotics [45]. **Because isolated maternal fever is a common occurrence during labor, when it occurs, antipyretics should be given and a clinical suspicion for triple I should be raised. If the fever persists without other clinical signs of triple I, it is reasonable to start antibiotics**, given evidence that the new criteria may not be inclusive enough to treat all those women and newborns who have potential to benefit from antibiotics. Furthermore, prospective, randomized controlled studies are still needed to better qualify the management of isolated maternal fever [4].

The source of triple I is thought to originate in the vaginal flora; coverage is therefore recommended to target beta-lactamase–producing aerobes and anaerobes. **Ampicillin and gentamicin** are the antibiotics most commonly used when the diagnosis of triple I is made in labor, based largely on clinical consensus, in the absence of data supporting other regimens [46]. **Twenty-four-hour dosing of the aminoglycoside** is equally effective as 8-hour dosing with the advantages of increased bactericidal effects, decreased nephrotoxicity, and decreased cost [47]. The two RCTs identified in a Cochrane review showed no statistically significant difference in maternal or neonatal outcomes when clindamycin was added to ampicillin and gentamicin [48, 49].

TABLE 24.3: Antibiotic Treatment for Triple I

Recommended Regimens

- Ampicillin and gentamicin[a] **or**
- Cefazolin and gentamicin **or**
- Clindamycin **or** vancomycin *and* gentamicin
- Add clindamycin (or metronidazole) for cesarean section

Duration

- Initiate treatment at time of diagnosis and continue intrapartum
- Vaginal delivery: Stop postpartum
- Cesarean: Single additional dose of chosen antibiotic regimen postpartum
- No indication for prolonged treatment in absence of clinical indications

Benefits

- Decreased rate of neonatal bacteremia, pneumonia, and sepsis
- Shorter maternal hospital stay
- Lower rates of persistent maternal fever

[a] Dosing recommendations: Ampicillin 2 g IV every 6 hours, gentamicin 5 mg/kg every 24 hours, cefazolin 2 g IV every 8 hours, clindamycin 900 mg IV every 8 hours, vancomycin 1 g IV every 12 hours.

For patients undergoing cesarean section, anaerobic coverage through antepartum **addition of clindamycin or metronidazole** to ampicillin and gentamycin is associated with fewer wound infections postpartum [50].

Antipyretics should be considered when maternal fever is present.

Delivery

Triple I itself does not necessitate cesarean section, unless otherwise motivated by standard obstetric indications, though there is an increased rate of cesarean delivery in the setting of triple I as described earlier. Time from initiation of antibiotic treatment to delivery has not been shown to affect outcomes; it is therefore **not recommended to expedite delivery for triple I alone**.

Postpartum

For women who had a vaginal delivery, antibiotics do not need to be continued postpartum, as shown by RCTs comparing antibiotics vs. placebo. The cure in these cases is the delivery itself.

In women who had a **cesarean delivery**, ACOG recommends at least **a single dose of the chosen antibiotic regimen after delivery** to decrease postpartum maternal morbidity, as the mode of delivery itself significantly increases the risk for postpartum maternal endometritis and wound infection. However, prolonged treatment has not been shown to improve outcomes [51–54].

Neonatal management

Maternal diagnosis of triple I can be associated with **serious implications for evaluation and management of the newborn**, even for well-appearing term infants. The NICHD, Centers for Disease Control and Prevention (CDC), and American Academy of Pediatrics (AAP) all recommend laboratory testing and antibiotic treatment for well-appearing infants born to mothers with either suspected or confirmed triple I [55, 56]. This often results in separation from the mother, admission to a neonatal intensive care unit (NICU), and potential exposure to drug-resistant bacteria in the NICU setting.

In addition to these health costs, the financial implications of triple I management of well-appearing infants has been estimated at $10,424,400 (treating all infants diagnosed each day for 2 days) [35]. **A "sepsis calculator" has been suggested as a tool to limit unnecessary treatment of well-appearing neonates**. The calculator combines categorical (GBS status, intrapartum antibiotic treatment) and continuous variables (peak febrile temperature, duration of ruptured membranes, gestational age) with the neonate's clinical presentation (clinically ill, equivocal, or well-appearing) during the first 6–12 hours of life. Studies have demonstrated that the incidence of early-onset sepsis in well-appearing neonates is extremely low (sepsis rate of 0.11/1000 [0.08–0.13]). Clinical application of the sepsis calculator has therefore reduced the proportion of unnecessary laboratory testing and antibiotic treatment, while not missing any cases of culture-positive sepsis [57, 58].

Neonatal management for well-appearing term infants with risk factors for sepsis is an evolving area of research. In general, if a maternal fever occurs prior to the delivery of a **neonate <34 weeks**, **workup and antibiotic treatment are recommended**. In **neonates ≥34 weeks born to mothers with a diagnosis of isolated maternal fever or suspected triple I, workup and treatment with antibiotics are recommended only for ill-appearing babies**, while most can instead be closely observed in the nursery. There is limited evidence regarding the length of neonatal antibiotic therapy. Antibiotics are usually continued for about 48 hours and stopped when culture results return as negative.

TABLE 24.4: Selected Strategies for Prevention of Triple I

- Decreasing length of labor
- Decreasing length of time of rupture of membranes (ROM)
- Antibiotic prophylaxis in labor if ROM to delivery >12 hours
- Decreasing number of digital exams

Prevention

Several interventions are associated with the prevention of triple I (Table 24.4).

Antibiotic prophylaxis for prevention of triple I in preterm PROM (**PPROM**) has been consistently shown to yield benefit for the neonate (see Chap. 20). Even in women with **term PROM**, antibiotic prophylaxis, especially in women expected to have latency from **PROM to delivery >12 hours**, has been associated with a significant reduction in the rates of triple I and endometritis [59] (Chap. 21). This benefit is extended to women with GBS isolated from vaginal flora, as shown in the PPROMT and PPROMEXIL studies [25].

Modifiable risk factors for triple I in term pregnancies present the opportunity for prevention, particularly length of ruptured membranes and length of labor [60].

Techniques used to shorten active labor have been shown to decrease maternal infectious morbidity. **Decreasing length of labor**, especially when ROM occurs, inherently decreases other risk factors associated with triple I, such as increased **number of digital exams**.

Perineal hygiene, in addition to prolonged supine positioning and digital exams, are suggested contributing factors to triple I [61]. A Cochrane review and another larger meta-analysis, however, showed no evidence that **vaginal chlorhexidine** during labor prevents triple I or neonatal infection and showed only a **statistically insignificant trend** toward a decrease in postpartum endometritis [62, 63]. Prophylactic antibiotics to reduce vaginal infections have been shown to lower rates of bacterial vaginosis and trichomonas, without a decrease in the risk of triple I or preterm birth [64, 65]. Two small trials showed that intrapartum amnioinfusion may decrease maternal temperature, but did not show consistent improvements in maternal or neonatal outcomes [66, 67]. A recent Cochrane review reinforced that there is insufficient evidence for amnioinfusion in reducing perinatal and maternal morbidity and mortality [68].

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25

MECONIUM

Meike Schuster and Justin S. Brandt

Key points

- Meconium-stained fluid becomes more common with advancing gestational age and occurs in over 25% of pregnancies past 42 weeks.
- Meconium-stained amniotic fluid (MSAF) is due to a combination of increased fetal bowel motility and decreased clearance of meconium by the fetus or placenta.
- **Meconium aspiration syndrome (MAS) occurs in about 5% of MSAF cases, and, of these, approximately 4% of affected neonates die**.
- Risk factors include pregnancy after 39 weeks, acute fetal acidemia, intrauterine infection, placental dysfunction leading to chronic hypoxia, uterine hyperstimulation, and prolonged labor.
- The most common ultrasound findings are ascites, dilated loops of bowl, calcifications, echogenic bowel, and polyhydramnios.
- **MAS is associated with neonatal morbidity and mortality, especially in a low-resource setting**.
- Discolored amniotic fluid <24 weeks (i.e. at genetic amniocentesis) is not due to meconium staining, but may be associated with intraamniotic bleed or infection.
- The presence of meconium or the change in thickness of meconium at term may be associated with possible nonreassuring fetal status and should prompt evaluation.
- **Induction of labor for 39 weeks' gestation is beneficial in reducing the risk of MAS**.
- **Amnioinfusion for MSAF is not associated with improvements in perinatal outcomes in settings with standard perinatal surveillance, but this intervention may be associated with improvements in perinatal outcomes in resource-poor settings**.
- There appears to be little benefit to the use of antibiotics during labor for MSAF and should be reserved for indications such as group B streptococcus (GBS) prophylaxis and chorioamnionitis.
- **Oropharyngeal and nasopharyngeal suctioning prior to delivery of the shoulders is not necessary and doesn't improve outcomes**.
- **Routine endotracheal intubation of nonvigorous newborns with MSAF should be avoided and discouraged**.
- The use of meconium and sections of the umbilical cord appear to be equivalent for the evaluation of in utero exposure to drugs, alcohol, and environmental factors, and either may be used for this purpose.

Historic notes

Meconium is a term derived from the Greek "mekoni," which means poppy juice or opium. Aristotle reportedly observed that meconium-stained amniotic fluid (MSAF) was associated with neonatal depression [1]. Confirming such clinical impressions, meconium passage was formally recognized to be associated with increased perinatal morbidity and mortality in the 1975 Collaborative Study of Cerebral Palsy.

Diagnoses/Definitions

Meconium is the intestinal fecal content of the fetus and is composed of mucopolysaccharides, blood by-products, hair, and squamous cells. The diagnosis of MSAF is made clinically on the basis of appearance (i.e. greenish or brownish staining) or by histopathologic examination of the placenta. Particularly in the preterm gestations, a clinical impression of MSAF may be false and instead reflect staining by another mechanism (i.e. hemosiderin). Meconium aspiration syndrome (MAS) is defined as neonatal respiratory distress requiring supplemental oxygen in the presence of MSAF without other causes of respiratory distress. MAS is classified as shown next.

Epidemiology/Incidence

The incidence of MSAF increases with gestational age. In a retrospective cohort study of 499,096 singleton births, the reported rates of MSAF were 5.1% in preterm gestations (<36 weeks), 16.5% in term gestations (37–42 weeks), and 27.1% in postterm gestations (>42 weeks) (Figure 25.1) [2]. Meconium in placental macrophages is documented in about 17%–19% of term placentas, and clinical evidence of MASF is present in about 12% (7%–22%) of term deliveries [3]. However, there is poor concordance between histologic and clinical evidence of meconium presence, probably due to the persistence of old meconium in macrophages after its clearance from the amniotic fluid, as well as new release of meconium by the fetus before uptake by placenta macrophages [4]. Moreover, there is discordance among histopathologists in the definition of the presence of placental meconium [5]. **In summary, meconium-stained fluid becomes more common with advancing gestational age and occurs in over 25% of pregnancies past 42 weeks**.

Etiology/Basic pathophysiology

Although regular fetal bowel movements occur as early as the second trimester [6], meconium does not become green (i.e. contains biliverdin pigments) until 22–24 weeks.

In term and postterm fetuses, physiologic increased motilin levels or pathologic increases mediated by fetal stress from hypoxia, infection, or cord compression may lead to meconium passage. Pregnancies >38 weeks show higher rates of MSAF and macrosomia, and these markers of neonatal morbidity and mortality are associated with MAS [3].

Aspiration of meconium can lead to respiratory compromise due to chemical pneumonitis associated with inhibition of

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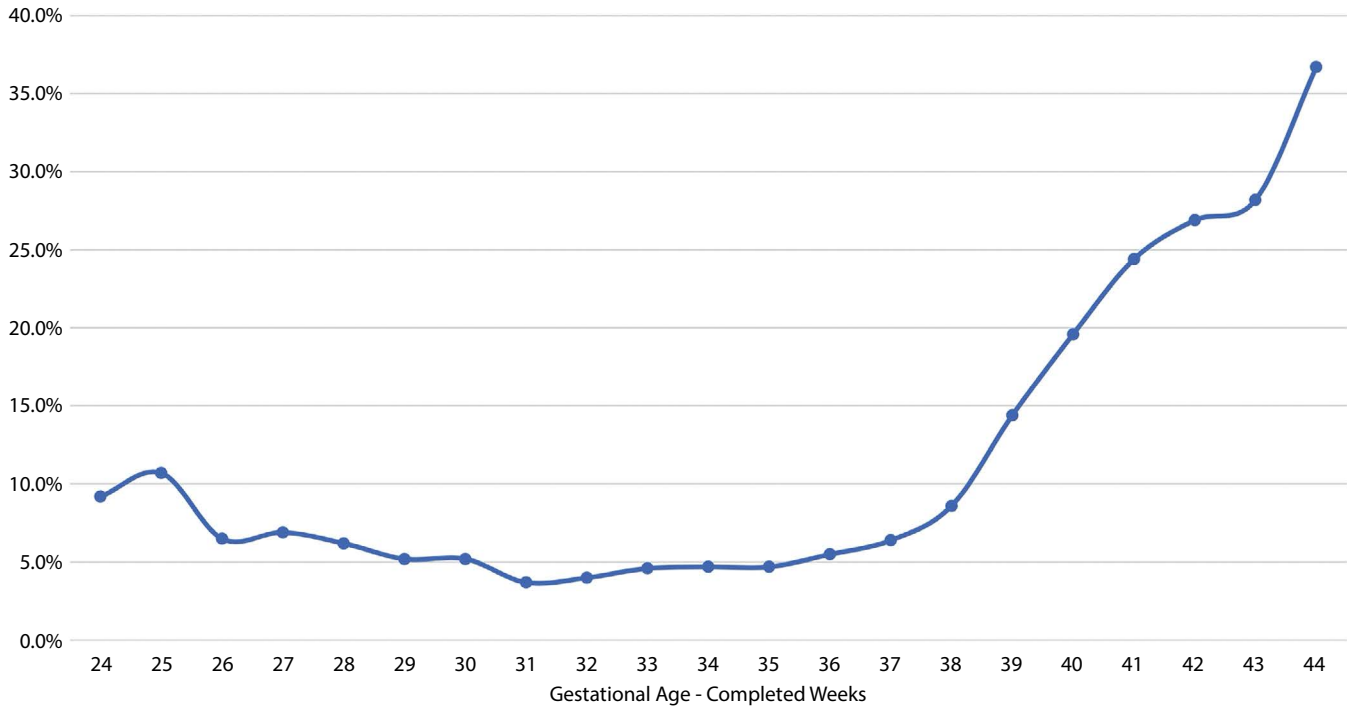


FIGURE 25.1 Percentage of births with meconium-stained fluid according to gestational age. (Adapted from Ref. 2.)

surfactant function, inflammation, and obstruction. However, respiratory compromise in the presence of meconium is more commonly due to other processes (such as chronic or acute asphyxia or intrauterine infection) than damage from meconium aspiration itself [7]. Factors such as intrauterine growth restriction, postmaturity (>40 weeks), nonreassuring fetal heart rate tracing, and caesarean birth have been associated with higher rates of MAS [8]. For example, hypoxia may stimulate colonic activity and fetal gasping, leading to meconium aspiration. In such cases, meconium is not causative of the respiratory compromise, but rather a manifestation of underlying chronic or acute processes leading to fetal compromise. **MAS occurs in about 5% of MSAF cases, and, of these, approximately 4% of affected neonates** die [9].

Symptoms

Symptoms of neonatal MAS include respiratory compromise, with tachypnea, cyanosis, and reduced pulmonary compliance. In some cases, pulmonary hypertension develops [9].

Classification of meconium aspiration syndrome

- Mild: Supplemental oxygen <40% for <48 hours
- Moderate: Supplemental oxygen ≥40% or for ≥48 hours
- Severe: Need for intubation (or primary pulmonary hypertension)

Risk factors

Postterm pregnancy; acute fetal acidemia; **intrauterine infection (as suggested by higher rates of histologic acute chorioamnionitis, clinical chorioamnionitis and endometritis, and neonatal sepsis in the presence of MSAF); placental dysfunction leading to chronic fetal hypoxia (e.g. fetal growth restriction, preeclampsia, oligohydramnios); uterine tachysystole (e.g. with misoprostol); and prolonged labor** (every 2-hour increase in duration of labor is associated with a 30% increase in the risk of MSAF) [10, 11]. The multiplicity of risk factors and the possible coexistence of independent risk factors (e.g. meconium and oligohydramnios) may explain why MSAF has inconsistently been associated with lower umbilical artery pH at birth.

Complications

Because the intrauterine processes underlying accumulation of meconium can jeopardize the fetus, MSAF and MAS can be associated with increased risk of fetal acidemia, neonatal seizures, neonatal intensive care unit (NICU) admission, neonatal sepsis, respiratory distress, neonatal encephalopathy, cerebral palsy, and neonatal death [3, 9, 12–14]. **MAS is associated with neonatal morbidity and mortality, especially in a low-resource setting**.

Pregnancy management

Prenatal diagnosis of meconium peritonitis (Figure 25.2)

Meconium peritonitis (MP) is a chemical peritonitis that occurs in utero from perforation of the intestines and is associated with cystic fibrosis, viral infections, and intestinal obstruction [15–17]. Incidence of MP is approximately 3.7 per 10,000 [18]. One study reported a prenatal diagnosis rate of 64.9%, with ascites being **the most common finding, followed by dilated bowel loops, calcifications, echogenic bowel, and polyhydramnios** [19]. Fetal MRI may assist in the diagnosis and planning for postnatal surgical repair of intestinal obstructions causing MP [20–22].

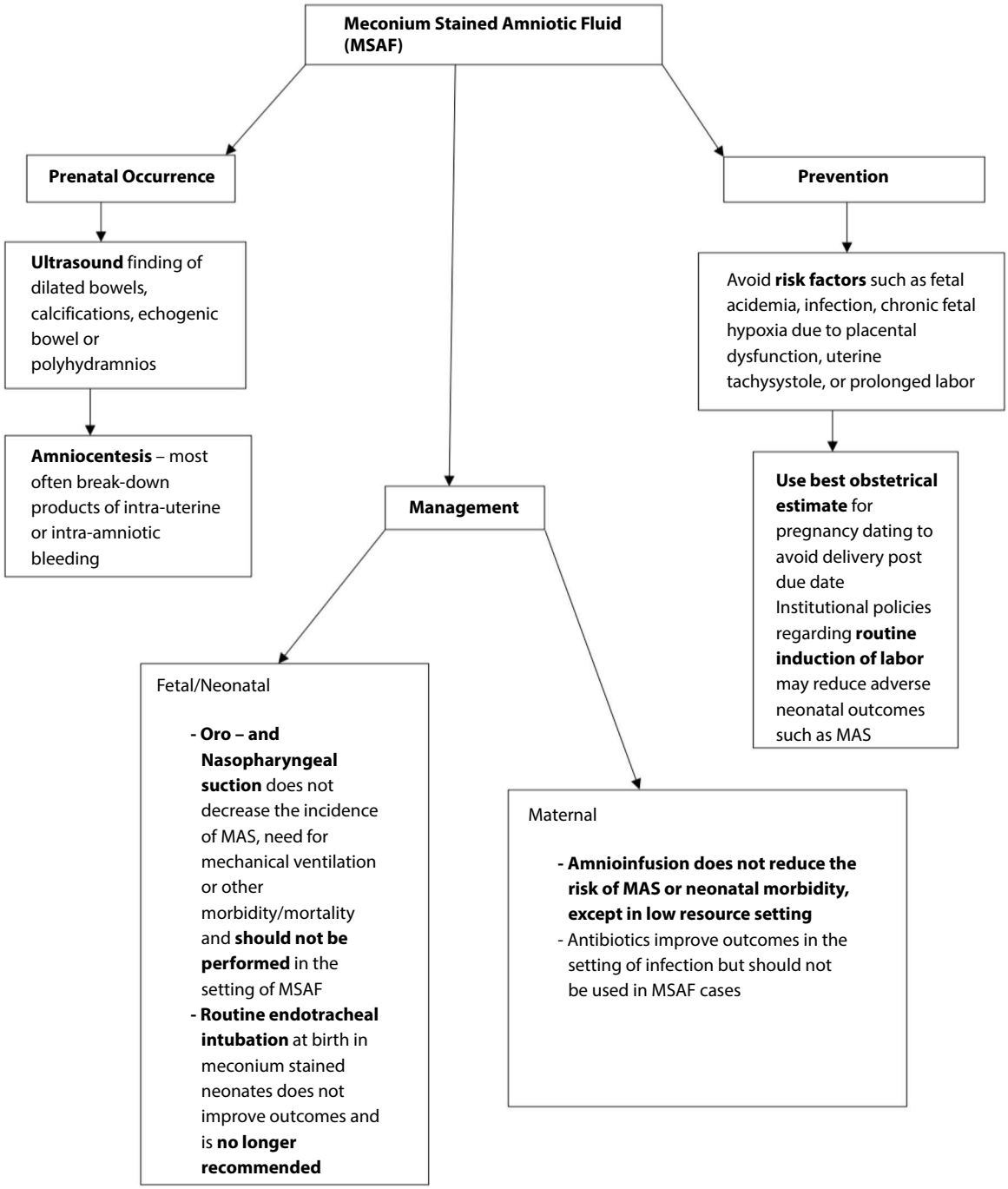


FIGURE 25.2 Suggested management of meconium-stained amniotic fluid.

Meconium at genetic amniocentesis

Discolored amniotic fluid <24 weeks (i.e. at genetic amniocentesis) is not due to meconium staining, but may be associated with intraamniotic bleed or infection. In this situation, evaluation for such causes of discolored amniotic fluid may be considered, including microbiologic studies on amniotic fluid; Kleihauer-Betke testing on maternal blood; careful sonographic examination for evidence of retroplacental or intraamniotic bleeding; and assessment of placental implantation by evaluating placental thickness, dimensions, echotexture, and cord insertion.

Meconium in the late preterm and early term fetus <39 weeks

MSAF in the late-preterm and early-term fetus should prompt evaluation for intrauterine infection and fetal hypoxia, as the finding is unlikely to be physiologic at these gestational ages.

Meconium at ≥39 weeks

Although fetal stress due to infection, hypoxia, and other causes may provoke meconium passage, MSAF in the term, late-term, or postterm fetus **may reflect normal physiology and maturation**

of the gastrointestinal tract. Progression in meconium consistency in labor from no/little meconium to the presence of thick meconium, or the occurrence of meconium in the setting of category II fetal heart rate tracings should elicit further evaluation, as these findings are associated with higher rates of fetal acidemia and lower Apgar scores at 5 minutes [23–25]. **The presence of meconium and fetal distress or the change in thickness of meconium is associated with possible fetal distress and should prompt evaluation**.

Prevention

Prevention of meconium passage and of MAS may be accomplished by reducing the rate of postterm deliveries. **Early ultrasound dating, stripping of membranes at ≥37-38 weeks, and induction of labor at 39 weeks decrease the incidence of postterm pregnancies** (see Chap. 23). Avoidance of fetal hypoxia may also reduce MSAF, but there is a lack of evidence-based strategies to achieve this aim. Induction has been shown to reduce the risk of MAS. In a meta-analysis of 11 randomized controlled trials (RCTs) that included term pregnancies and compared a policy of routine labor induction at or shortly after 41 weeks versus expectant management, there was a 23% reduction in the risk of MAS in the induction group versus expectant management group (relative risk [RR] 0.77 95% confidence interval [CI] 0.62–0.96) [26]. The ARRIVE trials, an RCT of 6096 patients, compared induction of labor vs. expectant management and showed an overall 20% reduction in perinatal composite adverse outcomes (RR 0.80, 95% CI 0.64–1.00), which included MAS, birth trauma, respiratory support, perinatal death, and other averse neonatal outcomes [27]. In summary, **induction of labor for 39 weeks' gestation reduces the risk of MAS** (see also Chap. 22) [28, 29].

Management techniques used in the setting of MSAF

Amnioinfusion

Amnioinfusion is instillation of isotonic fluid, typically normal saline, into the uterus via an intrauterine pressure catheter in a woman with dilated cervix and ruptured membranes. A "typical" approach involves instillation of 500 mL of normal saline over a period of 30 minutes. Amnioinfusion may be considered >34 weeks. For amnioinfusion in the presence of variable decelerations, see Chap. 11; for amnioinfusion for preterm prelabor rupture of membranes (PPROM), see Chap. 20; for amnioinfusion for oligohydramnios without PPROM, see Chap. 59 in *Maternal-Fetal Evidence Based Guidelines*.

The efficacy of amnioinfusion to "dilute" meconium, relieve cord compression, and reduce associated neonatal morbidity has historically been controversial. A recent meta-analysis on this topic included 14 RCTs [30]. Results were reported separately for clinical sites with and without capabilities for perinatal surveillance. The main outcome in the RCTs was usually occurrence of MAS. Under standard perinatal surveillance, amnioinfusion for MSAF was not associated with a reduction in MAS (RR 0.52, 95% CI 0.26–1.06), perinatal deaths (RR 1.00, 95% CI 0.29–3.45), or the combined outcome of perinatal death and severe morbidity (RR 1.13, 95% CI 0.88–1.47), compared with no amnioinfusion. There was considerable heterogeneity among studies for several secondary outcomes, such as presence of heavy meconium staining, caesarean delivery for nonreassuring fetal testing, occurrence of fetal heart rate decelerations, 5-minute Apgar score less than 7, presence of meconium below the vocal cords, and need for neonatal ventilation or NICU admission.

In a subgroup analysis that included three studies performed in settings with limited perinatal surveillance capabilities, amnioinfusion for MSAF was associated with a significant reduction in MAS (RR 0.17, 95% CI 0.05–0.52) and perinatal mortality (RR 0.24, 95% CI 0.11–0.53), as well as reductions in cesarean delivery for nonreassuring fetal testing, 5-minute Apgar score less than 7, neonatal ventilation or NICU admission, and neonatal encephalopathy, compared with no amnioinfusion.

In summary, **amnioinfusion for MSAF is not associated with improvements in perinatal outcomes in settings with standard perinatal surveillance, but this intervention may be associated with improvements in perinatal outcomes in resource-poor settings**.

Maternal antibiotics

There is insufficient evidence to assess the effectiveness of antibiotics for women with meconium in labor. A meta-analysis (including two RCTs, both of which utilized ampicillin-sulbactam, $n = 362$) found that antibiotic prophylaxis in women with MSAF is associated with a significant decrease in the risk of chorioamnionitis (RR 0.36, 95% CI 0.21–0.62) compared with normal saline, but is not associated with a significant reduction in the incidence of neonatal sepsis (RR 1.00, 95% CI 0.21–4.76), NICU admission (RR 0.83, 95% CI 0.39–1.78), and postpartum endometritis (RR 0.50, 95% CI 0.18–1.38) [31]. No serious adverse effects were reported. **In summary, based on the limited evidence available, there appears to be little benefit to the use of antibiotics during labor for MSAF, and they should be reserved for indications such as group B streptococcus (GBS) prophylaxis and chorioamnionitis**.

Neonatal [28, 29]

Oropharyngeal and nasopharyngeal suctioning

Although obstetric providers commonly suction the oropharynx and nasopharynx before delivery of the shoulders or the "first cry," there is insufficient evidence to support this practice. Indeed, an RCT of $n = 2514$ infants with MSAF who were randomized to suctioning versus no suctioning demonstrated no reduction in the incidence of MAS, need for mechanical ventilation for MAS, any other associated morbidities, or neonatal mortality [32, 33]. Another RCT that included over 500 infants was performed in a resource-poor community and also demonstrated no advantage of prenatal suctioning versus expectant management [34]. In summary, **it appears that oropharyngeal and nasopharyngeal suctioning prior to delivery of the shoulders is not necessary and doesn't improve outcomes**.

Endotracheal intubation

A policy of routine endotracheal intubation at birth with MSAF in neonates who are otherwise vigorous does not improve neonatal outcomes over routine resuscitation [35]. Neither the American Academy of Pediatrics (AAP) nor the American Heart Association recommends routine endotracheal suctioning for nonvigorous infants [36, 37]. In 2015, the AAP's Neonatal Resuscitation Program issued updated guidelines, which discouraged routine intubation of nonvigorous fetuses born through MSAF after an RCT showing that the rate of MAS and neonatal mortality was equal in those who were intubated and those who were not [38, 39]. Several studies have since evaluated the impact

of this change in management. Comparing outcomes of intubated neonates to those who were not, the studies found similar rates of MAS, inhaled nitric oxide and extracorporeal membrane oxygenation (ECMO), and morbidity and mortality, but lower rates of intubation (2.3% vs. 0.6%) and admission to the NICU (3.8% vs. 3.1%) [40–44]. One RCT following the change in recommendation found an increased risk of MAS (RR 1.4, 95% CI 0.792 – 2.470) and death (13.6% vs. 7.5%, $p < 0.05$) in those nonvigorous infants who were intubated in the delivery room [45]. Two large meta-analyses in 2020 revealed no difference in the rate of MAS between those infants intubated and those not intubated (RR 0.98, 95% CI 0.71–1.35) [46, 47]. **In summary, the routine endotracheal intubation of nonvigorous newborns with MSAF should be avoided and discouraged**.

Antibiotics and surfactant

Administration of surfactant and antibiotics to neonates with MAS reduces the length of hospital stay (mean difference –2.0, 95% CI, –3.66 to –0.34 and RR –4.68, 95% CI –7.11 to –2.24 days, respectively) and duration of mechanical ventilation (mean difference –1.31, 95% CI –9.76 to –1.03 days and mean difference 5.4, 95% CI –9.76 to –1.03 days). Rates of ECMO were also decreased (RR 0.64, 95% CI 0.46–0.91) [48]. In summary, **antibiotics and surfactant should be part of the standard of care when managing a neonate with MAS**.

Meconium and drug screening

Toxicologic evaluation of meconium is regarded as the gold standard for assessment of in utero exposure to drugs and alcohol during pregnancy [49, 50]. Its collection is cumbersome, and often samples are of insufficient quantity for use [51]. In a study that evaluated the detection of ethanol biomarkers in meconium samples, 15% of pregnant patients in Scotland consumed significant quantities of alcohol in the pregnancy [49]. A Canadian study revealed that the prevalence of alcohol in meconium was tenfold higher compared to what mothers had reported, contributing to approximately 1800 cases of fetal alcohol syndrome annually [52].

Meconium has also been used to screen for exposure to heavy metals, environmental exposures, and drugs (prescription and illicit drugs) [53–55]. Depending on the metal, some are more easily detected in maternal blood (i.e. zinc and iron), while others accumulate in meconium with greater abundance (i.e. copper) [56]. Postnatal testing of umbilical cord blood can detect amphetamines, barbiturates, and benzodiazepines, even at lower levels (4–10 ng/g vs. 30 ng/g) [51]. With respect to illicit drugs, umbilical cord blood analysis appears to have similar detection rates compared to maternal blood toxicology testing and may be easier to collect. The preferred testing modality should be chosen based on availability of testing in the area of practice [57, 58]. **In summary, the use of meconium and sections of the umbilical cord appear to be equivalent for the evaluation of in utero exposure to drugs, alcohol, and environmental factors, and either may be used for this purpose**.

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26

MALPRESENTATION AND MALPOSITION

Alexis C. Gimovsky, Andrea Dall'Asta, Giovanni Morganelli, and Tullio Ghi

Key points

- **Malpresentation, including breech, transverse and others**, is **associated** with **uterine anomalies, fibroids, placenta previa, grand multiparity, contracted maternal pelvis, pelvic tumors, prematurity** (the earlier the gestational age, the higher the incidence of malpresentation), **multiple gestation, polyhydramnios, short umbilical cord, fetal anomalies** (e.g. anencephaly, hydrocephalus), **abnormal fetal motor ability, and prior breech delivery**.
- **Complications** of breech presentation include **congenital anomalies, preterm birth (PTB), birth trauma, low Apgar scores, and low pH**, regardless of mode of delivery. **Cord prolapse, head hyperextension**, and **head or arm entrapment** are more common with vaginal breech delivery.
- **External cephalic version** (ECV) is a safe and effective intervention for malpresentation. **Urgent cesarean delivery (CD)** for nonreassuring fetal heart rate tracing (NRFHT) and placental **abruption** occur in <0.5% of ECVs.
- **ECV** is to be avoided with **any contraindications to vaginal delivery** such as placenta **previa**, or **prior classical uterine incision**. ECV is relatively contraindicated in rupture of membranes, oligohydramnios, known uterine or fetal anomaly, unexplained uterine bleeding, or active phase of labor.
- **ECV reduces the incidence of noncephalic birth by 54%** and **CD by 37%**. Because ECV is associated with a very low incidence of adverse events and with a significant decrease in CD, **all women at or near term with nonvertex presentations should be offered an ECV**. **Success rates** range **between 50% and 70%**. Success is increased with **higher parity, transverse or oblique lie, nonengaged presenting part, relaxed uterus, palpable fetal head, larger fore-bag and maternal weight less than 65 kg**.
- **Compared with ECV at term, ECV before term (e.g. 34–35 weeks) reduces noncephalic presentation at birth but does not reduce the rate of CD and may be associated with an increase in the incidence of PTB**. About **$36^{0/7}$–$36^{6/7}$ weeks is generally considered to be the optimal time for attempted ECV**.
- Tocolysis with **betamimetics** prior to attempt at ECV is associated with **fewer failures of ECV** and **fewer CDs**.
- **Anesthetic-dose neuraxial blockade (usually with spinal) is associated with a 63% increase in the success rate of ECV**.
- ECV should be performed, after appropriate counseling and consent, in a facility with ready availability for ultrasound and for emergency CD.
- **There is inconsistent evidence that moxibustion** at point BL67 alone or in combination with acupuncture **is associated with higher success rates of external cephalic version**, especially when performed in China.
- Compared with planned vaginal delivery (VD), **planned CD** for the **term breech** fetus is associated with **a small decrease in perinatal death and a reduction in serious neonatal morbidity, but no difference in death or neurodevelopmental delay at 2 years after delivery**.
- There is **insufficient evidence** to assess if outcomes of the **preterm** breech-presenting fetus are affected by mode of delivery.
- Planned VD of the **second nonvertex twin** by breech extraction is a reasonable management option by expert operator, as neonatal and maternal morbidities at planned CD or VD are equivalent.
- Manual rotation of the persistent occiput posterior or transverse malposition of the cephalic presentation to the occiput anterior position in the second stage is associated with a nonsignificant 14% decrease in operative (OVD and CD) delivery.

Definitions

Presentation: Fetal body part that is in the lower uterine segment (lowest in the uterus and closest to the cervix).

Malpresentation: Clinical entities where the presenting part is not the fetal vertex (Figure 26.1), such as the following: Breech presentation (Figure 26.2); transverse/oblique lie, compound presentation (Figure 26.3); shoulder presentation (Figure 26.4); and cephalic malpresentations secondary to deflexed fetal head: Sinciput (Figure 26.5), brow (Figure 26.6), and face (Figure 26.7) presentations.

Malpresentation

Symptoms

Maternal impression of fetal presentation based on fetal movement is suggestive but overall unreliable for predicting fetal presentation.

Epidemiology/Incidence

Breech presentation complicates **3%–4%** of all pregnancies at term (≥37 weeks) [1]. Its incidence is inversely proportional to gestational age, with an incidence of about 25% at 28 weeks, 11% at 32 weeks, and 5% at 34 weeks [2]. In 2003, **87% of all breech presentations resulted in cesarean delivery (CD)**; this is similar to 1990 (90%), but much increased from 1970 (12%) [3, 4]. Breech as an indication for CD accounts for 15% of all CDs and adds $1.4 billion to U.S. obstetric costs [4].

Transverse lie is reported to complicate less than 1% of the pregnancies at term [5]. **Oblique lie** is usually transitory and converts into longitudinal or transverse lie in early labor [5].

Sinciput, brow, and face presentations represent the three "classical" variants of cephalic malpresentation and are characterized by a progressive deflexion from vertex presentation. These malpresentations are quite rare with reported incidences of 1/600–1/2000 for face presentation [5] and 1/380–1/800 for

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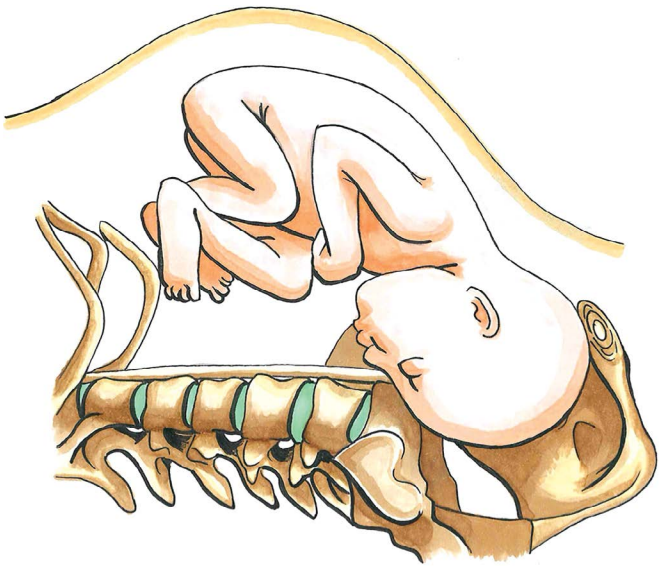


FIGURE 26.1 Vertex presentation.

brow presentation [6]. Sinciput presentation is likely to be underestimated, given its subtlety, but its incidence is largely unknown.

Classifications (see Figure 26.8 for a detailed algorithm)

Breech (Figure 26.2)

Fetus presents in longitudinal lie with head not in the lower uterine segment.

Fetal breech presentation is further classified as follows:

- *Complete*: Flexion of the fetal hips and knees
- *Incomplete*: Extension of one or both hips (includes footling)
- *Frank*: Flexion at the hips and extension at the knees

Transverse

The fetal longitudinal axis is perpendicular to the long axis of the uterus. The fetus can either present "back up" (fetal small parts present to the cervix) or "back down" (fetal spine or shoulder present to the cervix).

Oblique

The fetal longitudinal axis is diagonal to the long axis of the uterus.

Face (Figure 26.7)

The fetal head is hyperextended so that the fetal occiput is in contact with the fetal back and the mentum (chin) is presenting. The fetal chin may be anterior or posterior relative to the maternal pubic symphysis.

Brow (Figure 26.6)

The presenting part is the portion of the fetal head between the orbital ridge and the anterior fontanelle. The fetal head is positioned midway between full flexion and extension.

Sinciput (Figure 26.5)

The presenting part is the portion of the fetal head between the brow and the posterior fontanelle, corresponding to the anterior fontanelle. Sinciput represents a mild form of deflexion of the fetal head in the cephalic-presenting fetus.

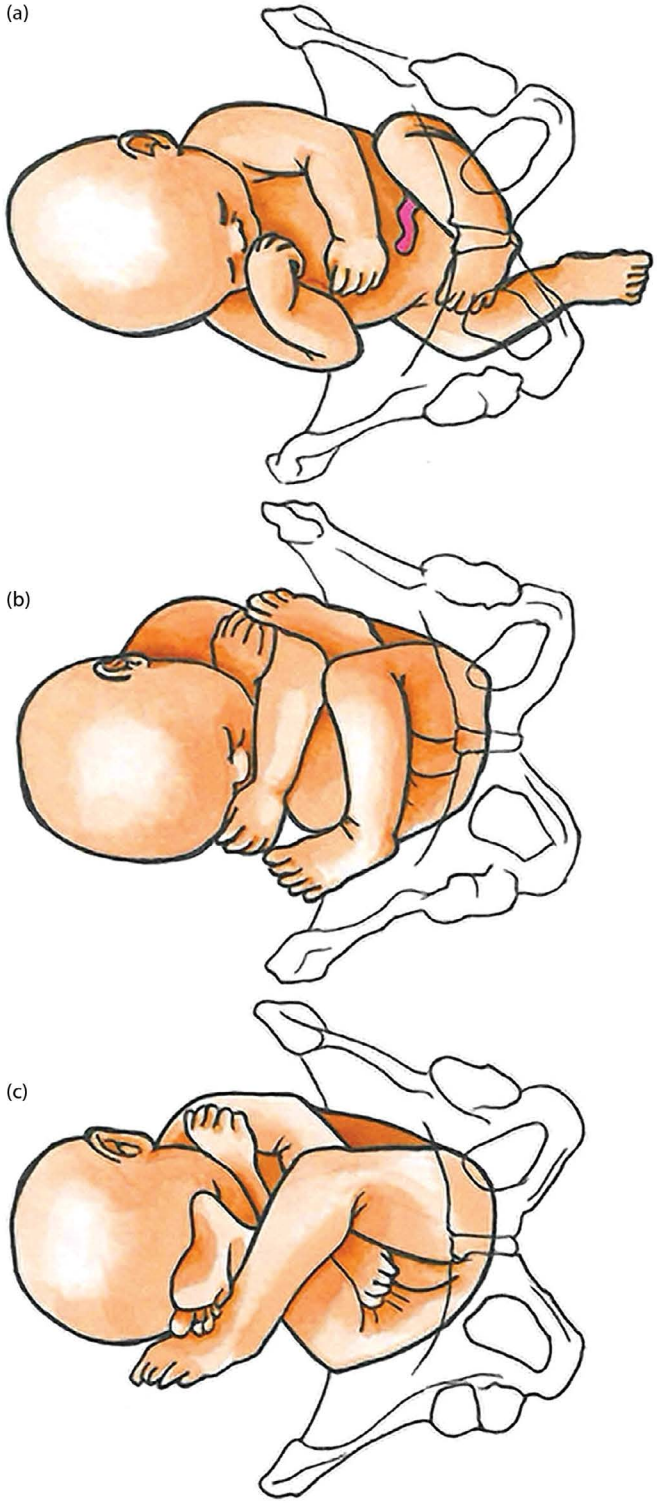


FIGURE 26.2 Breech presentation. (a) Footling breech; (b) complete breech; (c) frank breech.

Compound (Figure 26.3)

Simultaneous presentation of a prolapsing fetal extremity and the presenting part.

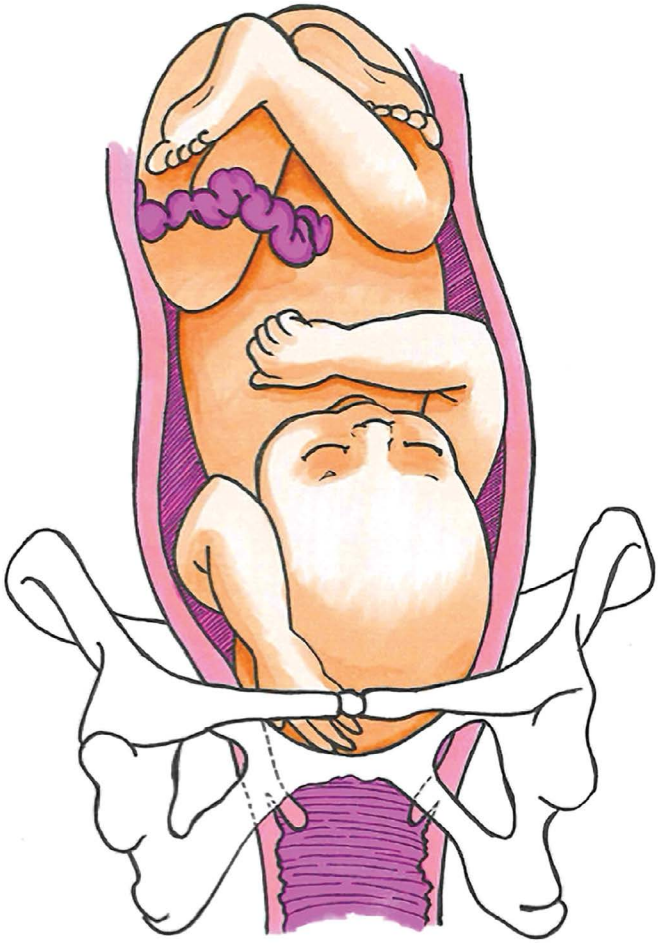


FIGURE 26.3 Compound presentation.



FIGURE 26.4 Shoulder presentation.

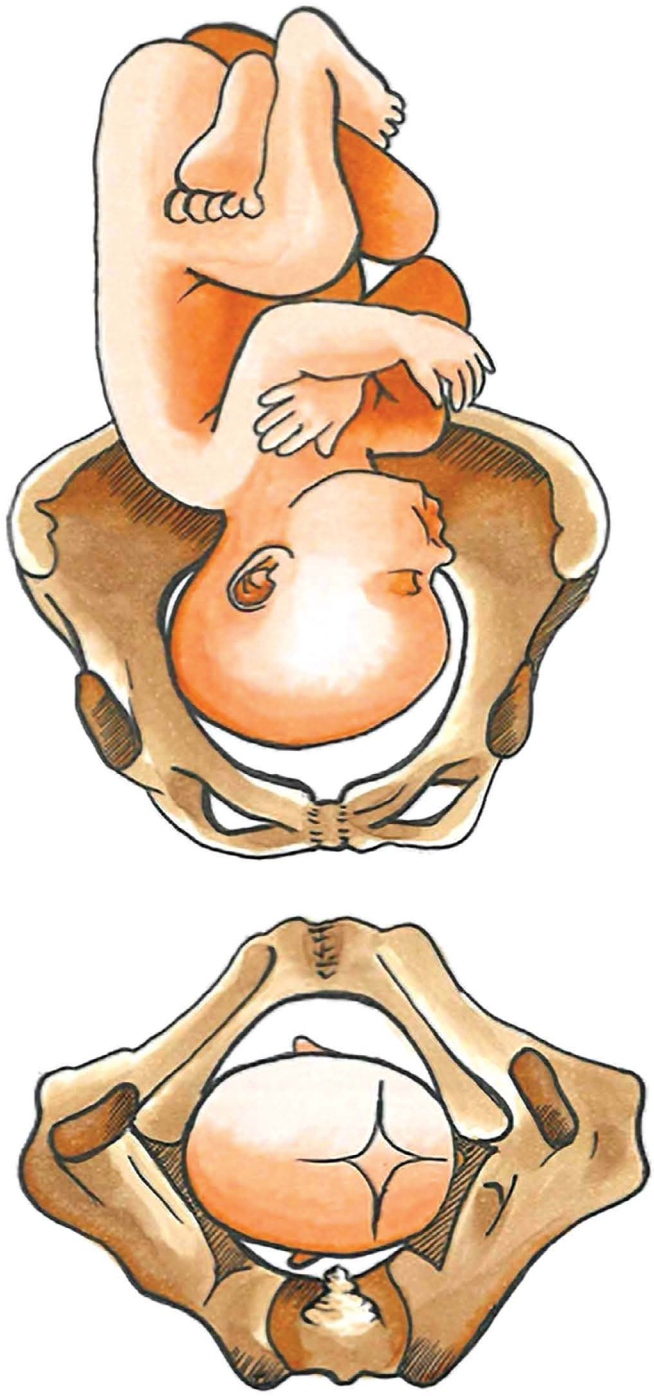


FIGURE 26.5 Sinciput presentation.

Shoulder (Figure 26.4)

The fetal shoulder is the presenting part.

Risk factors/Associations

Both maternal and fetal factors can lead to malpresentation, including **uterine anomalies, fibroids, placenta previa, grand multiparity, contracted maternal pelvis, pelvic tumors, prematurity** (the earlier the gestational age, the higher the incidence of malpresentation), **multiple gestation, polyhydramnios, short umbilical cord, fetal anomalies** (e.g. anencephaly, hydrocephalus), **abnormal fetal motor ability, and prior breech delivery**.

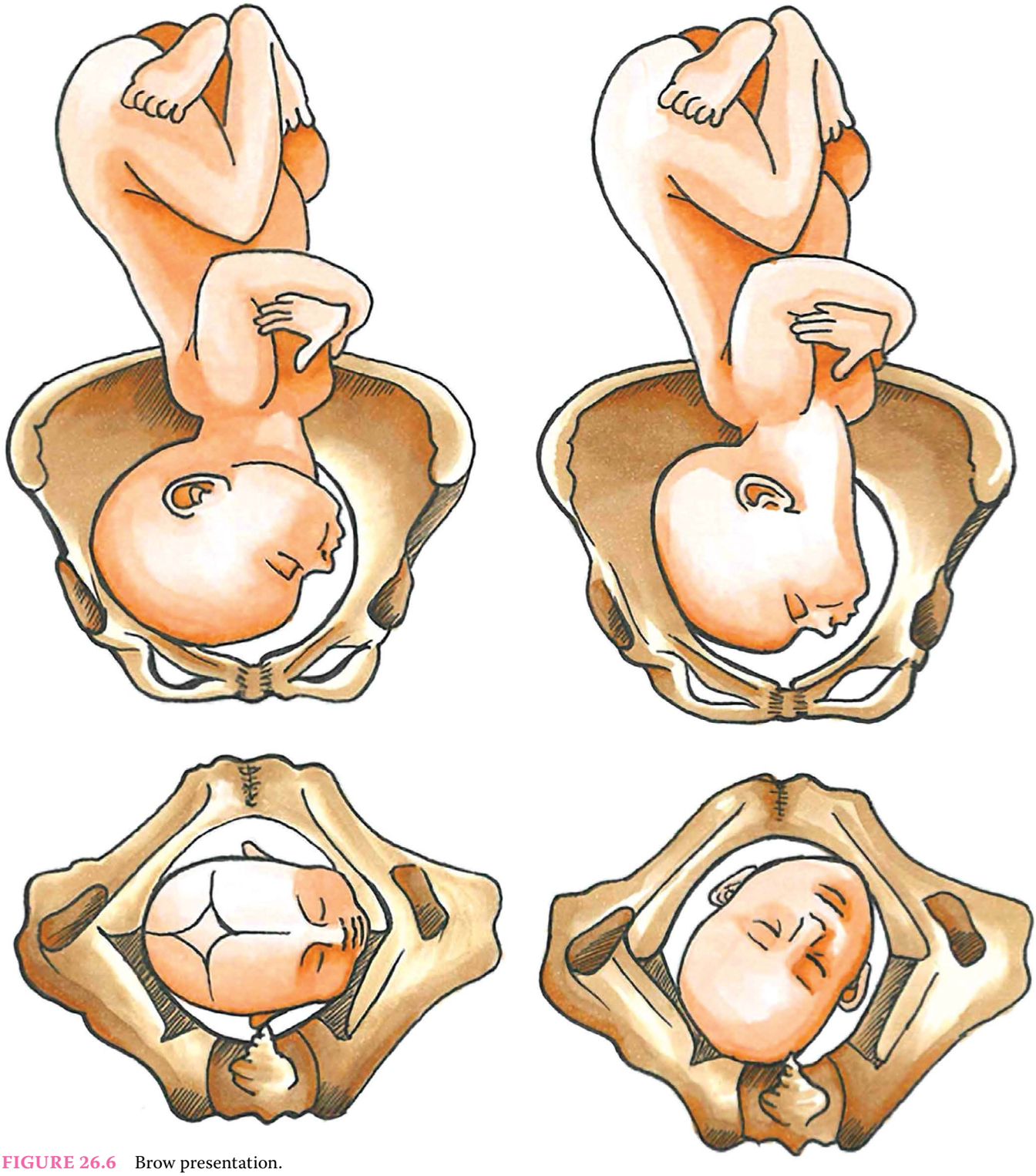


FIGURE 26.6 Brow presentation.

FIGURE 26.7 Face presentation.

There is a 9% risk of recurrence of malpresentation in subsequent pregnancies following a prior breech delivery.

Complications

Incidence of **congenital anomalies** (up to 6%), **premature birth (PTB), birth trauma, low Apgar scores, and low pH** are increased with breech presentation compared with vertex presentation, **regardless of mode of delivery**. Breech presentation may be both a sign and a consequence of fetal compromise, independent of delivery mode. Incidence of **cord prolapse** is the same with frank breech as with vertex presentations (<1%), 5% with complete breech, 15% with footling breech, and is inversely proportional to gestational age (GA). **Head hyperextension** (associated with spinal cord injury) and **head or arm entrapment** are associated with breech presentation, particularly with vaginal breech delivery. Presentation at birth does not seem to affect

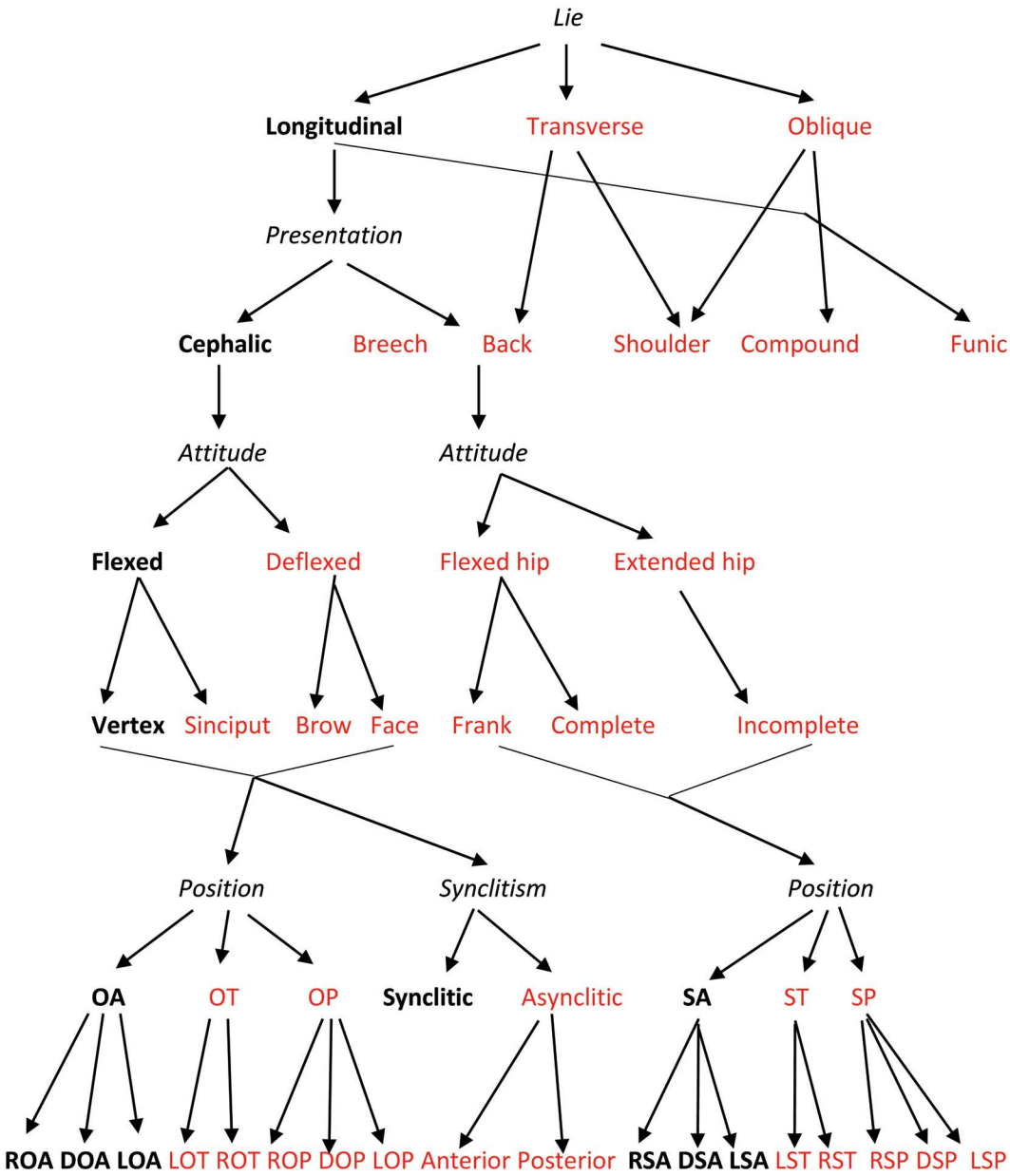


FIGURE 26.8 Malpresentations and malpositions. **Denominator**: The fetal reference point used in defining position. It is usually a prominent bony landmark at the circumference of the presenting part. For example, occiput for vertex, sacrum for breech, mentum for face, and acromion for shoulder presentation. **Fetal lie**: Orientation of the long axis of the fetus to the long axis of the uterus; Longitudinal orientation: Fetus and the mother's dorsal column are parallel; Transverse orientation: Fetus at 90 degrees to mother's dorsal column; Oblique orientation: Fetus is neither parallel nor 90 degrees to the mother's dorsal column, but is in transition between longitudinal and transverse lie. **Fetal presentation**: The lowermost structure of the fetus in the maternal pelvis. In the longitudinal lie, the fetal presentation can be either cephalic or breech. In the transverse lie, the presentation is usually the fetal back or shoulder; in the oblique lie, it is usually the shoulder or the arm. **Fetal attitude**: Degree of extension-flexion of the fetal head; the relation of various parts of the fetus to each other. For example, in the cephalic presentation: Vertex: Head is maximally flexed; Sinciput (military): Head is partially flexed; Brow: Head is partially extended; Face: Head is maximally extended. Breech presentation can be further defined based on the attitude or flexion of the hip and knee joints: **Frank breech:** Flexion at the hip and extension at the knees; **Complete breech:** Flexion at both the hip and knee joints; **Footling breech:** One or both hips and knees in a partial or intermediate extension. **Fetal position**: This is a description of the relation of the presenting part of the fetus to the maternal pelvis. In a longitudinal lie with a vertex presentation, the occiput of the fetal calvarium is the landmark used to describe the position. Direct occiput anterior: When the occiput is facing the maternal pubic symphysis. Right or left occiput anterior: If the occiput is between the ischial spines and the symphysis. Occiput transverse: If the occiput is located halfway between the promontorium of the sacrum and the symphysis; Right or left occiput posterior: The occiput approaches the sacrum. Direct occiput posterior: When the occiput is straight down (i.e. facing the sacrum or coccyx). In cases of breech presentation, the fetal sacrum is used for position. With transverse and oblique lies, the shoulder structures (acromion) can be used for the description of position. For a fetus in cephalic presentation and face or brow presentation,

FIGURE 26.8 (Continued)
the mentum is used for position. In a compound presentation, one or more extremities of the fetus will present in addition to the vertex or breech. **Asynclitism:** Malalignment of the head in relation to the axis of the birth canal; when one of the fetal parietal bones precedes the sagittal suture in the birth canal. *Abbreviations*: ROA, right occiput anterior; DOA, direct occiput anterior; LOA, left occiput anterior; LOT, left occiput transverse; ROT, right occiput transverse; ROP, right occiput posterior; DOP, direct occiput posterior; LOP, left occiput posterior; RSA, right sacrum anterior; DSA, direct sacrum anterior; LSA, left sacrum anterior; LST, left sacrum transverse; RST, right sacrum transverse; RSP, right sacrum posterior; DSP, direct sacrum posterior; LSP, left sacrum posterior. At term: In bold, normal; in red, abnormal.

adult intellectual performance. Cesarean or vaginal delivery for breech presentation does not differ in terms of long-term adult intellectual performance [7].

Transverse lie does not allow for the vaginal delivery of a term fetus, and the neglected transverse lie may lead to uterine rupture [5].

Cephalic malpresentations are estimated to account for approximately one-third of cesarean deliveries performed due to labor arrest [8–11].

Workup

Fetal presentation should be assessed by Leopold maneuvers at each prenatal visit starting at ≥34 weeks of gestation. If the clinician is unsure, a vaginal examination or an ultrasound may be indicated to assess fetal presentation. **Consideration should be given to a routine fetal position check by ultrasound at 36 weeks**.

In the cephalic-presenting fetus, the identification of malpresentations of the fetal head is most important in the context of labor abnormalities. In such conditions, **the use of intrapartum ultrasound** is **recommended** by the guidelines of the International Society of Ultrasound in Obstetrics and Gynecology [12], and several manuscripts have described the sonographic features of the malpresentations of the fetal head and their clinical role in the context of labor dystocia [13–24]. Intrapartum ultrasound can also be useful in the assessment of abnormal second stage of labor (see Chap. 9).

External cephalic version (see Figure 26.9 for suggested management)

Definition

Procedure performed by application of pressure and maneuvers to the maternal abdomen, with the goal to turn the fetus to a cephalic presentation, thus increasing the likelihood of vaginal delivery [1].

Complications

While the rate of short-term fetal bradycardia can be as high as 20%, the rate of the need for **urgent CD** for nonreassuring fetal heart rate tracing (NRFHT) after an external cephalic version (ECV) is about 1/600 [25]. Placental **abruption** (<1%) and **onset of labor** are uncommon complications. Rare fetal deaths following attempts at version have not been determined to be a result of the procedure [1]. Femur fracture has been reported. In a meta-analysis, there was a **4.7% risk of transient abnormal cardiotocography, 0.21% risk of abnormal cardiotocography leading to emergency CD** (with good neonatal outcomes), and **0.35% risk of emergency CD**. Other risks included 0.24% risk of stillbirth, 0.18% risk of placental abruption, 0.18% risk of cord prolapse, and 0.19% risk of fetal death. These complications were not found to be directly related to the ECV procedure. Vaginal bleeding related to ECV occurred in 0.34% of patients, and rupture of membranes related to ECV occurred in 0.22% of patients [26]. An additional retrospective review showed a 3.32% risk of spontaneous reversion to breech [27].

Contraindications

Any **contraindications to vaginal delivery** such as placenta **previa** or **prior classical uterine incision** are considered contraindications to ECV. There are no trials on ECV in **multiple gestations**, so the safety and efficacy of this procedure cannot be assessed in this population. Relative contraindications are **rupture of membranes, oligohydramnios, known uterine or fetal anomaly, unexplained uterine bleeding, or active phase of labor** [1, 28]. ECV in women with premature rupture of membranes has been studied in a systematic review of 13 cases. There was a 46.1% success rate, with a 33.3% incidence of cord prolapse. ECV in the setting of premature rupture of membranes should only be considered in a setting with immediate access to emergent CD [29]. ECV in women with prior CDs are associated with comparable success rates to those of women without prior cesarean deliveries, and no reports of uterine rupture have been noted, but there is insufficient data to assess the safety of this management [1].

Efficacy

Compared with no ECV, **ECV at term** is associated with a statistically significant and clinically meaningful 58% **reduction in noncephalic birth** (relative risk [RR] 0.42, 95% confidence interval [CI] 0.29–0.61) and a 42% **decrease in CD** (RR 0.58, 95% CI 0.40–0.82) [30]. There are no significant differences in Apgar score ratings <7 at 5 minutes (RR 0.63, 95% CI 0.29–1.36), low umbilical artery pH levels (RR 0.65, 95% CI 0.17–2.44), neonatal admission (RR 0.80, 95% CI 0.48–1.34), perinatal death (RR 0.39, 95% CI 0.09–1.64), or time from enrollment to delivery compared with no ECV [30]. Because ECV is associated with a very low incidence of adverse events and with a significant decrease in CD, **all women at or near term with nonvertex presentations should be offered an ECV**.

Success rates of ECV average **58%**, with a range of 25%–80% [1]. Success is increased with **higher parity** and with **transverse or oblique lie** (vs. breech). Lower amniotic fluid volume, anterior placenta, and high maternal body mass index (BMI) may decrease the success rate [1]. A meta-analysis showed that **multiparity, nonengagement of the breech, a relaxed uterus, a palpable fetal head, and maternal weight less than 65 kg** were predictors of successful ECV [31]. One model for predicting the probability of success of ECV found that maternal BMI, size of fore-bag, and parity were independent contributing factors of successful ECV with a prediction accuracy of 91.9% [32]. After successful ECV, the chance of spontaneous version to breech is low, but understudied. The chance of spontaneous version after failed ECV is about 6.6% in one study [33].

Timing of version

Compared with no ECV, **ECV before term reduces noncephalic births** [34–37]. **Compared with ECV at term, ECV before term reduces noncephalic presentation at birth, but does not reduce the rate of CD and may be associated with an increase in the**

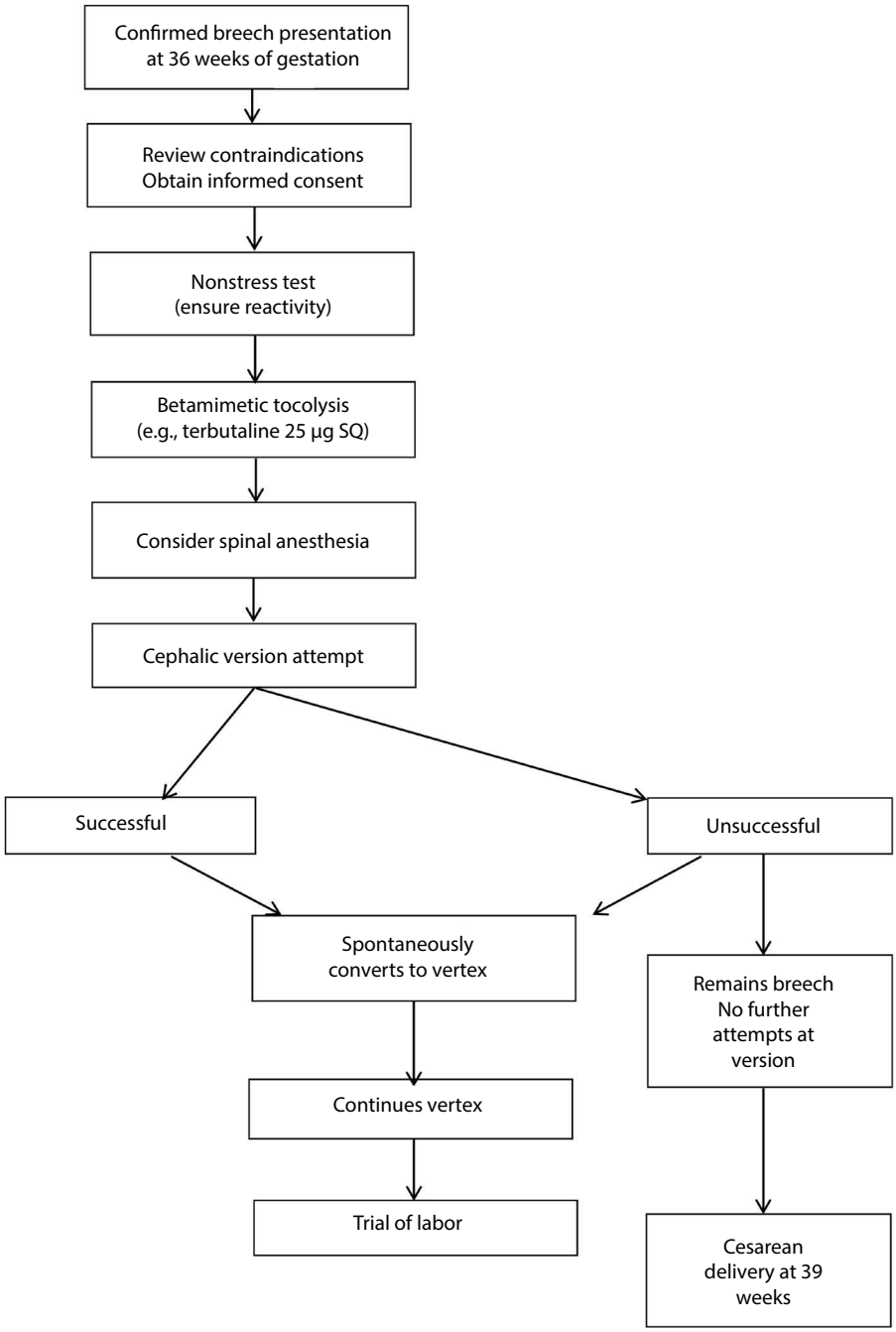


FIGURE 26.9 Suggested management of breech presentation. (Adapted from Ref. 1.)

incidence of PTB. There is **insufficient evidence to assess the best GA** at which to perform ECV. In general, the later the GA, the lower the success rate, but there are reports of successful ECV in women in term labor. About **36 weeks is generally considered to be the optimal time for attempted version**. At 36 weeks, there is felt to be adequate room to turn the fetus while minimizing the risk of return to breech presentation following a successful ECV. Additionally, if delivery becomes necessary, a 36-week infant has a low rate of respiratory distress syndrome or other complications of prematurity compared to a fetus of <36 weeks GA. Compared with ECV at $37^{0/7}$–$38^{0/7}$ weeks, ECV at $34^{0/7}$–$36^{0/7}$ weeks is associated with nonsignificant trends for slightly lower noncephalic presentation at birth (57% vs. 66%) and slightly lower CD (65% vs. 72%) [34–37]. In the largest randomized controlled trial (RCT) to date, compared with ECV at >37 weeks, ECV at $34^{0/7}$–$35^{6/7}$ weeks was associated with a decrease in the incidence of noncephalic presentation at birth (41% vs. 49%; RR 0.84, 95% CI 0.75–0.94), but no difference in rates of CD (52% vs. 56%; RR 0.93, 95% CI 0.85–1.02) or risk of PTB (6.5% vs. 4.4%; RR 1.48, 95% CI 0.97–2.26) [38].

Tocolysis

Tocolysis with **betamimetics** prior to attempting ECV is associated with 30% **fewer ECV failures**, a 32% reduction in noncephalic

presentations at birth, and 23% **fewer CDs** [39]. A common tocolytic used is terbutaline with a dose of 25 mg subcutaneously once, 10–15 minutes before ECV. Other different betamimetics have been used with no evidence as to the best one or its dosage and timing [39]. One RCT of adjusted doses of intravenous salbutamol tocolysis prior to ECV increased success rates, decreased the CD rate, and was well tolerated [40]. Tocolysis can also be used with success in a second ECV attempt on the same day after a first ECV attempt has failed [41].

Nifedipine as a uterine relaxant for ECV has also been evaluated. In a randomized, double-blind, placebo-controlled trial of 320 participants, nifedipine **did not significantly improve the success of ECV** [42]. In two RCTs evaluating oral nifedipine versus subcutaneous terbutaline tocolysis for ECV, there was higher ECV success with terbutaline (52.2%–58.1% for terbutaline vs. 34.1%–39.5% for nifedipine), fewer CDs, and no difference in neonatal outcomes, although more side effects were noted with terbutaline (maternal palpitations and tachycardia) [43–45].

Nitroglycerin has been studied as an agent to improve ECV success rates. In four small trials, sublingual nitroglycerin was associated with significant side effects and was **not** found to be **effective** [39]. One RCT demonstrated that treatment with intravenous nitroglycerin increased the rate of successful ECV in nulliparous women (24% compared to 8%, $p = 0.04$) but not in multiparous women [46]. In one trial, terbutaline 25 mg subcutaneous 5 minutes prior to ECV was found to have a significantly higher ECV success rate than nitroglycerin [47].

Fetal acoustic stimulation

Fetal acoustic stimulation to the fetal head for 1–3 seconds in midline fetal spine positions is associated with fewer failures of ECV at term in a very small study [28, 39, 48]. Eleven of 12 ECVs were successful following stimulation [48]. The crossover arm (patients who failed version without stimulation) were then stimulated, and 8 of 10 patients were successfully verted, for a total of 19 of 22 successful versions (86%) [47]. The success rate in the control group in this study was lower than expected (8%) [47]. The **evidence is limited and is insufficient** to make a recommendation.

Neuraxial anesthesia

There is evidence that regional anesthesia affects ECV success. ECV failure, noncephalic births, and CDs were reduced in two trials with epidural but not in three trials with spinal analgesia [39]. ECV success rates increased from 33% to 59% with epidural in one study and from 32% to 69% in another [4, 49]. Potential bias in both studies lies in that the care provider was not blinded to placement of the epidural [4, 49]. It is important to note that **the control groups had lower success rates than expected**; the average success rate in the literature, which is mostly without anesthesia, is about 58%. All patients in both studies received terbutaline prior to attempt at ECV. It has been postulated that large-volume preloading with epidural may increase the amniotic fluid volume [39]. The use of spinal anesthesia has not been associated with any benefit in the success of ECV in some RCTs [28, 39]. However, a meta-analysis including nine RCTs, of which seven used spinal and two used epidural anesthesia for ECV versus controls, demonstrated **anesthetic-dose neuraxial blockade (usually spinal) is associated with a 63% increase in the success rate of ECV** [50].

Inhalational anesthesia

In a systematic review of anesthesia and analgesia for ECV, the visual analog scores (VASs) of pain were also significantly lower with inhalational anesthesia. The VAS of patient satisfaction was significantly higher with intravenous anesthesia [51].

Systemic opioids

There is limited evidence that systemic opioids improve success rates for ECV. One RCT of 60 women showed that the frequency of CD was similar in the opioid (remifentanil) group vs. placebo (RR 0.9, 95% CI 0.20–4.27) 318). In one RCT comparing spinal anesthesia, systemic opioid (remifentanil) and control (no anesthesia/analgesia) for ECV success, ECV was most successful in the spinal anesthesia group (83%) versus opioid (64%) and control (64%). Pain relief was highest with spinal anesthesia, followed by opioid and then control. Incidence of CD for fetal bradycardia was similar among the groups [52].

In a systematic review, compared to control, ECV with neuraxial anesthesia has a significantly higher ECV success rate; however, the odds of maternal hypotension increase significantly. All anesthesia interventions provide a significant reduction of procedure-related pain. Intravenous anesthesia had a significantly higher score in patient satisfaction and lower odds of NRFHRT pattern [51].

Hypnosis

There is one RCT on hypnosis versus neurolinguistic programming for pain relief during ECV, and both groups reported a similar degree of relief [39].

ECV procedure

Given the possible complications, it is prudent to perform ECV in a **facility** with ready availability of emergency CD. **Consent** should be obtained after **counseling** regarding possible complications, alternatives (CD), prognosis, and explanation of the actual procedure. A **nonstress test** should be performed before and after ECV. Anesthesia is usually not necessary and has not been absolutely proven to benefit outcomes. **Betamimetic** prophylactic tocolysis should be given (e.g. terbutaline 25 μg subcutaneously 5–10 minutes prior to procedure). There are no trials comparing other technical aspects of ECV. One or two operators can be used. When the fetal back is accessible to palpation with no intervening placenta, the stimulation of the Galant or the stepping or walking fetal reflexes have been suggested to improve the outcome of ECV [53]. Frequent, if not continuous, **ultrasound** guidance to assess for fetal well-being and presentation is suggested. Rh-negative women should receive anti-D immunoglobulin. There is no evidence to support immediate induction after successful ECV.

There are no trials to evaluate the potential effects of hydration or transabdominal amnioinfusion on the success rate of spontaneous version or ECV.

In summary, regarding ECV, and as supported by the American College of Obstetricians and Gynecologists (ACOG) and the Royal College of Obstetricians and Gynaecologists (RCOG), **all women who are near term with breech presentations or transverse/oblique lie should be offered ECV** due to the benefit of a significant decrease in CD and the small risk of an adverse event. **Tocolysis** increases the chance of a successful ECV [1, 54]. ACOG also supports the use of **neuraxial anesthesia** to increase the success rate of ECV [1].

Moxibustion and/or acupuncture

Moxibustion is a form of traditional Chinese medicine that uses heat generated by burning herbs, most often *Artemisia*

vulgaris, to stimulate the acupuncture point BL67 (Zhiyin in Chinese) [55–59]. There is **inconsistent evidence** to assess if the use of moxibustion converts a breech to a cephalic presentation. Differences in interventions (e.g. moxibustion alone or with acupuncture) make it difficult to perform a satisfactory meta-analysis. Moxibustion may reduce the need for ECV by 53% and reduce the incidence of nonvertex presentation at term by 35%–70% in Chinese trials [56, 57]. In two trials performed in Italy, moxibustion was not well tolerated by 22% of women and therefore not effective [58]. Moxibustion was not effective when used with acupuncture [59]. Moxibustion may decrease the use of oxytocin before or during labor for women who had vaginal deliveries and might reduce noncephalic presentation at birth and CD compared to acupuncture [55]. A meta-analysis performed compiling data from six studies of both Western and Chinese databases shows that **moxibustion at point BL67, alone or in combination with acupuncture, is associated with higher rates of cephalic version** of 72.5%, compared with 53.2% in the control group (RR 1.36, 95% CI 1.17–1.58). These data should be viewed with caution, given the high degree of heterogeneity of the studies [60]. No significant differences were found in the safety of moxibustion compared with other techniques. A recent RCT of 328 women showed **no beneficial effect of moxibustion to facilitate ECV** compared to controls when looking at the percentage of fetuses in breech presentation at 37 weeks (72.0% vs. 63.4%; RR 1.13, 95% CI 0.98–1.32 [61]. It might be that acupuncture and not moxibustion (especially not at home) is beneficial [59], although a recent trial of acupuncture with a heating needle moxibustion technique (smokeless) showed no benefit [62].

Maternal change in posture

Maternal changes in position such as knee–chest and others have been suggested as a means to correct breech presentation in pregnancy. There is **insufficient evidence** from the small trials reported so far to support the use of postural management for breech presentation [63]. Meta-analysis could not be undertaken, since study designs and outcomes measured were different [64]. Postural management is not associated with a significant effect on the rate of noncephalic births, either for the subgroup in which no ECV was attempted or for the group overall (RR 0.98, 95% CI 0.84–1.15). No differences were detected for CDs (RR 1.10, 95% CI 0.89–1.37). To date **there is no solid evidence for this practice** [63, 64].

Delivery outcomes

It is important to note that the rate of CD after ECV is still about double that of pregnancies presenting with spontaneous cephalic presentation due to higher incidences of dystocia and NRFHT after successful ECV [65].

Mode of delivery

Singleton

Term breech

Three RCTs [66], including one large study (the Term Breech Trial) [67], have compared a policy of planned CD to a policy of planned trial of labor to attempt a vaginal delivery. CD occurs in about 45% of women allocated to a vaginal delivery protocol and >90% in those allocated to a CD protocol.

At 4–6 weeks after delivery, compared with planned vaginal delivery, **planned CD** is associated with a 67% **decrease in perinatal or neonatal death** (RR 0.33, 95% CI 0.19–0.56) (excluding fetal anomalies) **or serious neonatal morbidity** [66]. This reduction is less for countries with high national perinatal mortality rates [67]. Planned CD is associated with a 71% reduction (from 1.15% to 0.26%) in perinatal or neonatal death (excluding fetal anomalies) [66]. This reduction was similar for countries with low and high national perinatal mortality rates. One death could be prevented for every 112 CDs planned [66]. A secondary analysis [68] of the short-term outcomes of the Term Breech Trial [67] looked at factors associated with adverse outcomes. The lowest morbidity was found in patients with planned CD prior to the onset of labor. In a planned vaginal breech delivery, labor augmentation and a second stage greater than 60 minutes are associated with less optimal outcomes [68]. Factors not shown to affect outcome included induction, parity, use of continuous electronic fetal monitoring, or epidural [68]. A "skilled clinician" at the delivery was associated with lower adverse outcomes. "Skilled clinician" was best described by the clinicians themselves rather than by years of experience or being a licensed obstetrician [68].

Three months after delivery, women allocated to the planned CD group reported 38% **less urinary incontinence**, 89% **more abdominal pain**, and 68% **less perineal pain** [69].

Two years after delivery, there was **no difference in the combined outcome "death or neurodevelopmental delay."** Of 463 vaginal delivery patients followed at 2 years, there were only 6 deaths and 7 children with neurodevelopmental delay (2.8%), compared with 2 and 12 of 457 patients (3.1%) in the CD group [70]. The authors postulate that there was no difference seen at the 2-year follow-up (vs. immediate neonatal outcome) because the study was underpowered, the predictive value was low for an association of measures of early morbidity with later death and adverse neurodevelopmental outcomes, and planned CD is perhaps only reducing the risk of perinatal mortality/morbidity associated with fetal hypoxemia [70]. **Maternal outcomes at 2 years** were also very **similar**, with **constipation** significantly more **common** in the **CD** group (27% vs. 20%), while self-reported incontinence was not significantly different (18% vs. 22%) [71]. Incontinence was different (16% vs. 25%) if comparing women who actually planned and had a CD versus those who planned and had a vaginal delivery [71].

These results are from the Term Breech Trial [67] and its secondary analyses and follow-up [67–71]. These outcomes are based on deliveries done by "clinicians who were regarded as experienced at vaginal breech delivery" [67–71]. As the number of vaginal breech deliveries decreases, physician skill will continue to diminish, with the potential to make vaginal delivery less safe. While it is estimated that >90% of babies presenting nonvertex are currently delivered by CD, there might still be a role for vaginal delivery for the woman who declines scheduled CD or who presents in advanced labor. Postdates pregnancy [72], parity [73], and fetal leg position [74] showed no association with the outcome of intended breech vaginal delivery. A prospective study of 1054 women with intended breech vaginal delivery showed that a birth weight above 3.8 kg is associated with an increased rate of CD but no difference in terms of neonatal and maternal morbidity [75]. ACOG reaffirmed in 2018 and RCOG in 2017 that the decision of mode of delivery depends on the experience of the health care provider [76, 77]. CD is the preferred mode due to the limited experience of most physicians, but planned vaginal delivery of a term singleton fetus may be considered under specific hospital protocols [76, 77]. **All women with breech presentation with a large fetus (>3500 g estimation), unfavorable pelvis, hyperextended head, incomplete**

or footling breech presentation, NRFHT, severe fetal growth restriction, or lack of experienced obstetrics or anesthesiology providers should have a CD.

Technical aspects

Cesarean breech delivery: There are no trials to assess technical aspects of breech (or other malpresentation) CD. There is insufficient evidence to assess if intraabdominal version during CD before uterine incision affects outcomes.

Vaginal breech delivery: There are several technical suggestions for assisting a vaginal breech delivery, including the adoption of upright or "hands and knees" position instead of supine position [78]; none are based on trials. There is insufficient evidence to assess if clinical/radiologic pelvimetry affects outcomes in the management of breech presentation. One RCT and a cohort study showed that prelabor MRI is helpful in predicting the risk of emergency caesarean section in women with vaginal intended breech delivery by allowing the identification of the abnormalities of the pelvimetry [79] and the measurement of the obstetric conjugate [80].

A double setup is suggested: A vaginal delivery should be organized in the operating room and ready for possible CD.

Other suggestions are as follows: Minimal intervention until the abdomen up to the umbilical cord is delivered and prevention of head extension with prophylactic Mauriceau maneuver and proper use of Pipers forceps, if necessary. There is not enough evidence to evaluate the effects of expedited vaginal breech delivery (breech delivery from umbilicus to delivery of the head within one contraction) on perinatal outcomes [81].

The same management options exist for transverse/oblique lie as for breech. Fetal ECV, and CD if persistent malpresentation, are the standards of care, with limited trial evidence.

Preterm breech

There is **insufficient evidence** to assess if outcomes of the preterm breech-presenting fetus are affected by mode of delivery. Very little prospective data, mostly nonrandomized, exist regarding vaginal versus CD of the premature breech infant [1]. Two trials aimed at assessing this question failed to randomize the planned sample sizes. After 17 months of patient recruiting at 26 different hospitals, only 13 women had been randomized, making it impossible to confer any conclusions in one study [82]. The Iowa premature breech trial was somewhat more successful, recruiting 38 patients over 5 years, but had insufficient data for meaningful conclusions [83, 84]. In a meta-analysis of randomized trials ($n = 1$) and observational studies ($n = 14$), CD was associated with a 41% decrease in neonatal death and a 49% decrease in intraventricular hemorrhage between $23^{0/7}$ weeks and $27^{6/7}$ weeks, with the most benefit seen at 23 weeks and 0 days to 24 weeks and 6 days [85]. A retrospective cohort study evaluating morbidity and mortality of periviable breech fetuses in relation to the mode of delivery showed an almost fourfold and threefold higher chance of survival in the event of CD performed at 23 and 24 weeks of gestation, respectively [86]. A secondary analysis of a prospective study of 390 women with breech fetus and spontaneous onset of labor or preterm prelabor rupture of membranes (PPROM) between 26 and 34 weeks of gestation showed no benefit of planned CD in improving neonatal outcomes [87]. Outcomes in premature breech infants are mainly related to prematurity, with unclear conclusions regarding the preferred mode of delivery, as the majority of data is observational [88, 89].

Twins

Breech external cephalic version of the presenting twin

There is a small amount of data regarding ECV of the noncephalic-presenting twin in dichorionic twin pregnancies [90]. In a systematic review of 23 patients and attempted ECV of the nonpresenting twin, successful ECV occurred in 57% of women and 48% of women had a successful vaginal delivery. No adverse events occurred in this small series [91]. **ECV in twin gestations is insufficiently studied to make a conclusion about safety and efficacy** [92, 93].

Breech delivery of the nonpresenting twin

(See also Chap. 46 in *Maternal-Fetal Evidence Based Guidelines*.) Pregnancies at ≥35 weeks with vertex/breech presentation in twin gestations <7 cm dilation have similar Apgar scores and incidence of neonatal morbidity in the second twin delivered by vaginal or cesarean birth [93]. There was no incidence of birth trauma or intraventricular hemorrhage in any of the 27 breech deliveries of the second twin [93]. Maternal febrile morbidity and length of stay were increased in the CD group [93]. In the largest RCT that randomized women with twin pregnancies to planned CD or planned vaginal delivery, there was a large number of women with a noncephalic second twin. There was no statistically significant difference seen in composite fetal or neonatal morbidity, even when evaluating for interaction with fetal presentation, comparing perinatal morbidity in planned CD versus planned vaginal delivery (odds ratio [OR] 1.16, 95% CI 0.77–1.74). Morbidity included birth trauma, seizures, and assisted ventilation. There were also no significant differences noted in serious maternal morbidity (OR 0.86, 95% CI 0.65–1.13) [94]. In a secondary analysis of this study of women with a cephalic-presenting twin in spontaneous labor, again no difference was noted in neonatal or maternal outcomes based on delivery route [95]. **Vaginal delivery of the second nonvertex twin is a sound option**. Attempt at vaginal twin delivery of the second twin, especially for a second twin with an estimated fetal weight (EFW) of >1500 g, should be performed with adequate experience of the obstetrician, as well as with continuous availability of expert anesthesia in or very close to an operating room. **Total breech extraction of the second twin** is associated with shorter maternal stay, lower neonatal pulmonary disease, infection, and intensive care nursery stay compared with cephalic version [82, 84]. There are no trials for twins presenting with **first twin nonvertex** (about 26% of twins). Recommendation for CD under this circumstance is based mostly on data from singleton gestations.

Preterm twins

There are no RCTs of planned CD vs. vaginal delivery of preterm twins less than 34 weeks with malpresentation of the second twin. A retrospective cohort study of vertex/nonvertex twins with a trial of vaginal delivery between 24 and 28 weeks of gestation showed a high incidence of emergency CD for the delivery of the second twin but no difference in the risk of adverse outcomes compared to those submitted to CD at paired gestation [96]. In a meta-analysis of three observational studies on delivery mode of extremely preterm (24 weeks and 0 days to 27 weeks and 6 days) cephalic/noncephalic twin gestations, neonatal death and severe brain injury were not different between methods of delivery [97]. There are insufficient data to make a recommendation.

Triplets

Because vaginal delivery of **triplets** is usually associated with an increased risk for stillbirth or neonatal and infant deaths as compared with CD, **cesarean delivery is the route of choice**, even if some small series have recently reported similar outcomes for trial of labor or CD for triplets.

Malposition

Definitions

Position

Relationship of presenting part (usually occiput for head) to pelvic outlet.

Malposition

Fetal position that is not occiput-anterior for cephalic presentations (or sacrum anterior for breech presentations).

Asynclitism

Malalignment of the head in relation to the axis of the birth canal; when one of the fetal parietal bones precedes the sagittal suture in the birth canal (Figures 26.10 and 26.11) [98].

Compound presentation

When an extremity prolapses alongside the presenting part in the birth canal

Epidemiology/Incidence

Occiput posterior (OP) (Figure 26.12) is the most common fetal malposition. Only 5% of term fetuses are OP at time of delivery, but about 23% are OP at the beginning of labor [99].

Risk factors/Associations

OP position is associated with African American race, advanced maternal age, postterm pregnancy, birth weight >4000 g, and epidural anesthesia [100]. In a meta-analysis evaluating epidural vs. no epidural/analgesia in labor, malposition was higher in women in the epidural group (RR 1.40, 95% CI 0.98–1.99), although this was not statistically significant [101].

Diagnosis

Fetal malposition can be detected by provider digital exam, as well as by transabdominal ultrasound. **Digital (manual) vaginal examination correctly detects OP position about 80% of the time, while transabdominal ultrasonographic examination of fetal head position during the second stage of labor is correct >99% of the time. The use of transabdominal ultrasound to locate the exact position of the fetal head** should be mandatory when this knowledge influences management [102]. Additionally, ultrasound has the ability to predict persistent OP position during labor: Sensitivity and specificity of intrapartum ultrasound for prediction of persistent OP position were about 0.85 and 0.83, respectively. Sensitivity and specificity increased after 4 cm cervical dilation to about 0.92 and 0.85, respectively [103].

Management

Hands and knees posture

The effect of **hands and knees posture** to correct malposition has been evaluated **both before (for prevention) and during labor**.

There are trials on the effect of the hands and knees posture **before labor** [104]. Compared to a sitting position, 10 minutes in the hands and knees position is associated with a lower likelihood

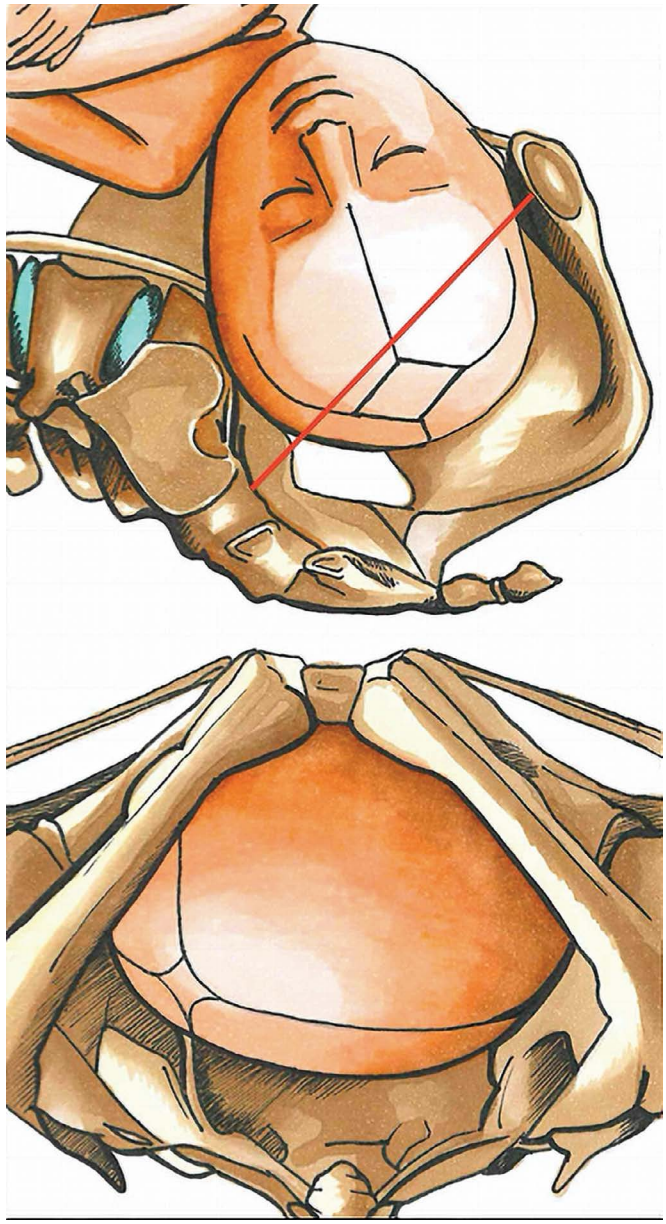


FIGURE 26.10 Anterior asynclitism.

of malposition of the presenting part of the fetus in a small trial, but assuming the hands and knees posture for 10 minutes twice daily in the last weeks of pregnancy had **no effect on the baby's position at delivery** or any of the other pregnancy outcomes measured in a larger trial [104]. One study evaluated the use of the hands and knees position **in labor** involving 147 women in labor at term who assumed the position for a period of at least 30 minutes. There was **no significant reduction** in OP or occiput-transverse positions at delivery or reduction of operative deliveries. However, there was a significant reduction in back pain [105]. An RCT studied women with OP fetal position during labor who were placed in the hands and knees position in first-stage labor at term for at least 10 minutes, which **showed no benefit of rotation** to occiput anterior (OA) [106]. In summary, the **hands and knees posture does not seem to be effective in preventing or treating malposition**.

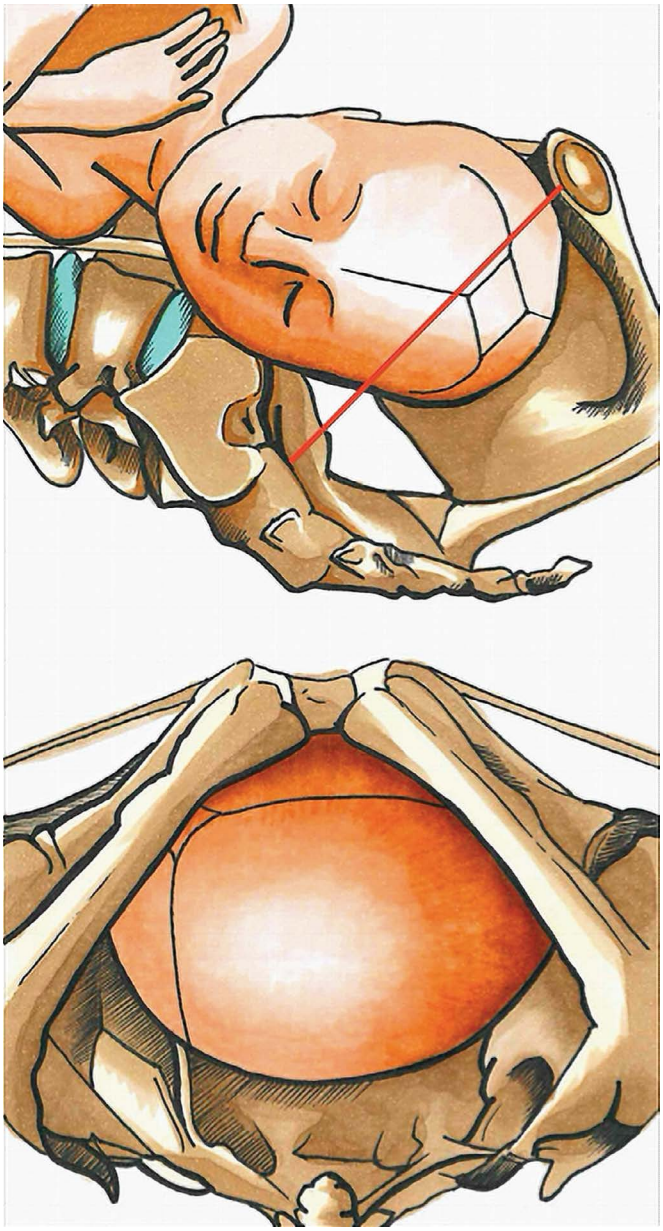


FIGURE 26.11 Posterior asynclitism.

Lateral asymmetric decubitus position

Lateral asymmetric decubitus position, or lying on the side opposite the fetal spine with the inferior leg positioned in the axis of the body and the upper leg in hyperflexion, has been proposed as a maneuver to help rotate a fetus from OP to OA. In an RCT of term women with singleton fetuses and ruptured membranes with ultrasound-confirmed OP position, for women who were placed in the lateral asymmetric decubitus position on the side opposite that of the fetal spine for at least 1 hour during the first stage of labor, **OA rates did not differ** at complete dilation or at birth and rate of CD was not different [107].

Manual rotation

Persistent fetal OP position has been historically considered a risk factor for prolonged labor and CD. Six RCTs have assessed the safety and efficacy of manual rotation of the persistent OP or Occiput transverse (OT) malpositioned fetal head to OA

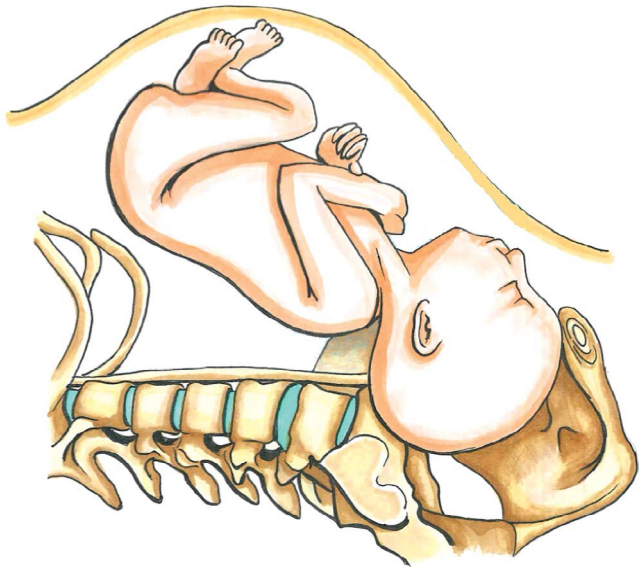


FIGURE 26.12 Occiput posterior.

(Table 26.1) [108–113]. Over 80% of labors end up spontaneously without OP position at the beginning of the second stage, so **manual rotation should not be done before the second stage**. **If fetal head position is assessed at the beginning of the second stage, it should be assessed by ultrasound**; digital diagnosis of fetal head position is wrong in at least 20 of cases. There seems to be a **nonsignificant 14% decrease in OD associated with manual rotation of OP fetuses performed at the beginning of the second stage** (Table 26.1). **The number of manual rotations needed to avoid an OD (number needed to treat) is 13.2**. Manual rotation seems to have a **higher chance of being beneficial when the fetal head is flexed** (OP position, vertex presentation) [108–113]. When assisted by ultrasound to detect the location of the fetal spine, manual rotation success was improved and spontaneous vaginal delivery (SVD) rate was improved without adverse neonatal effects in an RCT [114].

Operative delivery from malposition (OP)

There is insufficient evidence to make a recommendation on how OVD is performed from OP or if forceps or vacuum delivery is more successful.

Ultrasound

In a recent RCT that evaluated the influence of ultrasound on diagnosis of fetal head malposition and subsequent mode of delivery, using transabdominal ultrasound in active labor did not improve management of labor or increase the incidence of operative delivery (CD + operative vaginal delivery) (RR 1.24, 95% CI 1.08–1.43) and did not decrease maternal and neonatal morbidity [115].

Anesthesia

For vaginal breech delivery, an anesthesiologist skilled at the pharmacology of uterine relaxation (e.g. nitric oxide) should be present.

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TABLE 26.1: RCTs on Manual Rotation vs. No Rotation of the Malpositioned Fetal Head in the Second Stage of Labor

Study	Year	Origin	N	Head Position	Sham Control	OD	OVD	CD
Graham [94]	2014	Australia	30	OP	Yes	13/15 vs. 12/15	4/15 vs. 3/15	9/15 vs. 9/15
Broberg [95]	2016	United States of America	65	OP	No	10/33 vs. 8/32	8/33 vs. 7/32	2/33 vs. 1/32
Phipps (POPOUT) [96]	2021	Australia	264	OP	Yes	79/127 vs. 90/127	57/127 vs. 68/127	22/127 vs. 22/127
Blanc[a] (PROPOP) [97]	2021	France	257	OP	No	37/126 vs. 54/131	N/A	N/A
Phipps (TURNOUT) [98]	NP/C	Australia	160	OT	Yes	N/A	N/A	N/A
Verhaeghe [99]	NP/C	France	238	OP	No	N/A	N/A	N/A
Total			1014			139/301 (46.2%) vs. 164/305 (53.8%)	69/175 vs. 78/174	33/175 vs. 32/174
RR, 95% CI						0.86, 0.73–1.01	0.88, 0.68–1.14	1.03, 0.64–1.64

Note: Data are presented manual rotation versus control.

[a] Data are presented as manual rotation versus control.

Abbreviations: RCT, randomized controlled trial; NP/C, not published; recruitment complete; N/A, not available; OD, operative delivery; OVD, operative vaginal delivery; CD, cesarean delivery; OP, occiput posterior position; OT, occiput transverse; RR, relative risk; CI, confidence interval.

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27

SHOULDER DYSTOCIA

Julia Burd

Key points

- Risk factors for shoulder dystocia include **prior shoulder dystocia (recurrence risk ~1%–15%), maternal diabetes mellitus, obesity, postterm pregnancy, labor induction, epidural anesthesia, labor abnormalities (e.g. prolonged second stage), operative vaginal delivery, and fetal macrosomia** (Table 27.1).
- **In 50% of shoulder dystocia cases, no risk factors are identified**. Therefore, clinicians should be **ready for possible shoulder dystocia at every delivery**.
- **In 40%–60% of shoulder dystocia cases, birth weight is <4000 g**.
- Maternal complications of shoulder dystocia include obstetric anal sphincter injuries (OASI) and postpartum hemorrhage.
- A perinatal complication of shoulder dystocia is **brachial plexus impairment (BPI), which occurs in 4%–40% of shoulder dystocia cases; up to 90% are transient**. Approximately one-half of cases of BPI occur without documented shoulder dystocia.
- Other perinatal complications of shoulder dystocia include fractures, hypoxic-ischemic encephalopathy, long-term neurologic disability, and even death.
- **Preconception prevention of maternal obesity and diabetes, as well as prenatal prevention of excessive weight gain**, decrease the incidence of shoulder dystocia, mainly by prevention of fetal macrosomia.
- In women with prior shoulder dystocia, clinicians should review recurrence risk (1%–15%), which risk factors (Table 27.1) are present in the current pregnancy, and possible complications. If several significant risk factors are still present, the woman may opt for cesarean delivery. If risk factors are not present (except for prior shoulder dystocia), the woman may decide after counseling for either trial of labor or cesarean delivery.
- **Induction of labor at term for suspected fetal macrosomia** (estimated fetal weight [EFW] ≥4000 g) in women without diabetes is associated with a similar incidence of cesarean or operative vaginal delivery compared to expectant management, a **significant decrease in fetal fractures**, and higher incidences of hyperbilirubinemia and phototherapy. **Induction at ≥38 weeks** would prevent the neonatal complications and can be considered.
- **In pregnancies with EFW >5000 g in nondiabetic and >4500 g in diabetic women, the American College of Obstetricians and Gynecologists (ACOG) suggests that a planned cesarean delivery (without labor attempt) may be considered to avoid shoulder dystocia**.
- **In women with EFW >3800 g, prophylactic McRobert maneuver and suprapubic pressure are associated in one randomized controlled trial (RCT) with a trend towards a decreased rate of shoulder dystocia**.
- **Initial responses to shoulder dystocia involve asking for help and, as first maneuvers, use of McRobert maneuver and suprapubic pressure** (Figure 27.1).
- **Second-line maneuvers include direct fetal manipulation, such as delivery of the posterior arm (considered to be the most effective internal maneuver), then rotation of fetal shoulders. One-third of shoulder dystocia cases require the use of more than two maneuvers**. See Figure 27.1 for suggested management of shoulder dystocia.

Diagnosis/Definition

Shoulder dystocia is **diagnosed when additional obstetric maneuvers are required following failure of gentle downward traction on the fetal head to effect delivery of the shoulders in a cephalic-presenting neonate. Retraction of the delivered fetal head against the maternal perineum ("turtle sign") is an indication of a possible shoulder dystocia** [1]. Shoulder dystocia pertains only to vertex presentation. A quantitative definition of shoulder dystocia has been proposed as a prolonged head-to-body delivery time >60 seconds [2]. This definition categorizes 10% of vaginal deliveries as having a shoulder dystocia, while only 25%–45% of these cases were diagnosed as such by the delivering provider [3]. **Shoulder dystocia remains a subjective clinical diagnosis by the delivering provider, and this may account for some of the variability in the frequency of reported shoulder dystocia across various populations and different studies**.

Epidemiology/Incidence

The **incidence of shoulder dystocia is about 1%** (range 0.2%–3%) [1].

Etiology/Basic pathophysiology

Shoulder dystocia results from **size discrepancy between the fetal shoulders and the pelvic inlet that results in impaction of the anterior shoulders behind the maternal pubis symphysis or the posterior shoulder on the sacral promontory (uncommon), or both (rare)** [4]. Persistent anterior-posterior location of the fetal shoulders at the pelvic brim occurs most often due to increased resistance between the fetal skin and vaginal walls (e.g. fetal macrosomia), a large fetal chest relative to the biparietal diameter (e.g. infants of diabetic mothers), and when truncal rotation does not occur (e.g. precipitous labor) [1].

Risk factors/Associations

Table 27.1 lists antepartum and intrapartum risk factors associated with shoulder dystocia. These risk factors individually or in combination have a poor predictive value for shoulder dystocia. **In 50% of cases, no risk factors are identified**. The two risk

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TABLE 27.1: Factors Associated with Shoulder Dystocia

Antepartum	Intrapartum
Multiparity	Labor induction and/or augmentation
Postterm gestation	Labor abnormalities
	Prolonged first stage
	Short second stage
	Prolonged second stage
Maternal obesity	Epidural
Maternal diabetes	Operative vaginal delivery [forceps or vacuum] especially mid-pelvic station
Prior shoulder dystocia	
Prior macrosomic child	
Excessive gestational weight gain	
Fetal macrosomia	

Source: Data from Ref. [1].

factors for shoulder dystocia most studied are **maternal diabetes and fetal macrosomia**. The **frequency of shoulder dystocia increases with higher birth weight** (Table 27.2) [5]. However, it should also be remembered that **40%–60% of cases occur with birth weight <4000 g, and of deliveries with birth weight >4000 g, only 3.3% develop shoulder dystocia** [4, 6, 7]. Multiple studies, including those using advanced statistical models, have been unable to discriminate labor patterns (e.g. prolonged first and/or second stage) in a manner that improves intrapartum management to predict and avoid shoulder dystocia [8–12]. In a study, the statistical model that best predicted shoulder dystocia with injury included maternal height and weight, gestational age, parity, and birth weight and was able to identify 50.7% of cases with a false-positive rate of 2.7% [12]. Recent studies examining ultrasound asymmetry (ratio of biparietal diameter and abdominal diameter) have demonstrated a correlation between elevated asymmetry and shoulder dystocia [13–16].

TABLE 27.2: Relationship between Increasing Birth Weight and Maternal Diabetes and the Development of Shoulder Dystocia

Birth Weight (g)	No Diabetes	Maternal Diabetes
4000–4250	5.25%	12.2%
4250–4500	9.1%	16.7%
4500–4750	14.3%	27.3%
4750–5000	21.1%	34.8%

Source: Data from Ref. [5].

Complications

Maternal

Maternal complications involve increased post-partum blood loss and vaginal lacerations. Retrospective studies have noted an increase in obstetric anal sphincter injuries (OASIs) with fetal manipulation during shoulder dystocia, increasing with internal maneuvers and more than four maneuvers (Table 27.3) [17, 18].

Perinatal

Brachial plexus impairment

The most common major complication of shoulder dystocia is neonatal brachial plexus impairment (BPI), which occurs in **4%–40% of cases of shoulder dystocia**. In one of the largest series, the rate was 16.8% (Table 27.3) [19]. **Most cases of BPI are unilateral (right > left) and involve the C5–C6 roots (Erb-Duchenne palsy)**. Table 27.4 describes the most common palsies associated with shoulder dystocia. Most fully recover spontaneously, with physical therapy, or, in some situations, respond to neurosurgical treatment.

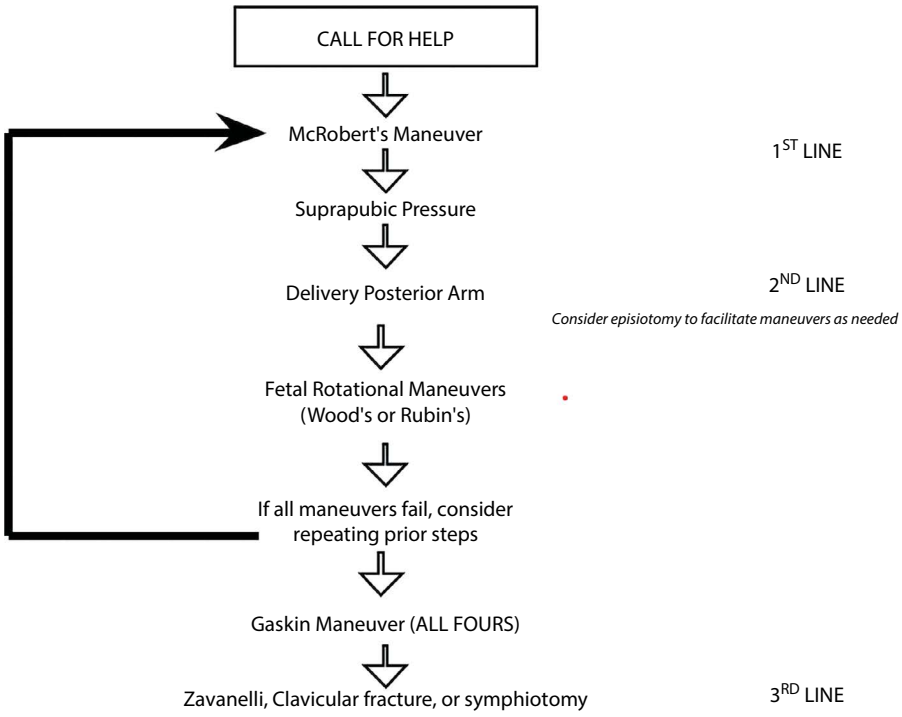


FIGURE 27.1 Suggested management algorithm for shoulder dystocia.

TABLE 27.3: Maternal and Newborn Complications of Shoulder Dystocia Reported at a Single Large Tertiary Care Center

Complication	Frequency
Maternal	
Postpartum hemorrhage	11%
Fourth-degree laceration (either extension of episiotomy or extension of laceration)	3.8%
Vaginal lacerations	19.3%
Cervical tear	2%
Perinatal	
Any fetal injury	24.9%
Brachial plexus injury	16.8%
Clavicular fracture	9.5%
Humeral fracture	4.2%

Source: Data from Refs. [7, 19].

Permanent BPI is very rare and occurs in 1–2 out of every 10,000 births. Signs and symptoms of BPI are a limp or unmoving paralyzed arm; lack of muscle control in the arm, hand, or wrist; and lack of feeling or sensation in the arm or hand. **Neonatal BPIs can occur without shoulder dystocia**: In a recent literature review of neonatal BPI with and without shoulder dystocia, approximately **45% of BPI cases in the United States and 47% outside the United States were not associated with shoulder dystocia at delivery** [20]. In fact, it is estimated that one half of all BPIs occur in the absence of shoulder dystocia and up to 4% of BPIs are associated with cesarean delivery [21, 22]. At least three studies provide evidence that BPI (both transient and permanent) can occur with cesarean delivery. Gherman et al. reported the finding of 17 cases of BPI (6 permanent) associated with cesarean delivery with 12- to 29-month follow-up [6, 23]. Chang et al. described 30 cases of BPI with cesarean delivery (out of a total 387 cases) where 60% were persistent at 1 year [24]. Torki et al. found 8 cases of severe BP injuries in 43,337 deliveries, 1 following a cesarean section [25]. These data indicate that **some cases of neonatal BPIs are unrelated to clinician-applied forces** and are due to a combination of mechanisms such as endogenous labor forces, the impaction and pressure effects of the shoulder dystocia itself, and/or in utero compression or maladaptation [26, 27]. External maneuvers such as excessive lateral traction are most likely responsible for some cases of BPI from shoulder dystocia, but not all.

Fractures

Fractures of the clavicle and humerus have also been associated with shoulder dystocia (up to 10.4%) and the maneuvers to resolve it. Both humeral and clavicular fractures heal well with conservative therapy [28].

TABLE 27.4: Types of Brachial Plexus Impairments

Palsy	Description	Level	Frequency
Erb palsy (also known as Erb-Duchenne palsy)	Paralysis of flexion, abduction, internal and external rotation of the forearm	C5, C6	>98%
Klumpke palsy	Paralysis of the thumb, fingers, and pronation of the forearm	C8, T1	<1%
Complete brachial plexus palsy	Both Erb and Klumpke	C5–T1	<1%

Umbilical artery pH

In a study of 134 cases of shoulder dystocia, mean umbilical pH was not clinically different from cases without shoulder dystocia, and there was no association between head-to-body delivery intervals and umbilical pH, base excess, or 5-minute Apgar scores [29]. However, another study of 200 cases of shoulder dystocia noted that the umbilical artery pH dropped 0.01 per minute for the head-to-body delivery interval (HBDI). They found an overall 2.5% rate of hypoxic-ischemic encephalopathy: The risk was 0.5% if HBDI was <5 minutes compared to 23.5% if HBDI was ≥5 minutes [30].

Demise

In a review of 56 cases of fatal shoulder dystocia reported to the *Confidential Inquiry into Stillbirths and Deaths in Infancy* between 1994 and 1995 from England, Northern Wales, and Ireland, the approximate incidence of fatal shoulder dystocia is 0.025 per 1000 deliveries. In 47% of these cases, the head-to-body ratio was less than 5 minutes and greater than 10 minutes in 20% [31].

Management

Principles

Shoulder dystocia is an obstetrical emergency and cannot be reliably predicted. Thus, prompt recognition and response are essential to optimizing outcomes once it develops. Obstetricians should be trained and ready to manage this complication at every delivery. Therefore, it is imperative that shoulder dystocia training occurs early and that at least one clinician experienced in the management of shoulder dystocia is present at every delivery.

Prevention

Preconception

Preconception prevention of maternal obesity (relative risk [RR] of shoulder dystocia 1.63, 95% confidence interval [CI] 1.33–1.99) [32] and diabetes, as well as prenatal prevention of excessive weight gain, decrease the incidence of shoulder dystocia, mainly by prevention of fetal macrosomia.

Prediction

Women with prior shoulder dystocia have a 1%–15% risk of recurrence [33–35]. In women with a prior shoulder dystocia, counseling should include review of prior delivery events, including severity of injury of prior child, which risk factors (Table 27.1) are present in the current pregnancy, and possible short-term and long-term complications of cesarean delivery. The suspected size of recurrent pregnancy related to the size of the first pregnancy was noted to be the most important risk factor for recurrent shoulder dystocia (odds ratio [OR] 7–12) [36]. If several significant risk factors are still present, the woman may opt for cesarean delivery. However, given that at least 85% of women will not have a recurrent shoulder dystocia and cesarean delivery does have surgical risks, a woman with a prior shoulder dystocia after counseling may choose to pursue vaginal delivery [1].

Antepartum

Fetal macrosomia has been noted to be an independent risk factor for shoulder dystocia in a meta-analysis (>4000 g OR 9.54 [6.76–13.46], >4500 g OR 15.64 [11.31–21.64]) [37]. This risk prediction is complicated by the known limitations of prenatal ultrasound to accurately estimate fetal weight, especially with increased fetal size [38, 39]. Only **at high estimated fetal weights (EFWs) (>5000 g in nondiabetic and >4500 g in diabetic women) does the American**

College of Obstetricians and Gynecologists (ACOG) suggest planned cesarean delivery (without labor attempt) be considered to avoid shoulder dystocia [39].

Labor induction for women with suspected macrosomia as an intervention to decrease the rate of shoulder dystocia has been tested in four clinical trials including 1190 women [40–44]. Women with EFW either >95% for gestational age or with macrosomia usually defined as EFW >4000 g, who were randomized to labor induction **≥38 weeks**, had a similar incidence of cesarean delivery (26.6% vs. 29.4%; RR, 0.90, 95% CI 0.75–1.09), operative vaginal delivery (13.0% vs. 15.2%; RR 0.86, 95% CI 0.65–1.13), spontaneous vaginal delivery (60.3% vs. 55.4%; RR 1.09, 95% CI 0.99–1.20), shoulder dystocia (2.4% vs. 4.2%; RR 0.57, 95% CI 0.30–1.08), intracranial hemorrhage (0.6% vs. 0.4%; RR 1.48, 95% CI 0.20–12.57), brachial plexus injury (0.0% vs. 0.3%; RR 0.21, 95% CI 0.01–4.28), Apgar score <7 at 5 minutes (0.7% vs. 0.5%; RR 1.51, 95% CI 0.25–9.02), cord blood pH <7 (0.2% vs. 0.4%; RR 0.44, 95% CI 0.06–2.97), and mean birth weight (mean difference [MD] –134.41 g, 95% CI –317.27 to 48.46) compared to women expectantly managed. The induction group had a **significantly lower time to delivery** (MD –7.55 days, 95% CI –8.20 to –6.89), **lower birth weight ≥4000 g** (30.7% vs. 61.8%; RR 0.50, 95% CI 0.42–0.59), **lower birth weight ≥4500 g** (3.2% vs. 14.8%; RR 0.21, 95% CI 0.11–0.39), **lower incidence of fetal fractures** (0.3% vs. 2.0%; RR 0.17, 95% CI 0.03–0.79), and a significantly higher incidence of hyperbilirubinemia (8.8% vs. 2.9%; RR 3.03, CI 1.60–5.74) and phototherapy (11.0% vs. 6.6%; RR 1.68, CI 1.07–2.66) compared to the expectant management group [43].

A qualitative systematic review of induction of labor versus expectant management for women with diabetes included one randomized trial and four observational studies. The randomized controlled trial (RCT) of 200 women found women induced at 38 weeks or with confirmed fetal lung maturity demonstrated larger fetuses in the expectant management group but was only able to demonstrate three shoulder dystocias, all in the expectant management group [45]. The authors draw the conclusion from the four observational studies that there is a potential reduction in both macrosomia and shoulder dystocia with induction of labor but that further study is required [46]. A recent RCT of induction of labor at 39 weeks versus expectant management in patients with gestational diabetes ($n = 425$) indicated similar rates of cesarean section (RR 1.06; 95% CI 0.64–1.77; $p = 0.81$) and similar rates of shoulder dystocia (induction vs. experimental group 3 [1.4%] vs. 1 [0.5%], RR 2.96 CI 0.31–28.21, $p = 0.62$) [47].

In summary, cesarean delivery is recommended for macrosomia at an EFW of >5000 g in nondiabetic and >4500 g in diabetic women. **Induction of labor at term for suspected fetal macrosomia (EFW ≥4000 g or EFW >95% for gestational age) in women without diabetes is associated with a similar incidence of cesarean delivery and shoulder dystocia compared to expectant management, a significant decrease in fetal fractures, and higher incidences of hyperbilirubinemia and phototherapy. Induction at ≥38 weeks would prevent some neonatal complications and can be considered**; however, it is not recommended by ACOG [1]. There is inadequate evidence to recommend for or against induction of labor in patients with diabetes to prevent shoulder dystocia.

Intrapartum

Prophylactic McRobert maneuver prior to the development of shoulder dystocia has not been shown to decrease subsequent shoulder dystocia in women at low risk for this complication [48]. In a small RCT of 40 women, compared to lithotomy position, the use of the McRobert maneuver was associated with the same incidence (7.1 vs. 7.7%) of shoulder dystocia in both prophylactic and lithotomy groups. The forced used in traction of the fetal head during vaginal delivery was the same in each group [48]. In another RCT, in 185 women likely to give birth to a large baby (EFW >3800 g), McRobert maneuver and suprapubic pressure were associated with a trend for a lower rate of shoulder dystocia compared to controls with no prophylactic maneuvers (9% vs. 21%; RR 0.44, 95% CI 0.17–1.14). There were significantly more cesarean sections in the prophylactic group, and when these were included in the results, significantly fewer instances of shoulder dystocia were seen in the prophylactic group (RR 0.33, 95% CI 0.12–0.86). In this study, 13 (18%) women in the control group required therapeutic maneuvers after delivery of the fetal head compared to 3 (5%) in the treatment group (RR 0.31, 95% CI 0.09–1.02). One infant in the control group had a BPI (RR 0.44, 95% CI 0.02–10.61), and one infant had a 5-minute Apgar score less than 7 (RR 0.44, 95% CI 0.02–10.61) [49, 50].

Therapy

There **are no interventional trials in human subjects that compare the safety or effectiveness of various shoulder dystocia therapeutic maneuvers** [50]. Thus guidelines are based on observational data and/or expert opinion. The most important feature of the **response to shoulder dystocia is that it should be a coordinated and orderly application and progression of obstetric maneuvers** (Figure 27.1) [1, 51]. Table 27.5 describes maneuvers employed to relieve shoulder dystocia [4, 52]. **Fundal pressure should always be avoided** in shoulder dystocia, as it may worsen impaction of the fetal shoulder(s).

After diagnosis of shoulder dystocia, the delivery provider should **call for help**. This includes utilizing the assistance of other caregivers present in the delivery room as well as alerting other obstetric, pediatric, and/or anesthesia providers on the labor and delivery unit. Most authorities recommend **McRobert as the initial maneuver** since it is easy to perform, is effective, and has a low complication rate. **McRobert alone is effective in 40%–90% of cases**. **Suprapubic pressure** is often done in direct conjunction by nursing personnel (Figure 27.2). In a series of 134 cases, more than one-third of patients required more than two maneuvers to relieve the shoulder dystocia [16]. In another series of 231 shoulder dystocia cases, 57.9% of cases responded to Mc Robert and suprapubic pressure alone and had a median duration of 29 seconds [53].

If McRobert combined with suprapubic pressure is not successful, direct fetal manipulation is attempted next. In a very large series (2018 shoulder dystocia cases), **delivery of the posterior shoulder** (Figure 27.3) was associated with the highest rate of delivery (84%) compared to all other maneuvers (24%–72%) [54]. Delivery of the posterior arm decreases the bisacromial diameter by approximately 2 cm and makes the arm available for additional rotational maneuvers, if necessary [55]. Compared with other maneuvers, delivery of the posterior arm has also been noted in models to cause the least stretch of the anterior brachial plexus compared to lithotomy alone [56]. Other helpful fetal manipulation interventions are either the **Wood corkscrew** (Figure 27.4) or **Rubin maneuver** (Figure 27.5). Some argue for axillary traction as an effective maneuver for relieving shoulder dystocia: The index finger is placed in the axilla of the posterior shoulder, the thumb on the shoulder, and the middle finger is used to apply pressure to keep the arm in contact with the fetal body. Using significant force, the posterior shoulder is delivered. A retrospective study in

TABLE 27.5: Description of Various Obstetric Maneuvers to Resolve Shoulder Dystocia

	Characteristics		
Maneuver	**Maternal or Fetal Manipulation**	**Type**	**Description**
McRobert	Maternal	First line	Hyperflexion and abduction of the maternal hips (knee to abdomen position). This causes cephalad rotation of the symphysis pubis and flattening of the lumbar lordosis, freeing the impacted shoulder.
Suprapubic pressure	Maternal	First line	Pressure directed posteriorly in an attempt to force the anterior shoulder under the symphysis pubis. It also may include lateral pressure from either side of the maternal abdomen or alternating between sides using a rocking pressure. It works by reducing the fetal bisacromial diameter and rotating the anterior shoulder into the oblique pelvic diameter.
Delivery of posterior arm	Fetal	Second line	The delivery attendant places their hands in the vagina and applies pressure at the antecubital fossa in order to flex the fetal forearm. The arm is subsequently swept out over the infant's chest and delivered over the perineum. Rotation of the fetal trunk to bring the posterior arm anteriorly is sometimes required. Fracture of the humerus can occur with grasping and pulling directly on the fetal arm, as well as application of pressure onto the mid-humeral shaft.
Rubis	Fetal	Second line	Pressure is applied to the posterior surface of the most accessible part of the fetal shoulder to effect shoulder adduction. It works by rotating the fetal shoulder into the oblique pelvic diameter.
Wood	Fetal	Second line	Pressure is applied onto the anterior surface of the posterior shoulder in order to abduct the posterior shoulder. It works by rotating the fetal shoulder into the oblique pelvic diameter.
Gaskin (Knee–chest, or all fours)	Maternal	Second line	Patient is rolled from her existing position onto her hands and knees. It works through the downward force of gravity and/or a favorable change in pelvic diameters, which causes disimpaction of the fetal shoulder.
Intentional fracture of clavicle	Fetal	Third line	This works by decreasing the fetal bisacromial diameter.
Zavanelli (cephalad replacement)		Third line	Cephalic replacement of the fetal head from the vagina back into the uterus and then delivery by cesarean section.
Symphysiotomy	Maternal	Third line	Surgical or traumatic separation of the pubis symphysis to facilitate disimpaction of the fetal shoulders.

Auckland, New Zealand, found that this was the most commonly used rotational maneuver with the highest success rate with no difference in maternal and neonatal outcomes between groups [57]. Regardless of chosen maneuvers, **the need for successive maneuvers is associated with higher rates of neonatal injury; 10% with three maneuvers, 16% with four maneuvers, and 23% with five or more** [54].

Since shoulder dystocia is a bony dystocia, **routine episiotomy is not advised**. In a systematic literature review including 14 studies of 9769 cases of shoulder dystocia, there was no reported benefit of episiotomy to prevent or assist with the management of shoulder dystocia [58]. However, **episiotomy can be considered to allow the delivering provider space for internal maneuvers**.

If these steps all fail, one can repeat the sequence of initial maneuvers, potentially with an alternative delivering provider, and/or attempt placement of the patient in the "ALL FOURS" position (Gaskin maneuver) to repeat the maneuvers (Figure 27.1). In cases of intractable shoulder dystocia, a technique called posterior axilla sling traction (PAST) has been described. The PAST technique makes use of a sling (e.g. suction catheter or firm urinary catheter) that is placed around the posterior axilla and then used to provide traction to either deliver the posterior shoulder or rotate it [59]. More aggressive, "heroic" maneuvers which have very high frequency of maternal and fetal complications may be considered after repeat failure of these first- and second-line interventions. Third-line maneuvers include intentional fracture of the fetal clavicle, Zavanelli (cephalic replacement), and symphysiotomy.

Counseling and documentation

After completion of all necessary medical interventions (e.g. repair of maternal lacerations or treatment of hemorrhage), the **delivery provider should sit down with the patient and her family to review the delivery events**, the management steps performed, and the need for close newborn follow-up to evaluate for any neonatal injuries. **Open and honest communication** with the mother and family after delivery is recommended.

It is **important to document in the medical record all maneuvers used in detail**, including which shoulder was anterior, and the time from delivery of head to complete delivery of the body (Figure 27.6) [60, 61].

Anesthesia

An anesthesiologist should be present during cases of shoulder dystocia to ensure adequate analgesia and prompt preparation for cesarean delivery if needed.

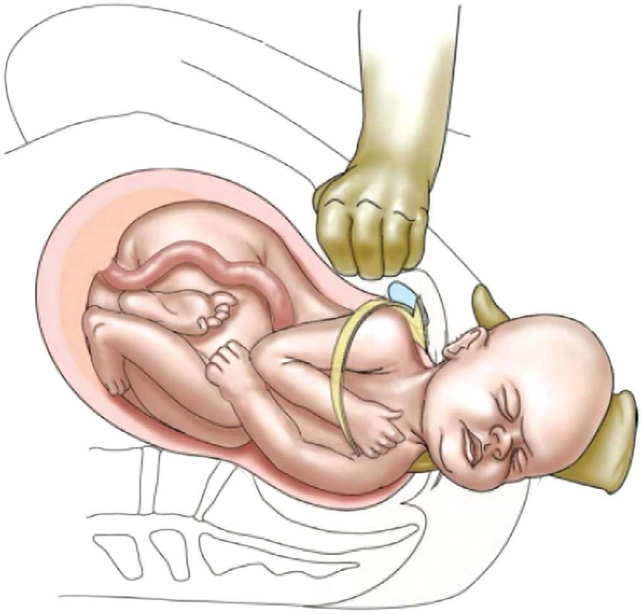


FIGURE 27.2 McRobert Maneuver and suprapubic pressure. Hyperflexion and abduction of the maternal hips, causing cephalad rotation of the symphysis pubis and flattening of the lumbar lordosis, opening space for delivery. Suprapubic pressure directed posteriorly in an attempt to force the anterior shoulder under the symphysis pubis. It also may include lateral pressure from either side of the maternal abdomen or alternating between sides using a rocking pressure. (Image by Henry Lerner, Wikimedia Commons with Creative Commons license.)

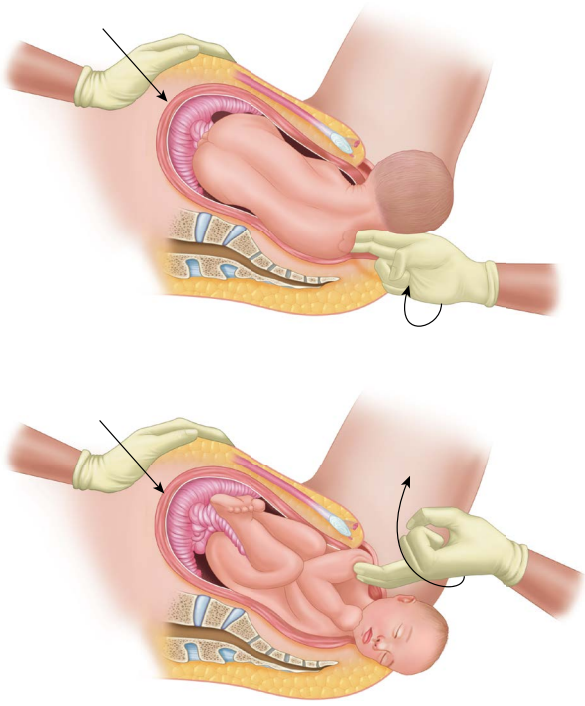


FIGURE 27.4 Woods corkscrew maneuver. Initial pressure exerted on the anterior surface of the posterior shoulder facilitates rotation of the posterior shoulder anteriorly (upper). With concurrent synchronized downward pressure, the shoulder "screws" though the maternal pelvis, disimpacting the previously impacted shoulder (lower). (Reproduced from Ramsey PS, Ramin KD, Field CS, et al. Shoulder dystocia: Rotation maneuvers revisited. *J Repro Med*. 2000;45:85–88 Ref. 70, with permission.)

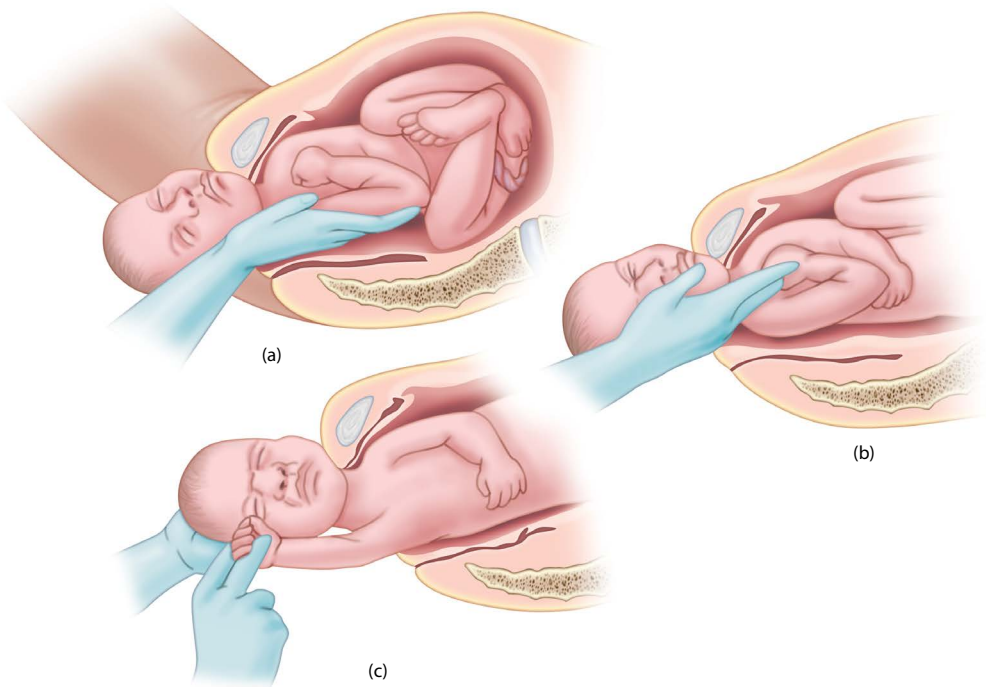


FIGURE 27.3 (a) Delivery of the posterior arm. (b) Hand placed in the vagina to apply pressure at the antecubital fossa in order to flex the fetal forearm. (c) The arm is subsequently swept out over the infant's chest and delivered over the perineum. (From Regional Perinatal Outreach Program of Southwestern Ontario & the Southwestern Ontario Perinatal Partnership, Perinatal Manual of Southwestern Ontario, "Shoulder dystocia", with permission.)

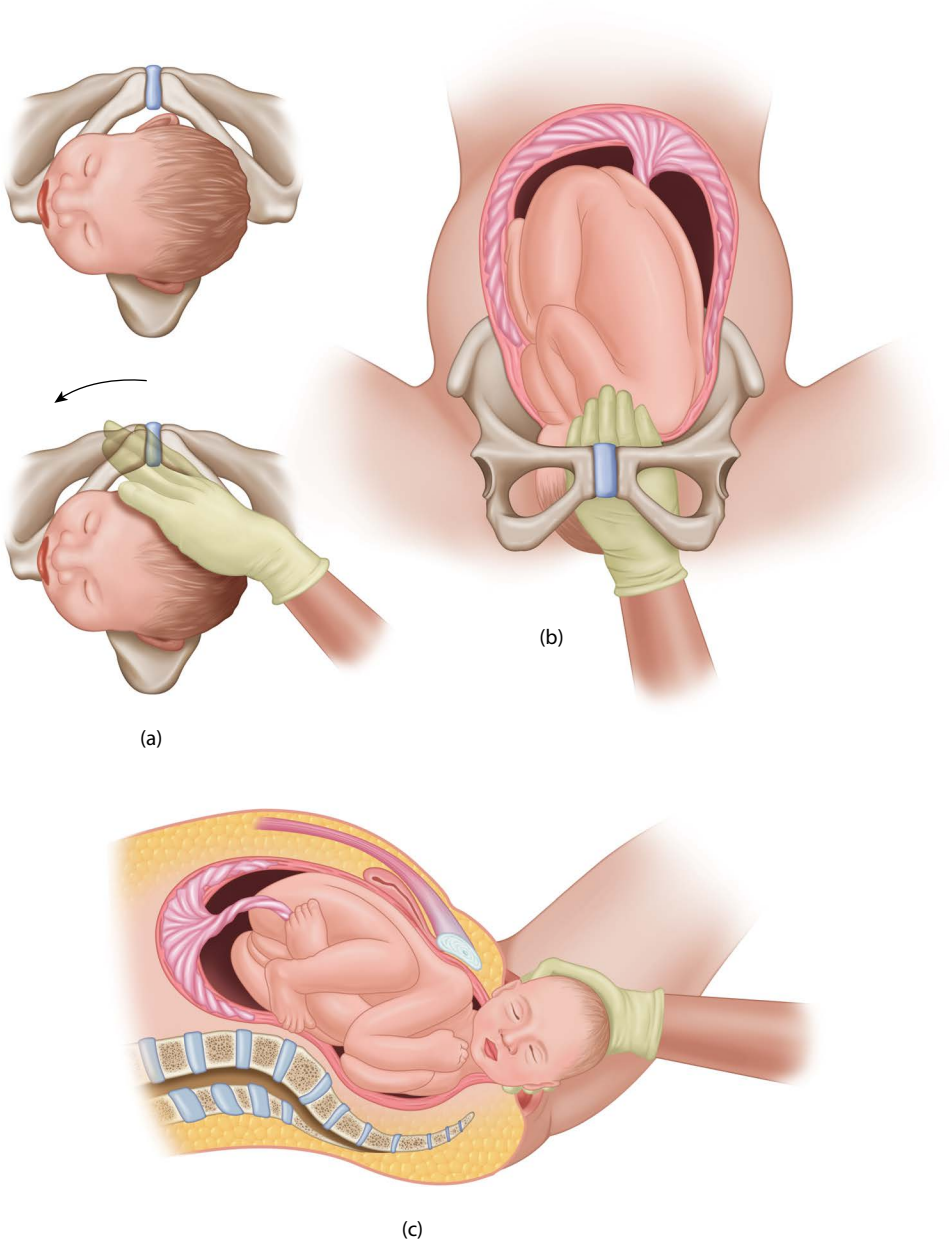


FIGURE 27.5 Rubin maneuver. (a) and (b) Pressure is exerted on the posterior surface of the most accessible part of the shoulder to facilitate abduction and disimpaction of the anterior shoulder. (c) Further rotation and adduction toward the fetal chest reduces the bisacromial diameter and results in the movement of the shoulders in a transverse position, facilitating passage of the anterior side of the shoulder beneath the pubic arch. (Reproduced from Ramsey PS, Ramin KD, Field CS, et al. Shoulder dystocia: Rotation maneuvers revisited. *J Repro Med*. 2000;45:85–88 Ref. [70], with permission.)

Neonatal/Infant follow-up

Table 27.4 describes the most common palsies associated with shoulder dystocia. It is important to underscore that causation has never been proven between shoulder dystocia and palsies, and many palsies develop in babies delivered without shoulder dystocia. **Erb palsy is by far the most common (>98%) and the one with the best prognosis (90% rate of full spontaneous recovery)**. For 65% of patients with Klumpke palsy, full spontaneous recovery can be expected, whereas in patients with a complete BPI, <50% will have this recovery. If sustained injury occurs, the evidence is mixed for the efficacy of surgery [62].

Training/Simulation

Multiple nonrandomized studies have shown the benefits of shoulder dystocia training on neonatal outcomes. In a single-center "before and after" study conducted in Jamaica, New York, between 2003–2006 (pre) and 2006–2009 (post), training decreased the rate of BPI associated with shoulder dystocia from 30% (pre) to 10.67% (post) even after adjusting for confounding factors [63]. Another "before and after" study in the United Kingdom showed a reduction in neonatal injury at birth after shoulder dystocia: (9.3% vs. 2.3%; RR 0.25; 95% CI 0.11– 0.57) [64]. This same group noted over 12 years continued reduction in BPI (pretraining 24/324 [7.4%], early training 6/262

1. Antepartum documentation:
    a. Prior shoulder dystocia? Yes no
    b. Estimated fetal weight _____
2. Mode of vaginal delivery
    a. Spontaneous
    b. Vacuum
    c. Forceps
3. How was the shoulder dystocia diagnosed? Turtle sign
   Failure to deliver shoulders with gentle downward pressure
   Other _____
4. Time fetal head delivered? _____
5. Time body delivered? _____

6. Total duration of shoulder dystocia (in minutes and seconds): _____

7. What shoulder was under the pubis symphysis (anterior) at delivery: Left Right Unknown

8. Please describe the obstetrical maneuvers were attempted, their order, and who performed:

Maneuver	**Order**	**By whom**
McRobert's (Hip flection)	12345678	_____
Suprapubic	12345678	_____
Delivery of posterior arm	12345678	_____
Rubin's (Anterior scapula)	12345678	_____
Wood's (Posterior scapula)	12345678	_____
Episiotomy	12345678	_____
Extension of Episiotomy	12345678	_____
Gaskin's (Knee-chest, all fours)	12345678	_____
Other _____	12345678	_____
Other _____	12345678	_____
Other _____	12345678	_____

Additional delivery comments: _____
_____

9. Was fundal pressure performed: Yes No

If yes, by whom and what was reason: _____

10. Who were the health care providers present at delivery?

Primary delivery attendant: _____
CNM: _____
Resident (s) [include PGY year]: _____
Nurse 1: _____
Nurse 2: _____
Nurse 3: _____
Pediatrician: _____
Anesthesiology: _____
Other providers (please add name and role): _____

11. Birth weight (grams) _____

12. Was baby moving his/her extremities: Left right Comment: _____

13. Was XRAY ordered for evaluation any bony fractures?	YES	NO
14. Were umbilical cord gases ordered?	YES	NO
15. Confirm that notes (e.g. medical, nursing, anesthesia, etc) are consistent	YES	NO
16. Has delivery note been dictated?	YES	NO
17. Family counseled	YES	NO
18. Debriefing with appropriate personnel involved	YES	NO
19. Follow-up about condition of neonate in nursery	YES	NO

Signatures:

_____ _____ _____
Primary Delivery Provider Primary delivery nurse Other care providers in attendance

FIGURE 27.6 Suggested checklist for documentation of delivery complicated by shoulder dystocia.

[2.3%], and late training 7/562 [1.3%]) [65]. In a university hospital setting in Chicago, the effects of a shoulder dystocia protocol were studied in three periods (6 months prior to training, 6 months during training, and 6 months post-training). Over the three periods, complete and consistent documentation improved (14%, to 50%, to 92%; $p<0.001$), and there was a decrease in BPI at delivery (10.1%, to 4%, to 2.6%; $p=0.03$) and BPI at neonatal discharge (7.6%, to 3%, to 1.3%; $p=0.04$) [60]. Multiple RCTs on simulation training demonstrate higher rates of successful delivery, improved timeliness, less application of force, and improved patient communication during drills on pelvic models [66–68]. Both the Joint Commission in the United States and the Royal College of Obstetricians and Gynecologists recommend such training. **Quality improvement initiatives that include components such as simulation, debriefing, multidisciplinary training, and recommendations for management of shoulder dystocia have demonstrated improved recognition and management of shoulder dystocia cases and decrease in BPIs** [60, 69].

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28

POSTPARTUM HEMORRHAGE, RETAINED PLACENTA, AND UTERINE INVERSION

Amy C. Hermesch and Jorge E. Tolosa

Key points

- **Primary postpartum hemorrhage (PPH) is defined as blood loss ≥1000 mL within 24 hours after birth**.
- **Gravimetric methods for quantifying blood loss**, including **weighing of pads and sponges**, and the use of **calibrated under-buttock drapes, as well as blood loss calculators, are recommended for the diagnosis of PPH**.
- The most common complications of the third stage of labor are postpartum hemorrhage (PPH), retained placenta, and uterine inversion. **Timely diagnosis**, physical exam, IV access, anesthesia, appropriate use of blood products, nursing support and teamwork are important for the management of third-stage complications.
- In cases of PPH, one should perform uterine massage, explore for and repair any vaginal or cervical lacerations, and manually explore the uterus.
- **Oxytocin** 20–80 IU in 500–1000 cc normal saline given as a fast IV infusion, 10 IU slow IV push, or 10 IU IM should be used as a primary uterotonic for PPH. **Pharmacologic therapy with a combination of oxytocin, misoprostol, tranexamic acid, methergine, and/or prostaglandin F2α should be employed quickly without delay after PPH is diagnosed**.
- **Misoprostol, tranexamic acid**, **methergine** (except in women with hypertension), and **prostaglandin F2α** (except in women with asthma) are all effective for the treatment of PPH and can be used in combination. Misoprostol may be particularly helpful in low-resource settings.
- There is insufficient evidence with RCTs to assess other interventions for the treatment of PPH.
- There is **insufficient evidence with RCTs to recommend pharmacologic agents for the treatment of retained placenta**.

Postpartum hemorrhage

Definitions

While controversial, the American College of Obstetrics and Gynecology (ACOG) **defines primary postpartum hemorrhage (PPH) as blood loss ≥1000 mL within 24 hours after birth** [1]. Secondary PPH is defined as excessive blood loss after 24 hours and <12 weeks postpartum. There is no single definition for PPH that has been agreed upon internationally, and multiple guidelines from various national and expert authorities exist (Table 28.1). Recent initiatives have focused on reassessing the existing PPH definitions in an effort to improve clinical management and outcomes [2, 3].

Incidence

Approximately **5%–15%** of deliveries are complicated by PPH.

Etiology

Common:

- Uterine atony: Lack of efficient uterine contraction (most common, accounts for 80%)
- Retained placenta
- Genital tract trauma: Vaginal, cervical, and vulvar

Less common:

- Uterine rupture
- Uterine inversion
- Retroperitoneal hematoma
- Consumptive coagulopathy
- Inherited or acquired bleeding disorders

Risk factors

At term, the uteroplacental circulation has a blood supply of 600–800 cc/minute. The blood volume expansion of 1.5–2.0 L in pregnant women provides a physiologic reserve for blood loss at delivery. **Cessation of placental site blood flow is due mostly to effective myometrial contractions**. Most major hemorrhage occurs within the first hour postpartum. Resources available to treat PPH vary greatly by setting (academic center versus community hospital). Location of planned delivery should be considered carefully for patients at high risk for PPH. Risk factors that contribute to decreased myometrial contractions include the following:

- Maternal factors:
  - First pregnancy
  - Maternal obesity
  - Previous PPH: 10% recurrence risk
  - High parity
  - Coagulopathy
  - Thrombocytopenia
- Antepartum bleeding: Placenta previa, abruption
- Chorioamnionitis
- Uterine fibroids
- Overdistension: Macrosomia, multiple gestation, polyhydramnios
- Uterine tocolytics: Magnesium, nitroglycerin, anesthetic gas
- Labor factors:
  - Precipitous delivery
  - Prolonged labor: First stage >24 hours
  - Prolonged oxytocin use and/or maximum of ≥40–50 cc/minute (prolonged labor)

Complications

The most reliable estimates of global **mortality** for mothers in childbirth are reported to be between 250,000 and 300,000 annually [4]. This number has decreased significantly over the past

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TABLE 28.1: Definitions for Postpartum Hemorrhage

Guidelines	Postpartum Hemorrhage (PPH) Definition
World Health Organization (2017)	Blood loss of ≥500 mL within 24 h after birth. Severe PPH: blood loss ≥1000 mL in 24 h after birth
American College of Obstetricians and Gynecologists (2017)	Blood loss of ≥1000 mL within 24 h after birth
Royal Australian and New Zealand College of Obstetricians and Gynaecologists (2017)	Blood loss ≥500 mL during puerperium and severe postpartum hemorrhage ≥1000 mL
Royal College of Obstetricians and Gynaecologists (2016)	Primary PPH: blood loss of 500–1000 mL in the absence of clinical signs of shock Major PPH: blood loss of ≥1000 mL
Society of Obstetricians and Gynaecologists of Canada (2018)	Any amount of bleeding threatening hemodynamic instability

Abbreviation: h, hour.

2 decades. Many of these deaths result from complications of the third stage of labor [4]. Ninety-nine percent of maternal deaths occur in low- and middle-income countries where maternal mortality remains unacceptably high. In sub-Saharan Africa, the risk of maternal death is very high, at 1:31, with at least 25% of those deaths due to hemorrhage [5], while in high-income countries, a woman's lifetime risk of death during or following pregnancy is 1:4300. Secondary PPH is a significant contributor to maternal death mainly, but not only, in low-income countries. PPH has other serious complications, including **hypovolemic shock, disseminated intravascular coagulopathy (DIC), renal failure, hepatic failure, and adult respiratory distress syndrome (ARDS)**.

Diagnosis

Regardless of the PPH definition being utilized, the appropriate management relies upon the clinician's assessment of risk for PPH (Table 28.2) and timely recognition of excessive blood loss. However, the assessment of peripartum blood loss has classically been determined by a provider's subjective visual estimation of blood loss (EBL). Visual EBL has consistently been shown to result in underestimation of large-volume blood loss (>1000 mL) by up to 30%–50% and overestimation of small-volume blood loss [6, 7]. These types of EBL errors have been shown to occur similarly among providers at all levels of training [7]. Formal training in visual blood loss estimation improves accuracy for a time, but skills tend to decline after several months [8].

TABLE 28.2: Example of Stratification System by Maternal Risk Factors for PPH

PPH Risk	Risk Factors	Preparation
Low	No previous CD Singleton pregnancy 4 or fewer prior VDs No bleeding disorder No prior PPH	Type and screen
Medium	Prior CD Multiple gestation > 4 prior VDs Chorioamnionitis Polyhydramnios Macrosomia Abruption Prolonged labor (>24 h) Prior PPH Large uterine fibroids	Type and screen or type and crossmatch
High	Placenta previa Suspected placenta accreta Coagulopathy Platelets <50,000 Multiple risk factors (see earlier)	Type and crossmatch Consider alerting blood bank

Source: Modified from Ref. [25].

Abbreviations: CD, cesarean delivery; VD, vaginal delivery; PPH, postpartum hemorrhage; h, hour.

Some obstetric centers have adopted **gravimetric methods for quantifying blood loss**, including **weighing of pads and sponges** and the use of **calibrated under-buttock drapes**. One study demonstrated that visual assessment of blood loss underestimated that calculated by weighing of pads and sponges by approximately 30% [9]. Another randomized controlled trial (RCT) showed that in a simulated environment, **visual blood loss estimation using non-calibrated drapes resulted in underestimation by 15%–40%** (greater error with larger volumes), whereas **use of calibrated drapes resulted in <15% error at all volumes** [10].

Blood loss calculators can be utilized by care teams to facilitate accurate quantification of blood loss after both cesarean and vaginal deliveries. Examples of calculation tools that can be integrated into an electronic medical record system can be found through the California Maternal Quality Care Collaborative (CMQCC) website (www.cmqcc.org/resources-tool-kits/toolkits/ob-hemorrhage-toolkit) and OB hemorrhage toolkit resources. In summary, **gravimetric methods for quantifying blood loss**, including **weighing of pads and sponges**, and the use of **calibrated under-buttock drapes, as well as blood loss calculators, are recommended for the diagnosis of PPH**.

Management (Figure 28.1)

Primary PPH

The management of PPH begins with a **diagnosis** of PPH and obtaining **help in a multidisciplinary fashion**, including obstetricians, nurses (including charge nurse), anesthesia, and the blood bank. The early identification of risk factors is the first step to facilitating increased surveillance, adequate preparation, and a more rapid response to hemorrhage if it does occur (Table 28.2). Risk factors should be evaluated in the prenatal period and reassessed throughout the intrapartum and postpartum course.

A commonly accepted approach to the evaluation and treatment of primary PPH includes:

- Obtain help
- Ensure adequate access with large-bore IV (may need two sites)
- Monitor vital signs serially
- Consider placing a Foley catheter to empty the bladder and monitor urine output

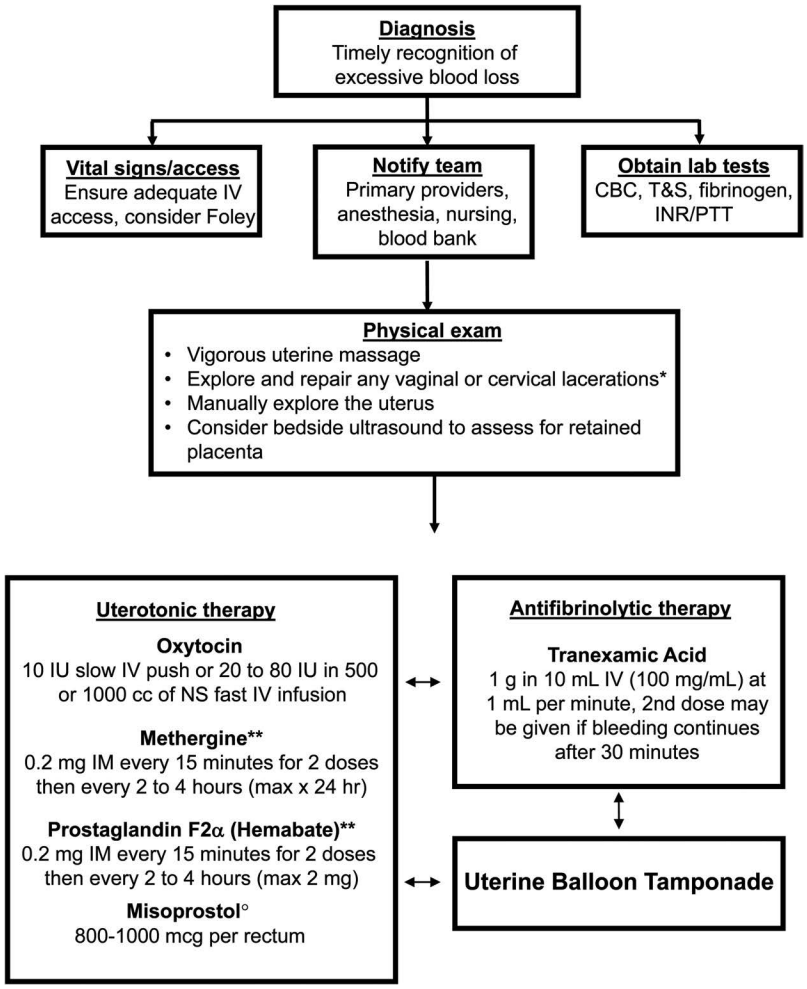


FIGURE 28.1 Suggested management protocol for primary postpartum hemorrhage. °Can be considered first-line in resource-poor settings, no IV access, or if contraindications to other medications, and also as an adjunct to first-line oxytocin in high-risk cases. *Consider transfer to operating room for complicated vaginal repairs or any cervical laceration requiring repair. **Consider contraindications to methergine [hypertension] and prostaglandin F2α [asthma]. ***Consider uterine balloon tamponade in particular if aggressive multiple agents [use all uterotonic and antifibrinolytic therapies] fail to control PPH. *Abbreviations:* IV, intravenous; CBC, complete blood count; T&S, type and screen, INR/PTT, international normalized ratio/partial thromboplastin time; IU, international units; IM, intramuscular.

- Obtain laboratory tests: Complete blood count with platelets, blood type, antibody screen, fibrinogen, fibrin split products, prothrombin time, and partial thromboplastin time

The first two critical steps in evaluating excessive bleeding are **(1) to obtain labs and (2) to perform a thorough physical exam to identity the etiology of PPH**. Although **uterine atony accounts for 80% of PPH**, failure to identify an alternative diagnosis could result in delayed surgical intervention or correction of underlying coagulopathy. Vaginal or cervical lacerations should be explored and repaired.

Primary management of uterine atony:

- Vigorous uterine massage until firm
- Manually explore the uterus and remove any retained clots or placenta. If unable to do so manually, consider ultrasound-guided sharp or suction curettage. Administer uterotonic drugs:
  - **Oxytocin 20–80 IU in 500 or 1000 cc of normal saline (NS), fast IV infusion; or 10 IU IM**
  - **Misoprostol 800–1000 mcg per rectum (side effects: Chills, fever) or 400–600 mcg buccal**
  - **Tranexamic acid (TXA) 1 g in 10 mL IV (100 mg/mL) at 1 mL per minute; second dose may be given if bleeding continues after 30 minutes**
  - **Methergine 0.2 mg IM every 15 minutes for 2 doses, then every 2–4 hours: Consider contraindications, including hypertension**
  - **Prostaglandin F2α (carboprost tromethamine, Hemabate) 0.25 mg IM every 15–90 minutes up to 8 doses (maximum 2 mg): Consider contraindications, including asthma**

TABLE 28.3: Blood Products

Product	Volume (mL)	Contents	Effect (per unit)
Whole blood[a]	400–500	RBCs, leukocytes, platelets, and plasma	Increase Hgb by 1 g/dL or Hct by 3%
Packed red blood cells	250–400	RBCs, leukocytes	Increase Hgb by 1 g/dL or Hct by 3%
Platelets	50	Platelets, plasma, small number of RBCs, and leukocytes	Increase platelet count by 5000–10,000 mm^3
Fresh frozen plasma	200–250	Fibrinogen, antithrombin III, clotting factors, plasma	Increase fibrinogen by 5–10 mg/dL
Cryoprecipitate	20–40	Fibrinogen, factor VIII, vWF, factor XIII	Increase fibrinogen by 5–10 mg/dL

[a] Can be used initially in MTP instead of recombined products.

Abbreviations: RBC, red blood cells; WBC, white blood cells; Hgb, hemoglobin; Hct, hematocrit; vWF, von Willebrand factor.

Limited evidence exists on which to base a protocol **with respect to the order of administration of uterotonics and antifibrinolytics for the treatment of PPH** following vaginal delivery. It is also important to note that the literature on the management of intraoperative and postpartum hemorrhage at the time of cesarean section is limited compared to vaginal delivery. Findings have been generalized to cesarean deliveries based on the assumption that they are likely to be beneficial. Traditionally, oxytocin and ergot alkaloids (e.g. methergine) are used as first-line agents due to their pharmacokinetic profile and speed of action, with prostaglandin F2α and misoprostol employed as adjunctive therapies. There are many RCTs directly comparing oxytocin, ergot alkaloids, and prostaglandin F2α to either placebo or to each other for treatment of PPH. Based on a recent systematic analysis, the addition of misoprostol to conventional injectable uterotonics conferred no added benefit with an increase in side effects [11]. Compared with oxytocin, misoprostol is less effective in the primary treatment of PPH. Studies comparing misoprostol to ergot alkaloids have demonstrated conflicting results, and the studies are small and heterogeneous. Thus, there is no compelling evidence to suggest an alteration in medical management at this time. However, it is important to note that **rectal or buccal misoprostol may be an appropriate first-line agent in the setting of no IV access, patients with contraindications to other uterotonics, or in resource-poor settings**. In addition to uterotonic medications, a growing body of evidence supports antifibrinolytic agents (i.e. **TXA**). A large international randomized trial demonstrated a reduction in the risk of death due to bleeding when TXA was administered (compared to placebo) early during PPH diagnosis [12]. A systematic review and meta-analysis showed a reduced risk of hysterectomy after PPH following vaginal delivery [13]. Together, these studies provide evidence that early administration of TXA in adjunct with other uterotonic agents is reasonable and supported by the World Health Organization (WHO) [14]. In summary, **pharmacologic therapy with a combination of oxytocin, misoprostol, TXA, methergine, and/or prostaglandin F2α should be employed quickly without delay after PPH is diagnosed** (Figure 28.1).

Secondary management of uterine atony (refractory uterine atony):

- Uterine balloon tamponade

Failed medical pharmacologic management of uterine atony is typically followed by intrauterine tamponade device placement. The most common device is a uterine balloon, with a high success rate—87.1%—in the setting of uterine atony [15]. Advantages of the uterine balloon include simplicity and minimal requirement for local resources and training. Alternative uterine tamponade techniques have recently shown promising observational data. The first technique uses a mini-sponge tamponade device, a type of trauma gauze, that provides mechanical compression of the uterine cavity [16]. The second device is an elliptical loop that creates a vacuum within the uterus [17]. Randomized controlled studies comparing these devices to currently used uterine balloon tamponade devices will be essential to determine how to incorporate these in current clinical practice.

If pharmacologic therapies and balloon/tamponade are not effective in stopping PPH, other interventions should be considered:

- Compression sutures
- Uterine artery ligation
- Uterine artery embolization
- Hysterectomy

Soon after the diagnosis of PPH, need for blood products and hemostatic drugs should be assessed:

- Transfusion of blood and blood products as necessary (Table 28.3).
- Hemostatic drugs.
  - Factor VIIa: A single RCT demonstrated that recombinant human FVIIa may reduce the need for surgical intervention for severe PPH that has failed medical management [18]. This RCT was small and not placebo-controlled or blinded. Thus, larger blinded and placebo-controlled trials are needed to assess efficacy and safety.
- If stable, consider pelvic arterial embolization done by interventional radiology (IR).
- If unstable (there are **no high-quality RCTs** investigating the following techniques):
  - Consider massive transfusion protocol (see Figure 28.2).
  - Laparotomy: Uterine artery ligation, compression sutures, internal iliac artery ligation.
  - Bimanual uterine compression.
  - Aortic compression (temporary) and pelvic packing.
  - Hysterectomy.

A nonpneumatic antishock garment (NASG) is a neoprene compression suit fastened around the body to reduce bleeding and reverse shock, to be used as a hemodynamic temporizing measure during transfer to a higher-level treatment facility.

Massive hemorrhage may exceed the clinical care team's ability to "keep up," leading to hemodynamic instability and shock frequently in the presence of acidosis, hypothermia, and coagulopathy. Damage control surgery during obstetrics is defined as abdominopelvic packing [19]. This can be utilized after arterial bleeding has been controlled. After packing, coagulopathy can

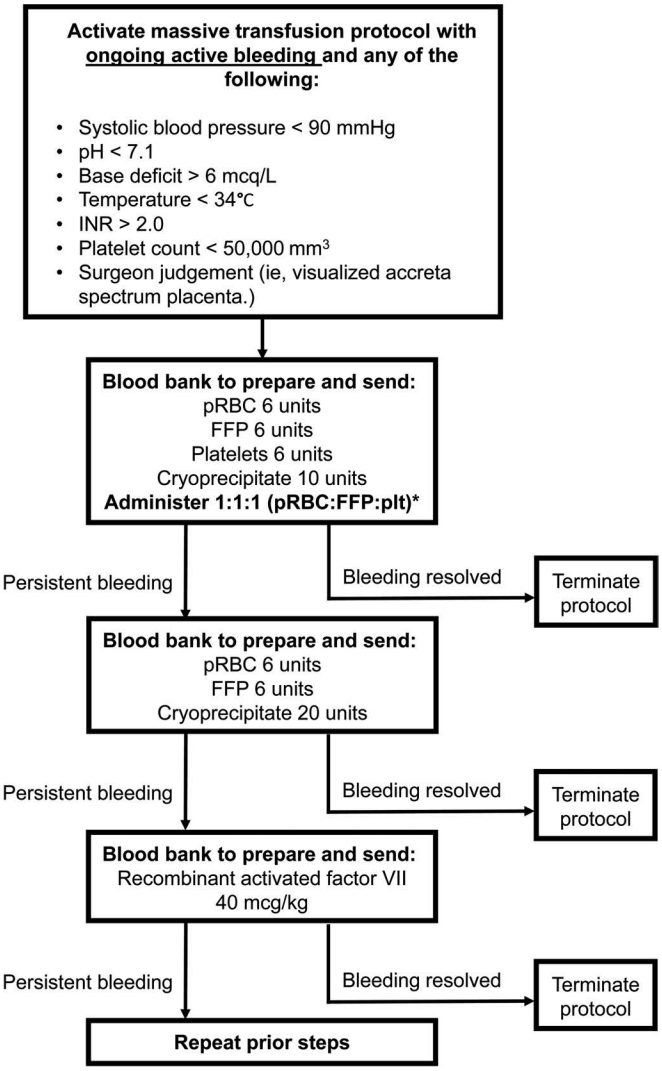


FIGURE 28.2 Suggested massive transfusion protocol. *Depending on institutional availability and blood blank protocol, whole blood may be used initially in MTP instead of recombined blood components. *Abbreviations:* INR, international normalized ratio; pRBC, packed red blood cells; FFP, fresh frozen plasma.

be corrected and interventional radiology can be utilized if the patient is stable and if it is available. Additional expertise and resources can be called on for surgical and transfusion support.

Secondary PPH

There is insufficient evidence to make recommendations for the management of secondary PPH [20]. Management similar to that for PPH is suggested, with high suspicion for retained placenta.

Retained placenta

Definition

Placenta undelivered ≥30 minutes after infant delivery.

Incidence

Between **0.5% and 3%.**

Complications

Hemorrhage, infection, and genital tract trauma.

Etiology

- Preterm birth: Inversely proportional to gestational age
- Cord avulsion: Incidence up to 3% with controlled cord traction, especially by inexperienced operators
- Placenta accreta (see Chap. 29)

Management

- Obtain adequate anesthesia.
- Attempt manual placental extraction.
  - One hand is placed over the abdomen to stabilize the uterine fundus, while the other hand is placed through the cervix into the uterus. The placenta is gently separated from the uterus starting at the superior placental edge. If possible, the placenta should be removed intact.
- Consider ultrasound to ascertain all placental tissue has been removed.
  - The ultrasonographic appearance of the uterus immediately following delivery is variable. **The sensitivity and positive predictive value of ultrasound for the detection of retained products of conception are relatively low** (44% and 58%, respectively). The specificity and negative predictive value are better (92% and 87%, respectively) [21].
- Palpate and massage the fundus until firm.
- Proceed to the operating room for curettage **under ultrasound guidance** if unsuccessful extraction or excessive bleeding.
- Consider diagnosis of placenta accreta.

Pharmacologic agents

In the past, pharmacologic interventions have been used in the management of retained placenta. The rationale was that stimulating uterine contractions with oxytocin or prostaglandins, or cervical relaxation with nitroglycerin, would facilitate spontaneous placental delivery and avoid further invasive interventions. However, a systematic analysis incorporating 16 RCTs and 1683 patients identified **no differences in the need for manual placental extraction with oxytocin (intraumbilical), prostaglandins** (e.g. F2α, E2, or misoprostol), **or nitroglycerin** [22]. The greatest number of studies investigated intraumbilical administration of oxytocin. They concluded that there is **no evidence supporting the use of intraumbilical oxytocin for retained placenta** and that there has not been adequate evaluation of other pharmacologic interventions by RCT. Therefore, there is **insufficient evidence to recommend pharmacologic agents for the treatment of retained placenta**.

Antibiotics

There is **insufficient evidence** to assess the effects of prophylactic use of antibiotics following manual removal of the placenta [23]. The WHO recommends single-dose penicillin or first-generation cephalosporin based on one retrospective study [14, 24].

Uterine inversion

Definition

The collapse of the uterine fundus into the uterine cavity.

Incidence

Approximately 1 in 2500 deliveries.

Risk factors

- Excessive umbilical cord traction
- Fundal pressure
- Fundal cord insertions
- Abnormal placentation

Management

There are no randomized trials to determine the optimal management for uterine inversion. Suggested management may include the following:

- Obtain assistance from other obstetricians or experienced providers and nursing staff.
- Obtain adequate anesthesia.
- Consider immediate transfer to the operating room.
- Obtain large-bore IV access.
- IV fluid therapy.
- If placenta has not yet delivered, avoid separation to reduce bleeding.
- **Consider uterine-relaxing agents**.
  - Nitroglycerin 50–500 mg orally or inhaled per anesthesia – usually preferred as first line.
  - Magnesium sulfate 4–6 g IV bolus.
  - Terbutaline IV 0.25 SQ.
- **Manual manipulation of the uterus**.
  - Manually reduce the uterine fundus by placing the hand through the cervix into the uterine cavity and applying gentle pressure to the inverted fundus. Cup the uterus in the palm with the fingers posteriorly and thumb anteriorly (no use of fist).
  - Once the fundus has been manually replaced, administer uterotonic therapy (oxytocin) followed by methergine to maintain uterine tone and prevent reinversion.
- **Surgical intervention: Laparotomy (rarely needed)**.
  - Huntington procedure: Clamps are placed on the round ligaments 2 cm deep in the inversion and gentle upward traction applied. Repeat clamping as necessary.
  - Haultain procedure: A vertical incision is made in the posterior portion of the inversion ring to increase its size and to reposition the uterus.
  - Uterotonic agents when uterus is repositioned.
- If present, treat PPH or retained placenta as described under 'Postpartum hemorrhage' or 'Retained placenta', above.

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29

PLACENTAL DISORDERS

Daniele Di Mascio and Francesco D'Antonio

Placenta previa

Key points

- Placenta previa is defined as a placental tissue that covers the internal cervical os.
- **Low-lying placenta** is defined as a placenta that comes within 0.1–2.0 cm of the internal os, but does not cover it.
- The **major risk factor for placenta previa is a previous cesarean delivery**.
- The majority of cases of placenta previa are usually **detected at the mid-trimester ultrasound** and are labelled "previa" with the presence of placental tissue completely extending over the internal cervical os.
- **Transvaginal ultrasound** should be preferred, as it can be safely performed in women with placenta previa, and it is more accurate than the transabdominal approach.
- The most common symptom of placenta previa is antepartum, painless bleeding in the second or early third trimester.
- The **risk that a placenta previa diagnosed in the antepartum period remains a placenta previa at the time of delivery depends on several factors, especially gestational age (GA) at detection, the placental distance from or extent of overlap of the internal os, and the a priori risk of placenta previa related to other risk factors (e.g. prior cesarean delivery). Most placenta previas diagnosed before the third trimester do not remain placenta previas at the time of delivery.**
- **Women who have the inferior edge of the placenta ≥1 cm from the internal os at around 20 weeks usually do not require further ultrasounds for placental location**.
- **All patients with the inferior placenta edge <1 cm from the internal os or overlying the os at around 20 weeks should be rescanned at least once at approximately 32–35 weeks' gestation to reassess for placental location**.
- **All patients with prior cesarean delivery and placenta previa that extends anteriorly should have evidence of placenta accreta assessed ultrasonographically**.
- Women with a placenta previa should be **delivered by cesarean. If the placental lower edge is within 1–19 mm of the internal os, a trial of labor can be attempted, but the risk of significant bleeding during labor may be higher, especially in those with a distance of only 1–10 mm**.
- The optimal GA for delivery of an asymptomatic woman (i.e. a woman without acute bleeding) with placenta previa is unknown, but many experts recommend **planned cesarean delivery at approximately $36^{0/7}$–$37^{6/7}$ weeks**.

Definition

Placenta previa is defined as a placental tissue that **covers the internal cervical os**, while **low-lying placenta is defined as a placenta that comes within 0.1–2.0 cm of the internal os, but does not cover it** [1].

The terms "complete" (when the placenta entirely covers the internal os), "partial" or "incomplete" (when the placenta covers the internal os only in part), or "marginal" (when placental tissue reaches the internal os, not covering it) traditionally used to characterize placenta previa should be avoided, as these belong to the "pre-ultrasound" period, when the diagnosis was made by physical examinations. Moreover, many studies have used these terms to signify different conditions. When the placenta does not cover the internal os, rather than use ambiguous language, it is best to describe the distance of the tip of the placenta from the internal os [1].

Epidemiology/Incidence

The overall prevalence rate of placenta previa ranges from 4.0 to 5.2 per 1000 births, and the prevalence significantly changes according to the regional area, with higher prevalence among Asian studies (12.2 per 1000 pregnancies) compared with those coming from North America (2.9 per 1000 pregnancies), Europe (3.6 per 1000 pregnancies), and sub-Saharan Africa (2.7 per 1000 pregnancies) [2, 3].

The frequency of placenta previa is higher earlier in gestation, but many of these cases will resolve. The likelihood of resolution is inversely proportional to gestational age (GA) at the time of examination (Figure 29.1) [4].

Risk factors

The major risk factor for placenta previa is a **previous cesarean delivery**: A prior cesarean delivery increases the risk of placenta previa by about 47%, as shown by both cohort and case-control studies [5–7], and this risk increases as the number of previous cesarean deliveries increases (Figure 29.2), with prelabor cesarean associated with a significantly increased risk of previa in the second delivery [8].

Other well-known risk factors for placenta previa are any other uterine surgery (e.g. myomectomy, dilation and evacuation [D&E], dilation and curettage [D&C], and hysteroscopy), smoking, maternal age, multiparity, cocaine abuse, and multiple pregnancies [1]. In particular, a large retrospective cohort study of singleton and twin pregnancies showed that dichorionic twin pregnancies were more likely to have placenta previa compared with monochorionic (odds ratio [OR]: 3.3) or singleton pregnancies (OR: 1.5) [9].

Diagnosis

The assessment of the position of the placenta is one of the recommended minimum requirements for basic mid-trimester fetal anatomic survey [10]. **Thus, the majority of cases of placenta**

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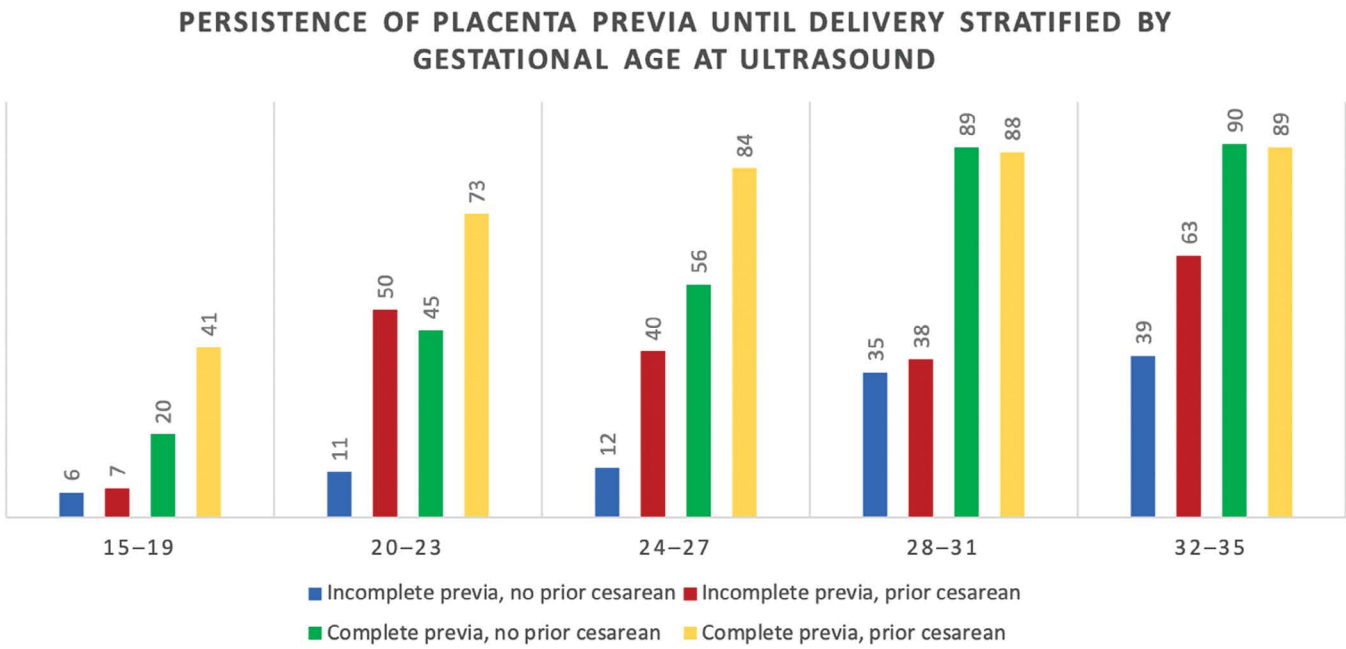


FIGURE 29.1 Persistence of placenta previa until delivery stratified by gestational age at ultrasound detection, type of previa, and prior cesarean delivery. All data presented as %; incomplete previa defined as inferior edge of the placenta partially covering or reaching the margin of the internal os. (Data from Ref. [4].)

previa are usually detected at the mid-trimester ultrasound and are labelled "previa," with the presence of placental tissue completely extending over the internal cervical os, or as "low-lying placenta" when the edge is within 2 cm of the internal os. In this scenario, the Eunice Kennedy Shriver National Institute of Child Health and Human Development recommend to always describe the location of the edge of the placenta when writing the ultrasound report [11].

When considering transabdominal ultrasound, a prospective cohort study of 1214 women aiming at evaluating the distance from the placental edge to the internal os (placenta–cervix distance) showed that a transabdominal placenta–cervix distance cutoff of 4.2 cm had a sensitivity of 93.3% and a specificity of 76.7% for detection of placenta previa, with a 99.8% negative predictive value at a screen-positive rate of 25.0%, while a cutoff of 2.8 cm had a sensitivity of 86.7% and a specificity of 90.5%, with a 99.6% negative predictive value at a screen-positive rate of 11.4% [12].

However, **transvaginal ultrasound (TVU) should be preferred**, as it can be safely performed in women with placenta previa, and few studies—including a randomized controlled trial—demonstrated that the transvaginal approach is more accurate than the transabdominal, with a sensitivity of 87.5%, a specificity of 98.8%, and a negative predictive value 97.6% [13–15].

Moreover, in women with placenta previa, **transvaginal cervical length** also allow to predict antepartum bleeding and emergency delivery, and in particular, a cervical length ≤30 mm, as well as a decrease in cervical length, was associated with a significantly higher incidence of antepartum hemorrhage and emergency cesarean delivery (CD) before 34 weeks of gestation when placenta previa was "complete." Women with a change in the transvaginal cervical length more than 6 mm between the second and third trimester are considered to be at higher risk of emergency CD [16–19].

Symptoms and complications

The most common symptom of placenta previa is antepartum, painless bleeding in the second or early third trimester, which occurs in more than half of women with placenta previa [21]. In some cases, bleeding might also present as painful, mostly as a consequence of uterine contractions due to partial placental separation. Finally, a small proportion of patients might not present any bleeding until labor [1].

Placenta previa is associated with both maternal and perinatal morbidity. Maternal morbidity is mainly associated with either antepartum or postpartum hemorrhage, which might occur, respectively, in up to 52% and 22% of cases of placenta previa [20, 21]. When comparing women with normal location of the placenta, those affected by placenta previa are at significantly higher risk of perinatal morbidity, mainly related to preterm birth before 37 weeks, admission to the neonatal intensive care unit (NICU), and both perinatal and neonatal death [22].

Intuitively, the incidence of both maternal and perinatal morbidity is lower in cases of low-lying placenta, but there is still a risk that is higher in women with placental edge at 1–10 mm compared with 11–20 mm from the internal cervical os (Table 29.1) [23].

Management

Principles

Placenta location should be assessed at the time of the fetal anatomic survey (usually 18–24 weeks). If placenta previa is suspected by transabdominal examination, TVU should be performed for confirmation of the diagnosis (Figure 29.3). A single antenatal ultrasound that detects a placenta previa, however, may not indicate that a placenta previa will be present at delivery, as the relative position of the placenta with respect to

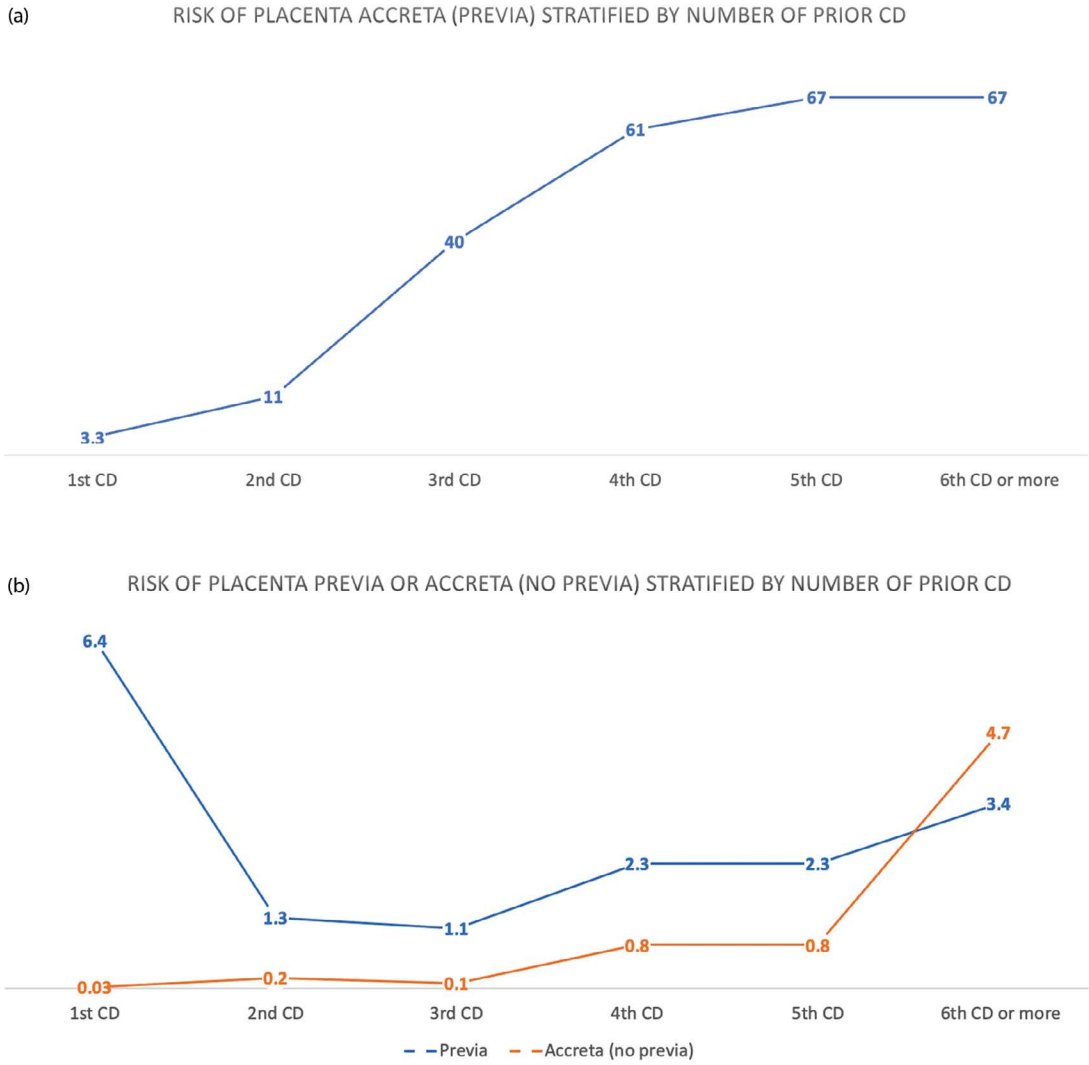


FIGURE 29.2 (a) Risk (%) of placenta accreta (in cases with previa) stratified by number of prior cesarean deliveries. (b) Risk of (%) placenta accreta (in cases with no previa) stratified by number of prior cesarean delivery. All data presented as %; CD, cesarean delivery. (Data from Ref. [7].)

the internal os will change as gestation progresses [4]. The reason for this change in relative position is not placental migration, but likely due to the growth and development of the lower uterine segment. Atrophy of placental cells overlying the os also has been postulated as a contributing factor to this apparent positional change. This phenomenon has been cited as the reason that **vasa previa** can be seen in this setting (i.e. when an initially diagnosed placenta previa resolves).

TABLE 29.1: Selected Outcomes with Low-Lying Placenta According to Placental Edge to Internal os Distance

	Distance between Placental Edge and Internal Cervical os	
	1–10 mm	**11–20 mm**
Cesarean delivery	75%	31%
Antepartum hemorrhage	29%	3%
Postpartum hemorrhage	21%	10%
Postpartum hemorrhage >1000 mL	8%	10%

Source: From Vergani P, Ornaghi S, Pozzi I, et al. Placenta previa: Distance to internal os and mode of delivery. Am J Obstet Gynecol. 2009;201:266.e1–5. Ref. [23], with permission.

Workup

Examination

Digital examination should NOT be performed. Because of the reliability of ultrasound for diagnosis of previa, the technique of double-setup examination is **unnecessary**. If employed, double-setup examination should be performed in a setting with the ability to proceed in a prompt fashion with CD if indicated.

Ultrasound

TVU is the gold standard for the diagnosis of placenta previa (Figure 29.4). Most previas diagnosed before the third trimester resolve (Figure 29.1). If a placenta previa "resolves" but remains proximate to the internal cervical os, a woman still may have an increased risk of third-trimester bleeding, intrapartum hemorrhage, and CD [23, 24].

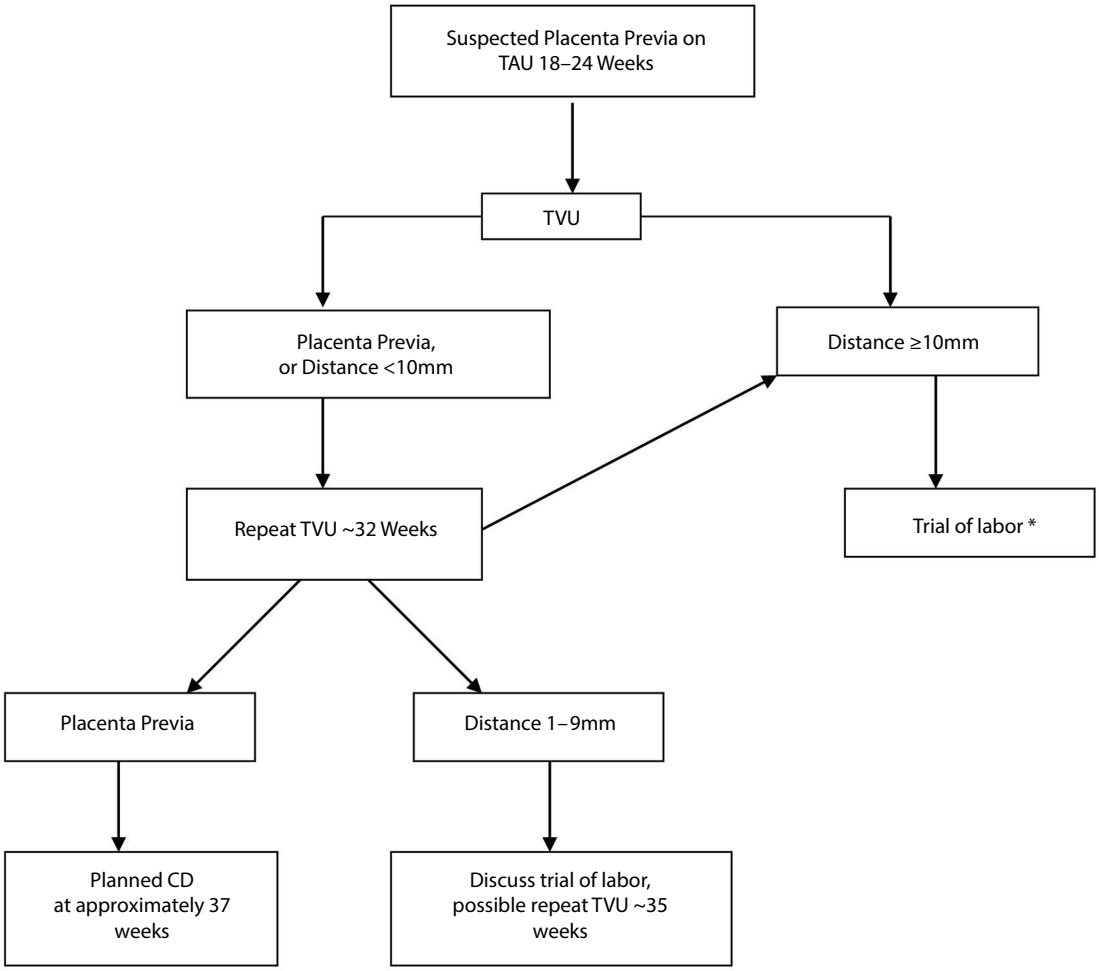


FIGURE 29.3 Management of suspected placenta previa. *Abbreviations:* Distance, distance between placental edge to internal cervical os; TAU, transabdominal ultrasound; TVU, transvaginal ultrasound; CD, cesarean delivery. *After discussion with the couple and if no contraindication.

Women who have the inferior edge of the placenta >1 cm from the internal os at around 20 weeks usually do not require further ultrasounds for placental location, as they are exceedingly unlikely to have a placenta that is low-lying or a previa at delivery. **Women who have the inferior placental edge overlapping the internal os by ≥25 mm at around 20 weeks have been reported to usually have persistence of previa even by term** (Figure 29.1) [25, 26].

All patients with suspected placenta previa in the second trimester should be rescanned at approximately 32–35 weeks' gestation to assess for persistence of placenta previa (Figure 29.3). Additionally, **even if a placenta previa is no longer present, measuring the distance from the placental edge to the internal os in the third trimester can help estimate the risk of bleeding with a trial of labor** [23, 24]. **All patients with prior CD (or other uterine surgery) and placenta previa that extends anteriorly should have evidence of placenta accreta assessed ultrasonographically** (see the section "Placenta Accreta Spectrum Disorders") [7, 27].

Prenatal care

All patients with placenta previa and antenatal bleeding in the third trimester should be advised about pelvic rest (no vaginal penetration). Pelvic rest recommendations in women with previa placenta that is near but not overlapping the internal os should be individualized and based on bleeding during the pregnancy, as well as the distance between the placenta and the internal os. There is insufficient evidence to support the use of routine bed rest in women with placenta previa or to be certain who are optimal candidates, when asymptomatic, for hospitalization [28]. Moreover, while pelvic rest, i.e. nothing per vagina, is often suggested, there is no evidence for its effectiveness. There is no evidence to support the use of autologous blood donation/transfusion for placenta previa [29].

Therapy/Interventions

Management at home versus hospitalization

There has been no evidence of any clear advantage to a policy of home versus routine hospital care, with similar maternal and

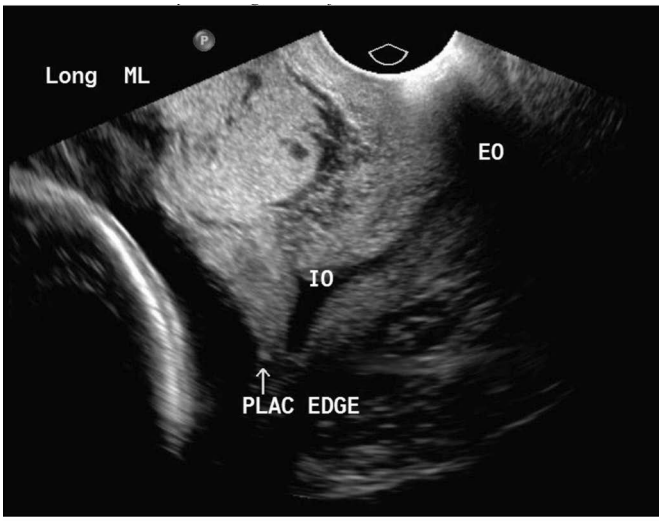


FIGURE 29.4 Transvaginal ultrasound showing anterior placenta previa, with placental edge covering over the internal Os. (Courtesy of the Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, Northwestern University Feinberg School of Medicine.) *Abbreviations:* IO, internal os; EO, external os.

fetal outcomes demonstrated in the trials that do exist. The only difference is that compared to hospitalization, management at home—not surprisingly—has been associated with a reduced length of stay in the hospital [28]. There are limited data to allow certainty as to who are the optimal candidates for inpatient management. **Women who traditionally have been more likely to be managed in the hospital even though they are not acutely symptomatic are those who have had recurrent episodes of antepartum hemorrhage (e.g. three or more episodes of bleeding)**; have other medical complications that increase their risks (e.g. congenital cardiac disease); or are unable to easily access the hospital in an emergency (e.g. lack of telephone at home and far distance from an adequate care facility).

Often, after an initial antenatal bleeding episode related to placenta previa, if several days of no further bleeding have occurred and there is no other indication for hospitalization, women may be managed as outpatients.

Cervical cerclage

Cervical cerclage has not been proven to be an effective intervention for women with placenta previa [28]. Although the meta-analysis in the Cochrane review that evaluated cervical cerclage in the setting of placenta previa revealed that women randomized to cerclage had a reduced length of inpatient hospitalization, as well as reduced risks of a small-for-gestational-age (SGA) birth or delivery <34 weeks, the benefits were evident in studies with lower methodological quality, and thus there is not yet sufficient evidence to justify this intervention.

Cervical pessary

Compared with progesterone alone, the use of the Arabin cervical pessary combined with progesterone in patients with placenta previa significantly reduced the rate of preterm delivery <34 weeks and bleeding during pregnancy in a recent randomized controlled trial of 217 women [30]. Given the limited data, pessary cannot be recommended for use in women with placenta previa.

Tocolysis

There is insufficient evidence to assess the benefits of tocolysis for treatment of preterm labor (PTL) specifically in women with a placenta previa. It is reasonable to consider tocolysis, as for women without a placenta previa, if PTL is diagnosed and a course of steroids has not yet been administered [31]. Acute bleeding with instability of the mother or fetus is considered a contraindication to tocolysis.

Steroids

In case of antenatal bleeding, a course of corticosteroids should be administered to women who are eligible and are managed expectantly if delivery is likely within 7 days, the GA is between $34^{0/7}$ and $36^{6/7}$ weeks of gestation, and antenatal steroids have not previously been administered [32].

Anti-D immune globulin

For prevention of RhD alloimmunization, anti-D immune globulin to D-negative should be administered to women who have bleeding from placenta previa.

Antepartum testing

There are insufficient data to assess the usefulness of routine antenatal testing in improving outcomes, and this strategy is presently not indicated.

Delivery

Timing: There is insufficient evidence to be certain of the optimal GA of delivery for women with placenta previa who are not acutely bleeding, although experts have recommended approximately **$36^{0/7}$–$37^{6/7}$** (Figure 29.3) [32]. In the setting of acute bleeding, the timing of delivery depends upon individualization of patient circumstances, taking into account GA, amount of bleeding, and other comorbidities.

Mode: Delivery of women with a placenta previa should be **by cesarean**. A recent randomized controlled trial aiming at evaluating the role of interventional radiology before CD showed that the use of prophylactic internal iliac artery balloon occlusion did not reduce postpartum hemorrhage or have any effect on maternal or neonatal morbidity [33]. **Preoperative ultrasonography to assess placental location is useful in determining the optimal place for the uterine incision**. **Those with a low-lying placenta not covering the internal os but within 20 mm of it may have a trial of labor offered**, with individual circumstances (e.g. the presence of antepartum bleeding) and the risk of bleeding at delivery taken into consideration (Figure 29.3). In a series, 26/28 (93%) women who had a placental edge–to–cervical os distance of 1–20 mm and who underwent a trial of labor delivered vaginally [23]. **Women with a placental edge that is within 1 cm of the internal os can have uncomplicated vaginal deliveries, although their risk of bleeding and requiring a cesarean is higher** than in those women whose placenta is 10–20 mm distant from the os (risks of cesarean are 75% and 31%, respectively) (Figure 29.1) [23]. As such, depending upon the distance of the placental edge from the internal os, as well as other factors, these patients (i.e. those with a placenta not covering the internal os but that is 2 cm or less from the internal os prior to delivery) should have their circumstances discussed

and be delivered in facilities with the capacity to perform emergent operative delivery if necessary [23]. In women with the placenta 2 cm or more from the internal os, a trial of labor should be encouraged.

Placenta accreta spectrum disorders

Key points

- Placenta accreta is diagnosed when anchoring placental villi are attached to myometrium rather than decidua, but without completely invading it; placenta increta is diagnosed when chorionic villi penetrate the myometrium, while the diagnosis of placenta percreta is considered when chorionic villi penetrate through the myometrium to the uterine serosa and/or adjacent organs.
- The incidence of placenta accreta spectrum (PAS) disorders significantly increased in the last decades, and the greatest contribution to the increasing pattern of PAS epidemiology is represented by the rising rates of CDs.
- In addition to placenta previa and CD, several other risks factors have been described to be associated with myomectomy, uterine curettage, hysteroscopy, multiparity, advanced maternal age, obesity, and assisted reproductive techniques.
- **Ultrasound is the gold standard imaging approach to diagnose PAS**.
- **Antepartum diagnosis significantly** reduces intrapartum blood loss and units of red blood cells and fresh frozen transfused, but most of all, it might allow to organize delivery with a multidisciplinary team in a tertiary center with the proper expertise.
- The diagnostic accuracy of MRI in detecting the depth of placental invasion is similar to ultrasound, and it might be useful to delineate the topography of placental invasion and to better evaluate the posterior placenta.
- PAS is associated with a high burden of adverse maternal outcomes and particularly **severe life-threatening hemorrhage, need for blood transfusion, damage to adjacent organs, and death**.
- There are limited randomized trials to assess the efficacy of different surgical interventions in or the approaches to the management of placenta accreta (e.g. balloon catheterization by interventional radiology, ureteral stents, etc.). Planned cesarean hysterectomy may be beneficial in cases in which the diagnosis is highly suspected, especially for the woman who does not desire further fertility.
- The American College of Obstetricians and Gynecologists (ACOG) recommends **planned delivery between 34+0 and 35+6 weeks** of gestation for stable (no bleeding or preterm labor) patients, while the Society for Maternal-Fetal Medicine (SMFM) suggests delivery between 34 and 37 weeks of gestation for stable women with placenta accreta.
- Women with PAS should deliver in **tertiary centers** that could provide a multidisciplinary team with significant experience in managing PAS.
- Cesarean hysterectomy with placenta left in situ is currently the gold standard surgical management of PAS disorders.

Definition

PAS disorders represent a heterogeneous group of conditions characterized by an abnormal invasion of trophoblastic tissue through the myometrium and uterine serosa [1]. The nosography of abnormal placentation was recently updated, and the new term "placenta accreta spectrum disorders" is now preferred to overcome possible confounding terms like "morbidly adherent placenta" that technically excludes the severe forms of the disease, or "placental adhesive disorders" and "abnormally invasive placentation," which ignore clinical and pathologic diagnostic standards.

Classification

PAS disorders are commonly classified according to the degree of invasion of the trophoblastic tissue through the myometrium and uterine serosa. **Placenta accreta** is diagnosed when anchoring placental villi are attached to myometrium rather than decidua, but without completely invading it; **placenta increta** is diagnosed when chorionic villi penetrate the myometrium, while the diagnosis of **placenta percreta** is considered when chorionic villi penetrate through the myometrium to the uterine serosa and/or adjacent organs [34]. However, some authors have cast doubt on this anatomy-based classification: It is retrospective; it does not consider the topography of placental invasion, which is one of the main determinants in predicting the surgical outcome; and it does not easily fit the clinical evidence that different degrees of placental invasion coexist in the same uterine specimen, making a precise histopathologic classification extremely challenging. For this reason, the International Federation of Gynecology and Obstetrics (FIGO) recently proposed a clinical based staging upon the difficulties in placental detachment during delivery and the gross visualization of invasion during surgery, which goes from grade 1 (complete placental separation at the third stage, with normal adherence of placenta) to grade 6 (placental tissue seen to have invaded through the serosa of the uterus and infiltrating the parametrium or any organ other than the urinary bladder) (Table 29.2) [35].

Etiopathology

The etiopathology of PAS has not been entirely elucidated yet, but it has been postulated that an abnormal decidualization process, particularly in the case of prior uterine surgery, can cause an excessive trophoblastic infiltration through the myometrium that might extend also beyond the serosa in the most severe cases. Also, other biologic factors linked to angiogenesis and inflammation processes have been claimed to play a role in the development of PAS [36].

Epidemiology/Incidence

A recent meta-analysis including 7001 cases of PAS of 5,719,992 births showed that the overall prevalence of PAS was **0.17%**. In this review, the incidence of placenta accreta, increta, and percreta was 63%, 15%, and 22%, respectively [37]. The **incidence of PAS significantly increased in the last decades, and the greatest contribution to the increasing pattern of PAS epidemiology is represented by the rising rates of CDs** (see "Risk Factors" next). The role of CDs in increasing the prevalence of PAS disorders is supported by strong epidemiologic data. Different

TABLE 29.2: Clinical Grading to Assess and Categorize Placental Adherence or Invasion at Delivery

Grade	Definition
1	*At cesarean or vaginal delivery:* Complete placental separation at third stage. Normal adherence of placenta
2	*(A) Cesarean/laparotomy*: No placental tissue seen invading through the surface of the uterus. Incomplete separation with uterotonics and gentle cord traction, and manual removal of placenta required for remaining tissue and parts of placenta thought to be abnormally adherent *(B) Vaginal delivery*: Manual removal of placenta required and parts of placenta thought to be abnormally adherent
3	*(A) Cesarean/laparotomy*: No placental tissue seen invading through the surface of the uterus. No separation with uterotonics and gentle cord traction with manual removal of placenta required and the whole placental bed thought to be abnormally adherent *(B) Vaginal delivery*: Manual removal of placenta required and the whole placental bed thought to be abnormally adherent
4	*Cesarean/laparotomy:* Placental tissue seen to have invaded through the serosa of the uterus but a clear surgical plane can be identified between the bladder and uterus to allow nontraumatic reflection of the urinary bladder at surgery
5	*Cesarean/laparotomy*: Placental tissue seen to have invaded through the serosa of the uterus and a clear surgical plane cannot be identified between the bladder and uterus to allow nontraumatic reflection of the urinary bladder at surgery
6	*Cesarean/laparotomy*: Placental tissue seen to have invaded through the serosa of the uterus and infiltrating the parametrium or any organ other than the urinary bladder

Source: From Jauniaux E, Chantraine F, Silver RM, et al; FIGO Placenta Accreta Diagnosis and Management Expert Consensus Panel. FIGO consensus guidelines on placenta accreta spectrum disorders: Epidemiology. Int J Gynaecol Obstet. 2018;140:265–273. Ref. [35], with permission.

worldwide evidences point out a parallel rise of PAS disorders and rate of CDs [35]. Furthermore, the increasing rate of CDs not only increases the overall risk of PAS, but significantly shifts the epidemiology towards the more advanced forms of the disease, including increta and percreta. This change is unambiguously outlined by the marked differences in the distribution of the different subtypes of PAS in the case series antecedent to the 1980 and the more recent cohort studies [35].

Risk factors

Placenta previa and previous CD are the major determinants of PAS and act as independent risk factors. Indeed, the risk of PAS dramatically increases with the number of prior cesareans, but this effect is much more evident when in the presence of placenta previa, with a prevalence ranging from 3% after one cesarean to **67% after five or more CDs in women with placenta previa** (Figure 29.2) [7, 38]. The detrimental effect of CDs on the risk of abnormal placentation can be further differentiated according to the characteristics of the surgical procedure, i.e. by distinguishing whether it was a prelabor or intrapartum CD, with the latter conferring a significantly reduced risk for PAS in later pregnancies [8]. In addition to placenta previa and CD, several other risk factors have been described to be associated with myomectomy, uterine curettage, hysteroscopy, multiparity, advanced maternal age, obesity, and assisted reproductive techniques, where altered endometrial status and receptivity possibly hamper the mechanisms of placental implantation [39–44]. However, epidemiology cannot conclusively help in identifying patients at high risk of PAS, as this condition can occur even in the absence of any classical risk factor. Therefore, despite the importance of the patient clinical profile, diagnostic imaging maintains a pivotal role in PAS assessment and prediction.

Diagnosis

The importance of an appropriate screening in the management of PAS is clearly outlined by the evidence of a recent meta-analysis aimed at evaluating the influence of prenatal diagnosis of PAS on maternal outcome that indicate how antepartum diagnosis significantly reduces intrapartum blood loss and units of red blood cells and fresh frozen transfused [45], but most of all, it might allow health care providers to organize delivery with a multidisciplinary team in a tertiary center with the proper expertise. **Ultrasound is the gold standard imaging approach to diagnose PAS** (Figure 29.5). A recent meta-analysis of 20 studies including more than 3000 patients showed that the sensitivity for depth of placental invasion was 90.6%, 93%, and 81.2%, respectively, and the specificity was 97.1%, 98.4%, and 98.9%, respectively (accrete, increta, percreta). Due to the high specificity, a negative ultrasound almost excludes PAS; moreover, diagnosis and staging of myometrial invasion are accomplished effectively. However, about 20% of women with placenta percreta remain undiagnosed, underscoring the need for developing more accurate prediction models to detect abnormal invasive placenta [46]. In order to improve diagnostic accuracy, the European Working Group on Abnormally Invasive Placenta proposed a standardization of the PAS imaging descriptors (Table 29.3) that were unified under a common heading, ultimately providing unambiguous definitions and with specific reference to the ultrasound modality (grayscale or color Doppler ultrasound) [47]. Prenatal diagnosis

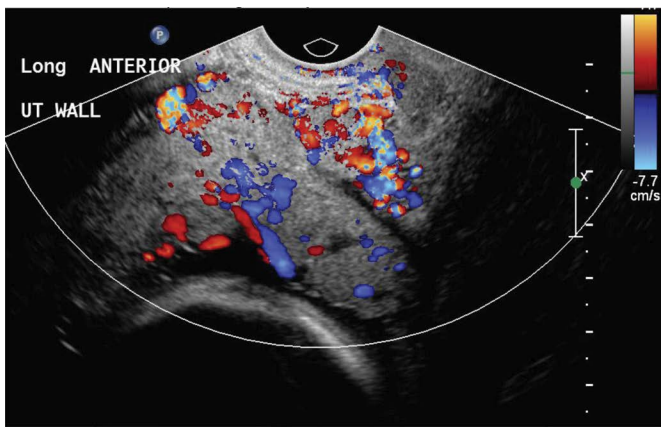


FIGURE 29.5 Transvaginal ultrasound showing loss of normal hypoechoic retroplacental zone and multiple vascular lacunae with turbulent blood flow within anterior placenta concerning for placenta accreta. (Courtesy of the Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, Northwestern University Feinberg School of Medicine.)

TABLE 29.3: Ultrasonographic Signs for Placenta Accreta Spectrum Disorders

Grayscale ultrasound signs are:

- *Loss of clear zone*, defined as a loss or irregularity of hypoechoic plane in myometrium underneath placental bed ("clear zone").
- *Placental lacunae*, defined as the presence of numerous lacunae, often containing turbulent flow visible on grayscale imaging.
- *Bladder wall interruption*, defined as loss or interruption of bright bladder wall (hyperechoic band or "line" between uterine serosa and bladder lumen)
- *Myometrial thinning*, defined as thinning of myometrium overlying placenta to <1 mm or undetectable.
- *Placental bulge*, defined as the deviation of uterine serosa away from expected plane, caused by abnormal bulge of placental tissue into neighboring organ, typically bladder; uterine serosa appears intact but outline shape is distorted.
- *Focal exophytic mass*, defined as placental tissue seen breaking through uterine serosa and extending beyond it; most often seen inside filled urinary bladder.

Two-dimensional color Doppler signs are:

- *Uterovesical hypervascularity*, defined as the striking amount of color Doppler signal seen between myometrium and posterior wall of bladder.
- *Subplacental hypervascularity*, defined as the striking amount of color Doppler signal seen in placental bed.
- *Bridging vessels*, defined as vessels appearing to extend from placenta, across myometrium and beyond serosa into bladder or other organs; often running perpendicular to myometrium.
- *Placental lacunae feeder vessels*, defined as vessels with high-velocity blood flow leading from myometrium into placental lacunae, causing turbulence upon entry.

Three-dimensional ultrasound plus power Doppler signs are:

- *Uterovesical hypervascularity*, defined as intraplacental hypervascularity in a complex, irregular arrangement of numerous placental vessels, exhibiting tortuous courses and varying calibers
- *Placental bulge* (as in 2D)
- *Focal exophytic mass* (as in 2D)
- *Uterovesical hypervascularity* (as in 2D)
- *Bridging vessels* (as in 2D)

Source: From Collins SL, Ashcroft A, Braun T, et al. European Working Group on Abnormally Invasive Placenta (EW-AIP). Proposal for standardized ultrasound descriptors of abnormally invasive placenta (AIP). Ultrasound Obstet Gynecol. 2016;47:271–275. Ref. [47], with permission.

of PAS is commonly performed during the second and third trimester of pregnancy, while there are limited data on the possibility of a first-trimester diagnosis. In a retrospective analysis of 105 women with PAS confirmed at delivery, a low implantation of the gestational sac was already detectable at 6–9 weeks and was present in almost 80% of cases at 11–14 weeks; also, most of the previously mentioned ultrasonography signs were already present at the time of the nuchal scan, but their prevalence did increase with advancing pregnancy [48]. Overall, in high-risk patients, abnormally invasive placenta can be searched at the time of the nuchal scan, while a longitudinal assessment during the third trimester accurately identifies the severity of the disorder.

Ultrasound remains the primary imaging modality for detecting and evaluating PAS, while **magnetic resonance imaging (MRI)** might be a **complementary diagnostic tool** to perform in women suspected to be affected by severe types of PAS in order to delineate the topography of placental invasion. In a recent meta-analysis of 20 studies involving 1080 pregnancies undergoing MRI mainly for the ultrasound suspicion of PAS, **the sensitivity of MRI for detecting placenta accreta, increta, and percreta was, respectively, 94.4%, 100%, and 86.5%, while the sensitivity was, respectively, 98.8%, 97.3%, and 96.8%, with the accuracy of MRI being significantly affected by the operators' expertise and experience** [49]. Thus, these findings showed that **the diagnostic accuracy of MRI in detecting the depth of placental invasion is similar to ultrasound, which might be partially explained by the fact that studies on ultrasound diagnosis of PAS include longitudinal assessment of women that could improve the diagnostic accuracy of ultrasound in detecting PAS**. An additional role for MRI can be inferred by considering that ultrasound rendered 27% of false-positive diagnoses of implantation disorder when in the presence of **posterior placenta previa**, while MRI rendered no false-positive diagnoses. This result was validated by other reports, leading to the current statement that posterior placentas are **better evaluated by MRI when in the presence of a suspected invasion** [50, 51]. **The most common MRI signs associated with PAS are intraplacental T2 dark bands, uterine bulging, heterogeneous placental signal intensity, focal interruption of the myometrium, tenting of the bladder, abnormal intraplacental vascularity, and focal exophytic mass** [52, 53].

Symptoms and complications

The first clinical manifestation of PAS generally occurs at delivery, with a massive, life-threatening hemorrhage usually associated with repeated attempts at manual placental separation.

PAS is associated with a high burden of adverse maternal outcomes and particularly severe life-threatening hemorrhage, need for blood transfusion, damage to adjacent organs, and death [35].

Composite maternal morbidity (including hysterectomy during CD, delayed hysterectomy, transfusion of ≥10 units of packed red blood cells, septic shock, acute kidney injury, cardiovascular failure, maternal transfer to intensive care, or death) is particularly higher in the case of placenta percreta compared with placenta accreta (86% versus 27%) [54].

Finally, pregnancies complicated by PAS are at increased risk for perinatal adverse outcomes—mostly preterm birth and SGA—but it seems that the occurrence of adverse outcomes is

not significantly associated with the severity of placental invasion (placenta accreta versus increta or percreta) [55, 56].

Management

Time of delivery

A general consensus about the optimal time of delivery in women with PAS is still lacking, as no randomized controlled trial has been specifically designed with this aim. The indications from different international societies range between 34 and 37 weeks of GA, mainly as a result of differences in balancing maternal risks versus the problems connected to fetal immaturity. The American College of Obstetricians and Gynecologists recommends planned delivery between **34+0 and 35+6 weeks** of gestation for stable (no bleeding or preterm labor) patients, while the SMFM suggests delivery between 34 and 37 weeks of gestation for stable women with placenta accreta.

The International Society for Abnormally Invasive Placenta recommends delivery at ≥36+0 weeks in asymptomatic women and no history of preterm birth or at about 34+0 weeks in women with a previous preterm birth, multiple episodes of minor bleeding, or a single episode of substantial bleeding [34, 57].

Preparation and place of delivery

If placenta accreta is suspected, appropriate counseling and preparations should be made (Table 29.4). The patient (and family members if available) should be counseled regarding risks, complications, and management. The possible need for hysterectomy as a lifesaving procedure should be discussed with the patient. Plans for future reproduction should be discussed and weighed against the risk of retaining the uterus.

Labor and delivery staff (nursing and anesthesia), as well as the blood bank, should be notified regarding delivery plans. As suggested by the International Society for Abnormally Invasive Placenta, women with PAS should **deliver in tertiary centers** that could provide a multidisciplinary team with significant experience in managing PAS and that can provide antenatal diagnosis and preoperative planning; this **team should be available 24 hours a day, 7 days a week**, to ensure that expertise is available for emergency situations; the multidisciplinary team should, at a minimum, include an **experienced obstetrician (often maternal-fetal medicine specialist), anesthesiologist with expertise in complex obstetric cases, surgeon experienced with complex pelvic surgery (often a gynecologic oncologist), urologist (with experience of open urologic surgery especially ureteric reimplantation), neonatologist, and interventional radiologist**. There should be on-site, rapid access to the following in case of emergency: **Colorectal surgeon, vascular surgeon, hematologist, adult intensive care facilities, NICU facilities, massive transfusion facilities, and intraoperative blood salvage (cell salvage) services** [57].

Maternal morbidity is greatly decreased when women with placenta accreta deliver in tertiary care hospitals with multidisciplinary teams, as shown by the reduced evidence of massive transfusions and early reoperation [58].

Mode of delivery

Cesarean hysterectomy with the placenta left in situ is currently the gold standard surgical management of PAS disorders. General intraoperative considerations include the **possibility of a planned vertical skin incision**. The **uterine incision should be made, if possible, away from the placenta**, the position of which can be determined by **ultrasound beforehand**. Intraoperative ultrasound with a sterile cover over the probe placed on the exposed uterus may be helpful if preoperative ultrasound is not informative. While there are different potential approaches for managing placenta accreta after delivery of the baby by cesarean, many experts would recommend that if there is proven placenta accreta (e.g. placenta directly visualized in the serosa), highly suspected accreta by history and radiologic studies (e.g. multiple prior CDs, placenta previa, and several ultrasonographic findings of placenta accreta), or if the mother plans no more childbearing (e.g. has requested tubal ligation), a reasonable course of action is to avoid disturbing the implantation of the placenta and proceed with a hysterectomy while the placenta remains attached. The long-standing main point in the technique of cesarean hysterectomy is the avoidance of any form of placenta manipulation, as avoiding attempted placental removal is associated with reduced maternal morbidity in women with suspected placenta accreta [59].

During hysterectomy, the **uterine serosa overlying the placenta should not be dissected, including trying to avoid bladder dissection**. The blood supply to the placenta is not just from the uterine arteries but also from many collateral vessels. Care should be given to dissection of this extensive blood supply by attempting uterine artery dissection laterally and then continuing down without incising the placenta. **Total hysterectomy is generally necessary**, as subtotal hysterectomy may leave in part of the lower segment, where the placenta is abnormally attached and causing bleeding if a previa is present.

If the diagnosis is possible but not certain and the patient desires to make attempts at avoiding hysterectomy despite having been counseled regarding the risks, it is not unreasonable to wait for signs of placental separation, although abnormal adherence or significant hemorrhage should be ascertained and acted upon promptly. If spontaneous placental delivery fails, the operator must decide if either manual placental removal in pieces or hysterectomy is the next intervention, based on several factors, including the degree of invasiveness and amount of bleeding.

If only a small area of the placenta is adherent and a focal area of the placental bed is bleeding, **sewing over this area with sutures can be considered**, **but usually these are in the very low uterine segment and cervix and often continue to bleed despite suturing or uterotonics**. Some have suggested **ligation** of the pelvic vessels (such as the internal iliac artery) in the setting of significant hemorrhage, although this may not be beneficial, given the many collateral vessels, and may incur risks as well. **Pelvic packing** has been used in some cases as a measure to temporarily lessen bleeding and allow attainment of hemodynamic stability. Hysterectomy may be necessary if uterine bleeding cannot be controlled, hopefully before massive blood loss and cardiovascular instability. When bleeding is from the lower part of the uterus in the setting of an accreta and placenta implanted low in the uterus (e.g. a previa), total hysterectomy is desirable, as subtotal hysterectomy may not control bleeding. Gravid hysterectomy has been associated with an incidence of maternal mortality of up to 7%, with a 90% incidence of transfusion, 28% incidence of postoperative transfusion, and a 5% incidence of ureteral injuries or fistula formation [60, 61].

In rare cases, a woman who has not completed childbearing may strongly want to avoid hysterectomy. There are several case reports of expectant (also called "conservative") or medical

TABLE 29.4: Preparations in Cases of Suspected Placenta Accreta

OUTPATIENT PROCEDURES

- Maternal-fetal medicine (MFM) and GYN oncology consultations as outpatient
- Interventional radiology (IR), urology, and anesthesia consultations as outpatient
- Prenatal care and ultrasounds with MFM. Specify:
  - Placenta location
  - Relevant ultrasound findings
  - Relevant MRI findings
  - Obstetric history
  - No. of prior cesarean deliveries
  - Other prior uterine surgery
  - Latest hemoglobin (within 4 weeks of surgery; aim for >10 mg/dL)
- Betamethasone at 33.5 weeks
- Third-trimester MRI if posterior placenta or concern for percreta
- Delivery:
  - Timing: 34–36 weeks
  - Designate and make aware primary surgical team (e.g. one MFM and one Gyn Oncology attending, at least; the presence of one urologist is useful)
  - Cesarean hysterectomy in main operating room
  - Arrange for cell saver

INPATIENT PROCEDURES

- Admit the day before
- Type and cross: 10 units packed red blood cells (pRBCs), 7 fresh frozen plasma (FFP), in room
  - Blood bank to be notified
  - Order the blood products before the case, not same day
- Clear liquid diet/consider bowel preparation if concern for bowel involvement

DAY OF SURGERY

- Labor and delivery for IV placement at 6 am
- If IR involved:
  - Fetal heart monitoring before IR
  - Preop for IR by 7 am. First case.
  - Heparin 5000 units SQ ×1: needs to be given prior to going to IR
  - Tylenol 950 mg, Lyrica 150 mg: needs to be given prior to going to IR
  - Preop balloon catheters (consider only)
  - Fetal heart monitoring after IR
  - Transfer directly from IR suite to main operating room
- Unasyn 3 g IV before ureteral stents
- Cell saver in room
- Surgical intensive care unit (SICU) bed on hold

INTRA-OP

- Regional anesthesia preferred before delivery of baby; then possibly general anesthesia as per gyn oncology and anesthesia preference
- Positioning: Lithotomy in Allen stirrups
- Sequential compression devices (SCDs) placed
- Urology: open-ended ureteral catheters
- Vertical skin incision
- C-section, evaluate need for hysterectomy
- Hysterectomy
- If hysterectomy not done, and placenta left in situ:
  - After operating room, to IR for gel foam embolization
  - After discharge will follow with MFM for weekly ultrasounds
  - High potential for infection, need for hysterectomy at a later date

POST-OP

- SICU: if necessary, decide intraoperatively which level of care is appropriate
- Possible post-op embolization with IR

Individual practices and circumstances will vary. This example does not indicate that certain evaluations or consultations are anticipated or expected in all cases.

Abbreviation: MRI, magnetic resonance imaging.

management in the setting of placenta accreta. In these circumstances, the placenta is left in situ and the cord ligated close to its origin, either with no therapy or with an adjunctive therapy such as **methotrexate and/or arterial embolization**. There is no proven efficacy for methotrexate; therefore, it is not actually recommended. Antibiotic prophylaxis has been suggested, given the risk of infection, as have short-term uterotonics for postpartum hemorrhage prevention, but there are no trials of these interventions. Follow-up is also not based on good evidence, but serial ultrasounds (to monitor involution and decrease in placental vascularity) and quantitative human chorionic gonadotrophin (HCG) levels have been proposed. If HCG levels plateau or uterine size or placental vascularity does not decrease by 72 hours, methotrexate has been given as 1 mg/kg on alternate days for a total of four to six doses, or according to HCG levels and ultrasonographic findings [62]. Women on methotrexate should be monitored with liver function tests (LFTs), platelet counts, and creatinine levels. However, **conservative management, especially for placenta percreta, has been associated with significant morbidity**, including severe vaginal bleeding in 53%, sepsis in 6%, secondary hysterectomy in 19%, and death in 0.3% of cases, although a subsequent pregnancy can be achieved in 67% of cases [63]. Thus, conservative management might be considered when PAS is discovered at surgery in a hemodynamically stable patient with no skilled team or hospital resources available or for patients who desire to preserve fertility, but only after an extensive counseling that balances the high maternal morbidity and mortality risks with the outcomes on future fertility.

Interventional radiology

Although a recent meta-analysis of 15 studies including 958 women with PAS provided low-quality evidence that interventional radiology procedures might be associated with lower estimated blood loss and need for transfusion [64], the only two **randomized controlled trials evaluating the role of precesarean prophylactic internal iliac artery balloon occlusion for suspected placenta accreta did not show any significant improvement in terms of mean number of packed red blood cell units transfused or in the calculated blood loss, as well as in the number of women with blood loss greater than 2500 mL, number of plasma products transfused, and duration of surgery** [65, 66]. Furthermore, in one of these studies, hospitalization costs and the incidence of postoperative fever were significantly higher in the balloon group [65].

Vasa previa

Key points

- Vasa previa consists of **fetal blood vessel(s)**, unprotected by the umbilical cord or placental tissue, that run through the membranes and **over the cervical internal os**.
- Risk factors for vasa previa are represented by **placenta in the lower uterine segment (e.g. low-lying, or previa earlier in pregnancy), velamentous cord insertion, succenturiate or bilobed placenta, and multiple gestations**.
- **TVU with color Doppler is standard for the diagnosis of vasa previa**.
- Vasa previa are commonly asymptomatic unless membranes rupture, at which time vaginal bleeding may be noted.
- The optimal **GA for delivery** of an asymptomatic woman (i.e. a woman without acute bleeding) with vasa previa is unknown, but many experts recommend **planned cesarean delivery** at approximately **$34^{0/7}$–$35^{6/7}$ weeks**.

Definition

Vasa previa consist of fetal blood vessels, unprotected by the umbilical cord or placental tissue, that run through the membranes and over the internal os.

Classification

Two types have been described: **Type I**, when there is a velamentous cord insertion, and **type II**, when the placenta contains a succenturiate lobe or is multilobed and fetal vessels connecting the two placental lobes course over or near the internal os [67].

Epidemiology/Incidence

The incidence of vasa previa is about 1/2500–1/5000 deliveries, but is higher in assisted reproductive technology pregnancies, in bilobate or succenturiate placenta, and in multiple gestations [1, 68].

Risk factors

As also discussed in "Epidemiology/Incidence," risk factors for vasa previa are represented by the **placenta in the lower uterine segment (e.g. low-lying, or previa earlier in pregnancy), velamentous cord insertion, succenturiate or bilobed placenta, and multiple gestations** [68].

Screening and diagnosis

TVU with color Doppler is the standard for the diagnosis of vasa previa (Figure 29.6). Women with risk factors that are judged to increase their risk of vasa previa **(low-lying placenta, or previa, velamentous cord insertion, succenturiate or bilobed placenta, and multiple gestations) should be screened with TVU for this condition, usually at the time of the 20-week anatomy ultrasound or in general when these ultrasound diagnoses are made** (Table 29.5). **Vasa previa is diagnosed if a vessel is visualized over the cervix with color Doppler demonstrating a rhythm consistent with the fetal heart rate**. The American Institute of Ultrasound in Medicine (AIUM) and ACOG recommend that the placental cord insertion site be documented whenever technically possible [69]. A recent systematic review showed a **high accuracy of TVU color Doppler (median detection rate**

TABLE 29.5: Conditions Which Warrant Transvaginal Ultrasound with Color Doppler Screening for Vasa Previa

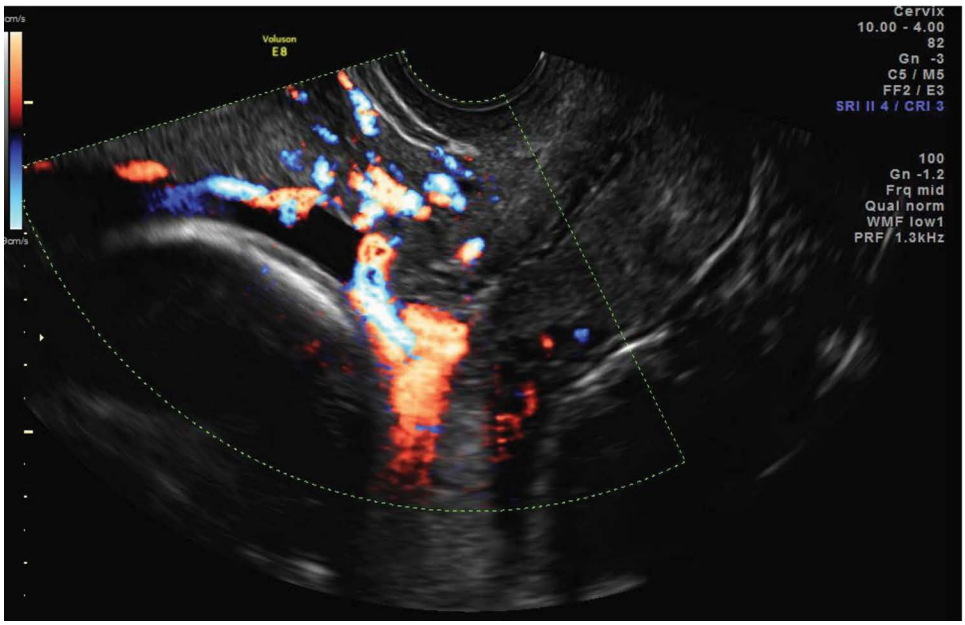
- Low-lying placenta
- Second-trimester placenta previa
- Velamentous cord insertion
- Succenturiate or bilobed placenta
- Multiple gestations
- In vitro fertilization pregnancies

Source: Adapted from Ref. [68].

of 93% and specificity of 99%), but also noted that the quality of the available studies was relatively poor [70]. Thus, not all vasa previa will be detected prenatally, even by adequate examinations and experienced operators using color Doppler. Women whose vasa previa has been diagnosed prenatally have been reported to have lower perinatal mortality than those with vasa previas that are undiagnosed (3% versus 56%) [71]. The Apt test may be used to distinguish between fetal and maternal sources of vaginal bleeding, although this test may be of little use in many clinical situations with bleeding from a vasa previa, as bleeding can lead to rapid deterioration of the fetal status and require urgent delivery before an Apt test can be completed.



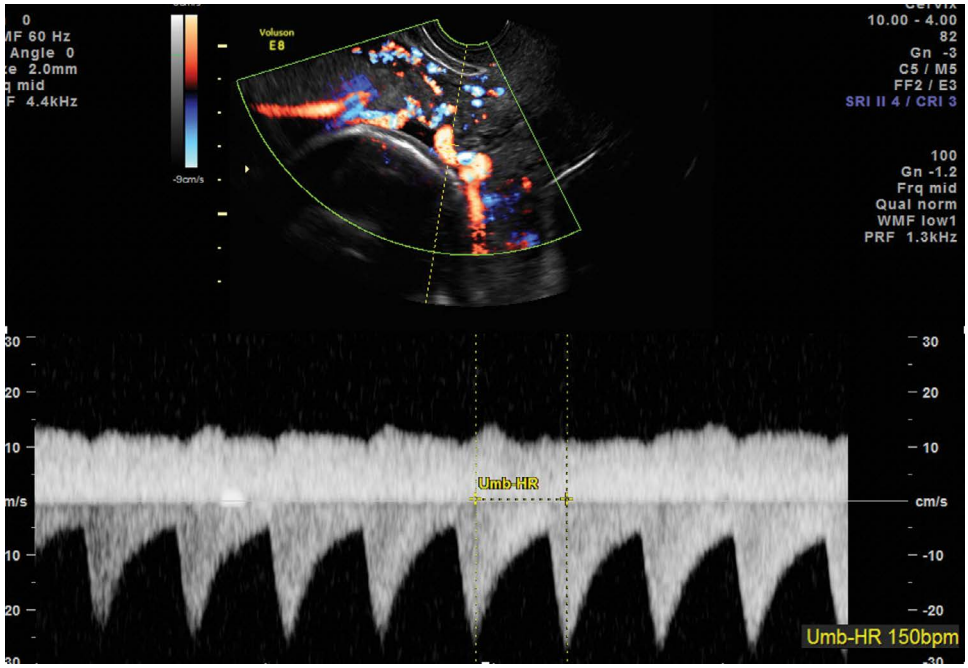
(a)



(b)

FIGURE 29.6 Ultrasound images showing vasa previa. (a) Left lateral placenta with a posterior succenturiate lobe. (b) Transvaginal ultrasound with color Doppler showing vessels visualized over the cervix. (Courtesy of the Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, Northwestern University Feinberg School of Medicine.)

(*Continued*)



(c)

FIGURE 29.6 (Continued) Ultrasound images showing vasa previa. (c) Color Doppler of vessel overlying the cervix demonstrates a rhythm consistent with the fetal heart rate.

Symptoms and complications

Vasa previa are commonly asymptomatic unless membranes rupture, at which time vaginal bleeding may be noted. Perinatal morbidity (e.g. neonatal anemia) and mortality (up to 56%) due to acute fetal hemorrhage are among the most frightening complications of this condition [71]. In a minority of cases, suspected second-trimester vasa previa resolves over time, as shown in a recent retrospective cohort study in which 14–39% of antenatally diagnosed cases of vasa previa resolved spontaneously later in gestation [72, 73].

Management

Principles

Timing of bleeding with antenatally diagnosed vasa previa is variable and impossible to predict. Since the fetal vessels are not protected by placental tissue or Wharton jelly, compression may lead to reduced fetal blood flow and bradycardia, and rupture of membranes with subsequent vessel laceration may result in rapid fetal exsanguination. It is paramount to make the diagnosis of vasa previa antepartum and not intrapartum.

Therapy

Level 1 data to guide the management of antenatally diagnosed vasa previa are currently lacking. While some experts suggest that hospitalization at some time after viability may be reasonable, this strategy is unsupported by any adequately powered trials. Many admit women with proven vasa previa around 28–32 weeks. However, a retrospective cohort study comparing women with vasa previa managed inpatient versus outpatient showed that the rate of elective cesarean section and exposure to antenatal steroids was higher in patients with vasa previa who were admitted electively at 34 weeks of gestation compared with patients who were managed as an outpatient [74]. It is reasonable to consider administration of antenatal corticosteroids at 28–33 weeks of gestation, if indications do not develop prior, to prepare for the possible need for urgent preterm delivery [75]. Women with vasa previa should be delivered by cesarean at a center capable of providing immediate neonatal blood transfusion if needed [76]. Timing of delivery is controversial, with suggestions for **CD anywhere between $34^{0/7}$ and $35^{6/7}$ weeks**, although earlier when preterm prelabor rupture of membranes (PPROM), PTL, or significant bleeding occurs [1].

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30

PLACENTAL ABRUPTION

John F. Visintine

Key points

- Approximately 0.2%–1% of all pregnancies are complicated by placental abruption.
- **Nearly 50% of women with placental abruption have no identifiable risk factors**. Risk factors include abruption in a prior pregnancy, maternal hypertensive disorders, smoking, cocaine use, polyhydramnios, multiple gestation, preterm and term premature rupture of membranes, chorioamnionitis, elevated maternal serum alpha-fetoprotein (MS-AFP), pregnancy-associated plasma protein-A (PAPP-A) ≤5th percentile, leiomyoma, subchorionic hematoma, vaginal bleeding <20 weeks, previous cesarean delivery, abdominal trauma, subclinical hypothyroidism, anti-thyroglobulin, and anti-thyroperoxidase antibodies. The association with thrombophilias has, for the most part, not been confirmed by prospective studies.
- Complications include antepartum and postpartum hemorrhage, disseminated intravascular coagulopathy (DIC), and acute renal failure, as well as growth restriction, preterm delivery, fetal hypoxia and/or exsanguination, and perinatal mortality.
- **The diagnosis of placental abruption is primarily clinical**. History, physical exam, laboratory tests, and ultrasonographic studies guide management. Ultrasound is primarily useful in ruling out other causes of third-trimester bleeding.
- The following clinical staging system can be used in the management of placental abruption:
  - **Stage 1**: No evidence of maternal or fetal compromise
  - **Stage 2**: Nonreassuring fetal status or fetal death, no evidence of maternal compromise
  - **Stage 3**: Maternal systemic involvement: Severe hemorrhage, hemodynamic shock, or DIC, with or without fetal compromise
- **Placental pathology** has been shown to confirm the presence of abruption in **25%** of those with an **acute clinical abruption** and in **60%** of those with a **chronic clinical abruption**.
- **Prompt delivery is indicated if placental abruption is diagnosed late-preterm or term**. However, if less than 34 weeks, expectant management for stage 1 abruptions may allow time for glucocorticoid administration. Maternal or fetal compromise may necessitate delivery. A decision-to-delivery interval of 20 minutes or less is associated with a substantial reduction of neonatal morbidity and mortality in placental abruption with nonreassuring fetal heart testing.
- Mode of delivery is dependent primarily on the condition of the mother and fetus.
  - Stage 1 abruption (no evidence of maternal or fetal compromise): In most cases, **vaginal delivery** is indicated.
  - Stage 2 abruption (nonreassuring fetal status): Rapid delivery is indicated typically by **cesarean**. With fetal demise, **vaginal delivery** is also indicated (unless otherwise contraindicated).
  - Stage 3 abruption (maternal compromise, often with DIC): Vaginal delivery or cesarean, highly dependent on maternal condition.

Definition/Diagnosis

Placental abruption (also called abruptio placentae) is defined as a premature separation of a normally implanted placenta. The diagnosis is a clinical diagnosis of exclusion, based usually on vaginal bleeding and abdominal pain in the second or third trimester unexplained by other etiologies (see also "Etiology/Basic Pathophysiology").

Signs and symptoms

Signs and symptoms are shown in Table 30.1 [1, 2]. About 10%–31% of abruptions present with only concealed (occult) bleeding. Occasionally, the presenting sign is fetal death.

Epidemiology/Incidence

- Approximately **0.2%–1%** of all pregnancies are complicated by placental abruption [3–5]. The incidence in the United States has increased, especially in the African American population, the ethnic group at highest risk in particular for severe abruption [3].
- About 60% of abruptions occur preterm, and 50% occur prior to labor.
- The incidence of abruption is possibly highest at 24–26 weeks (up to 9 per 100 births) [6].
- There is over a 5% recurrence risk in a subsequent pregnancy for women with a history of an abruption [4].

Genetics

A genome-wide association study identified several candidate genes associated with placental abruption. The strongest association was with the FLI-1 gene (a megakaryocyte-specific transcription factor). Genes involved in lipid metabolism, cell signaling, mitochondrial biosynthesis, and oxidative phosphorylation are also associated with the risk of placental abruption [7]. The association with thrombophilias has not been confirmed in prospective studies. See "Risk Factors/Associations" and Chap. 29 in *Maternal-Fetal Evidence Based Guidelines.* A recent study evaluating ischemic placental disease (preeclampsia, placental abruption, and small for gestational age [SGA]) found a correlation with a family history of preeclampsia, suggesting a familial inheritance [8].

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TABLE 30.1: Clinical Findings in Women with Placental Abruption

Clinical Findings	%
Vaginal bleeding	67–78
Uterine tenderness or abdominal/back pain	52–66
Nonreassuring EFM category II/III	60–78
Uterine contractions >5 per 10 minutes	17

Source: Data from Refs. [1, 2].
Abbreviation: EFM, electronic fetal monitoring.

Etiology/Basic pathophysiology

The etiology is not completely understood, but appears to occur as the result of two mechanisms: Mechanical separation or as the end result of **defective deep placentation** [9]. Placental separation occurring in association with **mechanical trauma or rapid decompression of a distended uterus** is believed to occur due to shearing forces resulting from a change in the surface area of a relatively elastic uterine wall in relation to an inelastic placenta. Blunt trauma to the uterus resulting in abruption or rupture of membranes with rapid decompression of an overdistended uterus resulting in abruption are examples of this mechanism.

Evidence in support of a defective deep placentation mechanism comes from placental bed biopsies from cases of placental abruption, which show an **absence of physiologic trophoblastic invasion, dilated vessels, and recent thrombosis of spiral arteries** [10]. These changes are seen not only in abruption but also in preeclampsia, fetal growth restriction (FGR), and preterm prelabor rupture of membranes (PPROM), suggesting that placental abruption represents one **manifestation of a long-standing pregnancy disorder** [9]. Moreover, abnormalities in circulating angiogenic factors have been observed in women who subsequently developed placental abruption. In a nested case-control study, serum levels of the proangiogenic factor placental growth factor (PIGF) were lower, and levels of the potent inhibitor of PIGF, soluble FMS-like tyrosine kinase-1 (sFlt-1), were increased [11].

The resultant hemorrhage and initiation of the clotting cascade is believed to play a major role in increasing uterine activity, PPROM, and ultimately preterm birth (PTB). Thrombin has been found to be a potent uterotonic factor, comparable to both oxytocin and prostaglandin F2-alpha [12]. Thrombin has also been demonstrated to increase interleukin-8 expression in decidual cells. The subsequent neutrophilic infiltration of the decidua is believed to result in release of elastase and matrix metalloproteinases, and ultimately PPROM [13]. A functional progesterone withdrawal mediated by thrombin has also been demonstrated in the decidual cells from those with an abruption, which may also play a role in resultant PTB [14].

Gross pathology findings associated with placental abruption include **adherent retroplacental clot with depression or disruption of the underlying placental tissue**. Microscopic changes associated with abruption resulting in perinatal mortality include **thrombosed arteries and necrosis of the decidua basalis and large, recent infarcts and stromal fibrosis** in the terminal villi of the placental parenchyma [15]. Severe cases of abruption can result in hemorrhagic infiltration between myometrial fibers that extends to the serosal surface, giving the uterus a **dark purple discoloration, also known as Couvelaire uterus** in honor of the French obstetrician who first described this pathologic finding in the early 20th century (Figure 30.1) [16]. The **pathologic diagnosis of a placental abruption often does not correlate with the clinical diagnosis**. In a large series of placental pathologic evaluations, a placental abruption, defined as an adherent clot with disruption of the underlying tissue, was demonstrated in 3.8% of specimens, which is higher than the generally accepted incidence based on a clinical diagnosis (0.2%–1%) [17]. Most of those "abruptions" called by pathologists do not have clinical diagnosis of abruption, and many clinical abruptions have no pathologic evidence of abruption. This chapter has been structured around a clinical definition of abruption. A retrospective review of abruption cases diagnosed on clinical grounds or by pathologic criteria were analyzed based on risk factors, acute (cocaine use, trauma <12 hours from delivery) or chronic (hypertension, preeclampsia, acute chorioamnionitis, trauma occurring >12 hours prior to delivery). **Placental pathology confirmed the presence of abruption in only 25% of those with acute risk factors for abruption and 60% of those with chronic risk factors for abruption** [18].

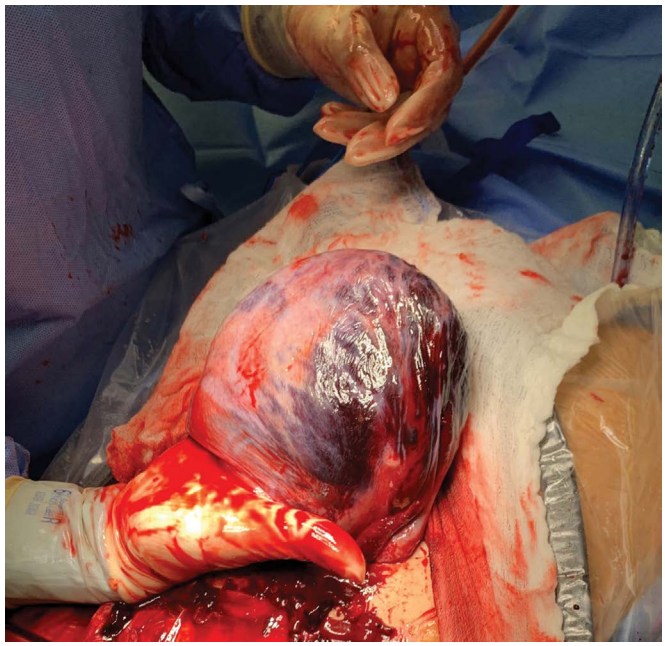


FIGURE 30.1 Couvelaire uterus noted at the time of cesarean delivery due to a placental abruption.

Classification

At least since the early 1950s, clinicians have sought to develop a useful clinical classification system to guide management decisions [19]. **Yet to date, a uniformly accepted classification system for placental abruption does not exist**. The clinical classification system originally published by Page in 1954 has been used by several authors as a means of grouping placental abruptions in those that can be potentially managed conservatively (grade 0 and 1) and those that require more aggressive management (grades 2 and 3) [20, 21]. The inclusion of clinical data obtained after delivery (gross or pathologic placental evaluation) into these grading systems limits the usefulness for the everyday clinician faced with an urgent management decision with grave consequences.

TABLE 30.2: Clinical Staging for Placental Abruption

Stage	Disease Extent	Maternal Clinical Findings	Fetal Clinical Findings
I	• Clinically recognized abruption	• No signs of maternal systemic complications • We include concealed abruptions, diagnosed by imaging as stage I.	• No signs of NRFT
II	• Clinically recognized abruption, with placental dysfunction (local complication)	• No signs of maternal systemic complications	• NRFT or fetal death • FGR
III	• Clinically recognized abruption, with maternal systemic complications (serious nature)	• Maternal systemic complications: • DIC • Maternal hemodynamic instability • Other system involvement	• No signs of NRFT, or NRFT, or fetal death

Abbreviations: NRFT, nonreassuring fetal testing; FGR, fetal growth restriction; DIC, disseminated intravascular coagulation.

A more recent classification defines **severe abruption** as at least one maternal (disseminated intravascular coagulation [DIC], hypovolemic shock, blood transfusion, hysterectomy, renal failure, or in-hospital death), fetal (nonreassuring fetal status, intrauterine growth restriction, or fetal death), or neonatal (FGR, PTB) complication. Using these criteria, **two-thirds of placental abruptions are defined as severe** (overall abruption rate 9.6/1000, severe abruption 6.5/1000). It should be noted that the definition of placental abruption in this study does not include abruptions only identified through pathologic evaluation of the placenta. The author recognizes that this definition cannot be used prospectively due to inclusion of outcome measures, but may guide further research toward a better understanding of the disease [5].

We use a **staging** system in our clinical practice which employs many of the elements of the earlier grading systems but only allows for data clinically available prior to delivery (Table 30.2). While staging systems are necessarily arbitrary, the advantage for the clinician is that they allow for integration of the clinical findings at presentation (history, physical exam, laboratory and imaging studies) into a system that allows for tailoring of treatment and estimation of prognosis [22].

Risk factors/Associations

Nearly 50% of women with placental abruption have no identifiable risk factors [23]:

- History of an **abruption in a prior pregnancy**: The risk of recurrence is about 5%–17% [24]. After two abruptions, the risk of recurrence is about 25%.
- Maternal **hypertensive disorders**: Associated with up to almost 50% of grade 3 abruption cases. In particular, chronic hypertension (incidence 1.5%–2.5%, odds ratio [OR] 2.8), superimposed preeclampsia (about 3%), and severe preeclampsia (OR 4.1) are associated with placental abruption [25, 26].
- **Abdominal trauma** is a recognized cause of placental abruption, but is responsible for only 1% of cases [27]. See also Chap. 41 in *Maternal-Fetal Evidence Based Guidelines.*
- **Smoking:** 90% increase in abruption in women who smoke compared with controls. Smoking is responsible for 15%–25% of episodes of abruption [25].
- **Cocaine:** 1.9% rate of abruption [28].
- **Previous cesarean** delivery is associated with an increased risk of abruption in subsequent pregnancies (OR 1.3) [29].
- **Polyhydramnios** has been associated with placental abruption in patients >37 weeks' gestation [30].
- **Multiple gestation:** 1.2% risk of abruption in twins, 1.5% in triplets [31].
- **PPROM:** OR 3.5 [32]. Evidence of old decidual hemorrhage can be found in nearly 40% of placentas from patients with PPROM [33].
- **Chorioamnionitis:** OR 9 [32]. Neutrophil infiltration of the fetal membranes and cervix is seen in premature rupture of membranes (PROM), and chorioamnionitis is associated with placental abruption [13].
- **Leiomyomas** detected at second-trimester ultrasound are associated with a small increase in the risk of abruption (OR 2.1) [34].
- **Ultrasound-detected subchorionic hemorrhage** before 22 weeks of gestation results in an increased risk of placental abruption (OR 2.6) [34].
- **Vaginal bleeding <20 weeks** is associated with an increased risk of abruption (relative risk [RR] 1.6) [35].
- Unexplained **elevated maternal serum alpha-fetoprotein (MS-AFP)** in the second trimester: OR 6–10 for placental abruption [36, 37].
- **Pregnancy-associated plasma protein-A (PAPP-A)** ≤5th percentile in the first trimester is associated with placental abruption (OR, 1.9) [38].
- **Inherited thrombophilias** have been associated with abruption in case-control studies [39, 40]. However, **most prospective studies have shown no increased risk of abruption** [41–43]. A retrospective cohort study comparing thromboprophylaxis with heparin for women with an inherited thrombophilia demonstrated no difference in rates of abruption or other adverse outcomes regardless of treatment [44]. But one large prospective cohort study did demonstrate an increased risk of abruption for women with the prothrombin gene mutation 20210A (OR 12), but not for factor V Leiden mutation, MTHFR C677T or A1298C mutations, or thrombomodulin gene mutation [45].
- **Advanced maternal age**: It is unclear if there is an association with abruption, as the data are conflicting [46, 47].
- **Thyroperoxidase antibodies** have been associated with an increased risk of placental abruption in two large cohort studies (OR 1.5–3.4) [48, 49]. An association with abruption was also seen with **thyroglobulin antibodies** (OR 1.4–1.7) [49]. The association with abruption was confirmed in a cohort of low-risk women with **subclinical hypothyroidism** [50].
- Elevated uterine artery pulsatility index (PI) >90th percentile is associated with an increased risk of placental abruption RR 2.7 (2.7–12) [51].

Complications

- **Maternal**
  - **Serious maternal complications** (pulmonary edema, acute respiratory failure, acute heart failure, acute myocardial infarction, cardiomyopathy, puerperal cerebrovascular disorder, coma, and amniotic fluid embolism) occur at a higher ratio for women with **severe abruption** (141.7/10,000 births) compared to those with a **mild abruption** (33.3/10,000 births) or nonabruption (15.4/10,000 births) (Table 30.3) [5].
  - **Antepartum hemorrhage** remains a leading cause of maternal mortality. For pregnancies ending in stillbirth, hemorrhage related to placental abruption is the leading cause of maternal mortality [52].
  - **DIC** was first reported to occur in association with placental abruption by De Lee in 1901 [19]. The development of DIC is thought to be due to a release of thromboplastins, as well as consumption of coagulation factors secondary to an enlarging hematoma. Nearly 30% of patients who present with a severe abruption develop DIC.
  - **Acute renal failure** is a potential maternal complication associated with abruption. Fortunately, the incidence of acute renal failure appears to be decreasing, possibly due to improved medical management.
  - **Postpartum hemorrhage secondary to uterine atony** is associated with abruption, as is postpartum anemia and **infection**.
- **Perinatal**
  - **Perinatal mortality** (both fetal and neonatal deaths) varies from 4 to 12/1000 [53]. This high perinatal mortality with abruption is attributable, in part, to its association with **preterm delivery**.
  - Of the excess perinatal deaths, about 55% can be attributed to prematurity. The other is associated with **fetal hypoxia** and/or **exsanguination** or **growth restriction**.
  - Among abruption cases from a large multicenter case-control study, 60% were found to be small for gestational age; the authors concluded that this association was primarily due to preterm birth [54].
  - Of children with spastic quadriplegic or dyskinetic cerebral palsy, 5.7% are associated with placental abruption [55].

TABLE 30.3: Severe Abruption Is Clinically Defined as ≥1 of the Following Maternal, Fetal, or Neonatal Findings

Maternal	Fetal	Neonatal
DIC	NRFT	PTB complications
Hypovolemic shock	FGR	SGA complications
Blood transfusion	Fetal death	Neonatal death
Hysterectomy		
Renal failure		
In-hospital death		

Note: See Ref. [87] for more information.

Abbreviations: DIC, disseminated intravascular coagulation; NRFT, nonreassuring fetal testing; FGR, fetal growth restriction; PTB, premature birth; SGA, small for gestational age.

Management (Figure 30.2)

Evidence-based decisions involving the clinical management of placental abruption are limited by a paucity of level I data [56]. Only one randomized controlled trial (RCT) has been conducted to address the clinical management of abruption, specifically the use of magnesium sulfate [57]. However, most recommendations for management are based on expert opinion or, at best, retrospective case-control studies. High-quality data from randomized treatment trials for hypertensive disorders in pregnancy provide some guidance regarding prevention strategies for abruption due to the close association of these disorders.

Prevention

- Women supplemented with vitamin C alone or in combination with other supplements compared with placebo or no control were at decreased risk of having a placental abruption (RR 0.64, 95% confidence interval [CI] 0.44–0.92) in a Cochrane review [58].
- Women supplemented with vitamin E in combination with other supplements compared with placebo were at decreased risk of having a placental abruption (RR 0.64, 95% CI 0.44–0.93) in a Cochrane review [59].
- A reduction in the risk of placental abruption was demonstrated with **prenatal vitamin C and E supplementation in smokers** (RR 0.09; 95% CI 0.00–0.87) but not in nonsmokers (RR 0.92; 95% CI 0.52–1.62). This study was not included in the Cochrane reviews cited earlier [60].
- The use of **magnesium sulfate for women with preeclampsia** was shown to reduce the risk of placental abruption (RR 0.64; 95% CI 0.5–0.83) [61].
- **Smoking cessation counseling, avoidance of cocaine**, and, if possible, **avoidance of other risk factors** may prevent placental abruption.
- **Routine delivery at 39 weeks** may reduce the risk of placental abruption in a low-risk population [62]. This secondary analysis of data from a multicenter RCT of aminosalicylic acid (ASA) for reduction of preeclampsia risk found that over 30% of placental abruptions occurred at 39 weeks and beyond.
- Systematic reviews of early intervention (delivery) trials for preeclampsia provide secondary analysis data regarding the relative risk of abruption, with mixed results.
  - **No difference in risk of placental abruption** (RR 0.64, 95% CI 0.17–2.34) with planned early delivery versus expectant management from 34 weeks to term [63].
  - Of note, a large nationwide cohort study demonstrated a **reduction in placental abruptions RR 0.35 (0.25–0.49)** in the 6 years after adoption of HYPIAT-1–driven guidelines for delivery of preeclampsia at term [64].
  - **A reduction in the risk of placental abruption** (RR 0.42, 95% CI 0.18–0.96) with planned early delivery versus expectant care for severe preeclampsia between 24 and 34 weeks' gestation [65].
- A large meta-analysis **for treatment of CHTN** in pregnancy (including 5 RCT's with over 1000 women reporting abruption data) demonstrated a **lower risk of placental abruption when treated with antihypertensives**. The use of nifedipine and methyldopa were associated with significantly **lower placental abruption rates** (odds ratio, 0.29 [95% confidence interval, 0.15–0.58] and 0.23 [95% confidence interval, 0.11–0.46], respectively) [66].

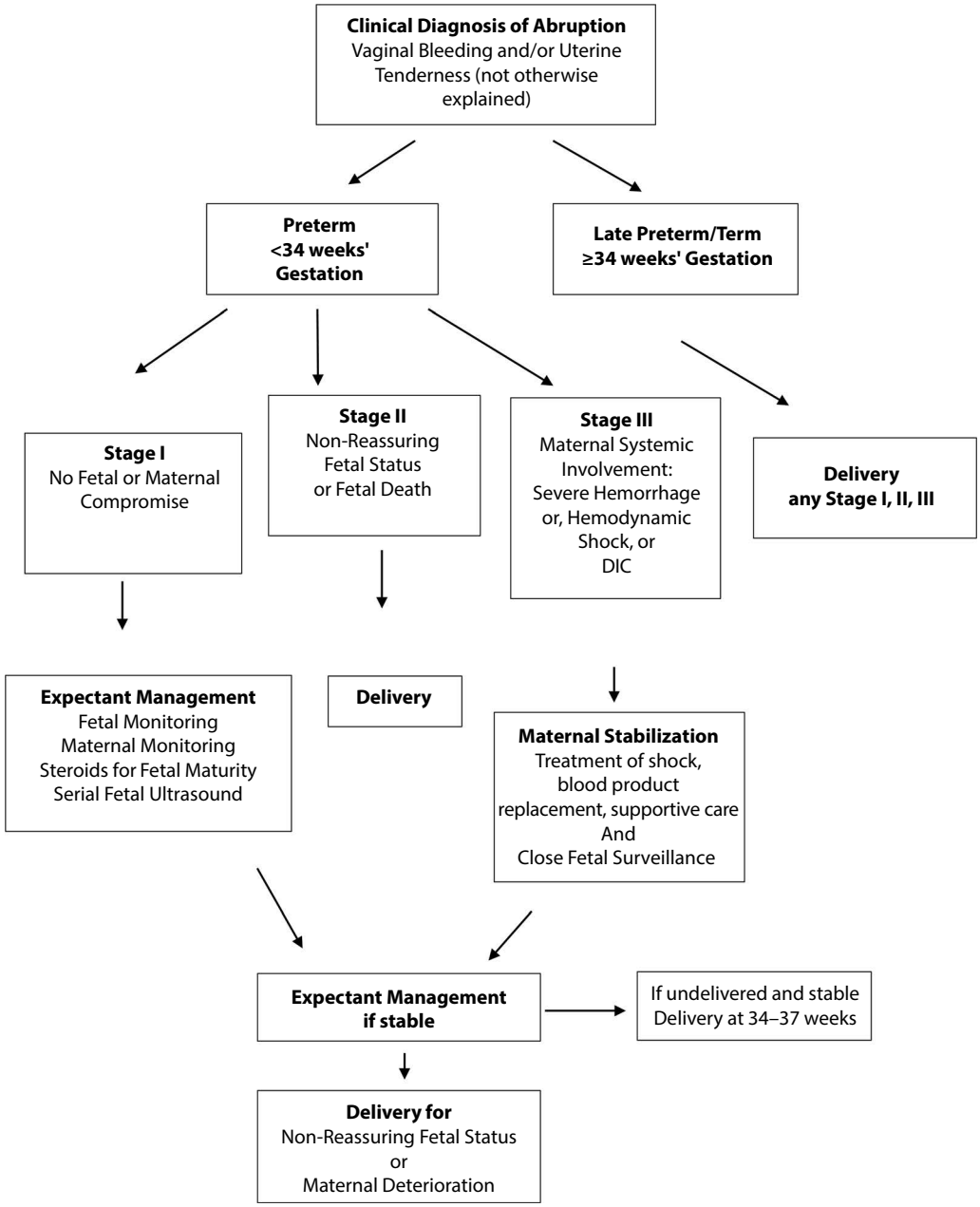


FIGURE 30.2 Management of placental abruption.

- A recent multicenter RCT evaluating treatment of chronic hypertension (CHTN) in pregnancy with labetalol or methyldopa or no medication demonstrated a reduced risk of abruption for those who were treated [67].
- Intensive fetal surveillance for women with an elevated uterine artery PI >90th percentile **was not** associated with an increased risk of placental abruption [51].

Preconception counseling

Women with risk factors should be counseled regarding the risk factors (Table 30.3) and complications of placental abruption, as well as interventions for its prevention. In addition, counseling should be provided for women with a history of a placental abruption, as they are at significant increased risk of recurrence (5%–17%) [24]. For those with a history of two or more placental abruptions, delivery at 37 weeks has been recommended [6].

Workup

- **The diagnosis of an abruption is made clinically (vaginal bleeding with abdominal pain and/or uterine tenderness). Nonreassuring fetal testing, uterine tachysystole, and coagulopathy are often present as well**. Pathologic evaluation of the placenta may confirm the diagnosis in some cases (25% of acute and 60% of chronic abruptions), but the absence of pathologic findings does not exclude an abruption [18]. Placental abruptions may be occult. At times presenting as preterm labor, they may go undiagnosed until after delivery with examination of the placenta. If a **pathologic** diagnosis (rather than clinical diagnosis) of placental abruption is used, the incidence of placental abruption is 3.8% [17] compared to around 1% in epidemiologic studies that employ a clinical diagnosis.

- **History and physical exam**, as well as appropriate **laboratory and ultrasonographic studies**, guide management. Routine assessment should be conducted, including **vital signs, oxygenation status, and urine output**. **Laboratory** assessment may include a **hematocrit, platelet count, coagulation studies** (prothrombin time **[PT]**, **partial** thromboplastin time **[PTT], and fibrinogen**), **blood type and screen, or crossmatch, serum creatinine, and a drug screen**. Other causes of third-trimester bleeding must be excluded. The **differential diagnosis** includes placenta previa, vasa previa, cervical lesions (for example, malignancy), and vaginal lesions.
- An **ultrasound examination** is useful primarily in excluding placenta previa or vasa previa. The sensitivity and specificity of ultrasound in the diagnosis of placental abruption were 24% and 96%, respectively [68]. Of note, a placental abruption was defined in this study by clinical signs or symptoms or by placental examination. So **while ultrasound is very helpful in ruling out other causes of third-trimester bleeding, it lacks the sensitivity needed to reliably detect placental abruption** [68]. The echogenicity of the collection of blood of an abruption depends on the time the ultrasound was performed relative to the onset of symptoms [69]. Acute hemorrhage is hyperechoic to isoechoic compared with the placenta. Resolving hematomas become hypoechoic within 1 week and sonolucent within 2 weeks.
- **Computed tomography (CT)** has been used to identify abruptions in trauma patients. A retrospective study of pregnant trauma patients who were evaluated with CT found a high sensitivity (86%) and specificity (98%) in the detection of placental abruption [70]. In a retrospective review of pregnant trauma patients, **as placental enhancement on CT imaging decreased, the presence of clinical findings of placental abruption were found to increase**. The authors found that clinical signs and/or symptoms of abruption were significantly more likely with placental enhancement on CT imaging <50% and that the likelihood of delivery for abruption increased as the placental enhancement decreased to less than 25% [71].
- **Magnetic resonance (MR)** imaging has also been used to identify placental abruption. In a prospective series of 60 consecutive patients with clinical suspicion of abruption, ultrasound imaging and MR imaging were compared. Placental abruption (defined as adherent clot or fibrin by placental examination at delivery) was found in 19 patients. Abruption was identified in 10 of the 19 patients (52%) with ultrasound and in all 19 (100%) with MR imaging ($p = 0.002$) [72]. This study underscores the relative ability of imaging modalities to identify retroplacental collections, but the presence or absence of adherent placental clot does not always correlate with a clinical abruption.
- A **vaginal speculum examination** should be performed to rule out cervical or vaginal sources of bleeding.
- **Laboratory findings**: A **prolonged PT, prolonged PTT, hypofibrinogenemia, and thrombocytopenia can occur in women with abruption for whom DIC develops**. D-dimer, a fibrin degradation product, has been evaluated as a diagnostic tool for abruption in two small studies with conflicting results [73, 74]; at present, the data do not support its routine use. The Kleihauer-Betke (KB) test has been used for over 50 years to detect fetal hemoglobin containing red cells in the maternal circulation and to attempt to quantitate the extent of fetal-maternal hemorrhage (FMH) [75]. More recently, **flow cytometry** has been found to be a **sensitive test for the detection of fetal red cells in the maternal circulation** [76]. Both of these tests use normal maternal and fetal blood volume estimates to quantify the amount of FMH; in the presence of significant maternal hemorrhage, quantitative results may not be as reliable. While the KB test has often been included in the laboratory workup of abruption, it appears to be a low-yield test. In a recent retrospective study of women with a clinical abruption who were screened with KB, only 3 of 65 were positive (sensitivity 4.4%) [77]. An earlier retrospective study reported **no positive** KB tests out of 27 cases of abruption confirmed by pathology [78]. While FMH as a result of or related to placental abruption has been well described, the clinically utility of these tests for the diagnosis or management of an abruption is an open question.

General principles

Once the diagnosis of placental abruption has been made, attention should be focused on ensuring maternal and fetal well-being. **Maternal status** should be addressed, with attention paid to signs or symptoms of hemorrhage, hypovolemic shock, and DIC. The frequency of repeated evaluations is dependent primarily on the acuity and severity of the abruption. Preparations should be made in anticipation of potential maternal complications. This should include **intravenous access**; **two large-bore peripheral lines** will allow for rapid fluid or blood component replacement. The **availability of blood** or blood components may be lifesaving; therefore, close cooperation with blood banking services is essential.

Fetal status is typically assessed with **continuous electronic fetal monitoring**, at least in the acute setting. For women with a chronic abruption, once clinically stable, intermittent monitoring may be a consideration.

Tocolytic use is generally discouraged due to maternal safety concerns. Multiple retrospective studies have evaluated tocolytic use (mostly magnesium sulfate) in the setting of placental abruption, without suggestion of increased maternal risk and possible pregnancy prolongation [79–82].

Magnesium sulfate as a tocolytic for women with a mild (stage I) abruption prior to 34 weeks was **not found to be effective**, as reported in a well-designed but underpowered **RCT**. Thirty women were enrolled, short of the 48 planned. While there was no significant prolongation in pregnancy with the use of magnesium sulfate, we cannot conclude with certainty that this treatment is ineffective due to the small study size. The authors recognize that significant power was not achieved and that with the relatively high rate of pregnancy prolongation in the placebo group, it was recognized that a much larger study population would in actuality be need. Further enrollment was not attempted due to changes in clinical practice as a result of the BEAM trial. Of note, while adverse outcomes due to tocolysis in the face of abruption were not primary outcome measures, safety concerns were not raised in the trial [57].

Timing of delivery (Figure 30.2)

Level I evidence is not available on delivery decisions [56, 83].

Term placental abruption: ≥37 weeks

- Delivery is recommended by most authors [6]. Rapid labor often ensues as a result of an abruption.

Late preterm placental abruption: 34–36 weeks

- Delivery is recommended by most authors [82, 84, 85]. Delivery timing should be individualized and based on the clinical situation [83].
- For women with a stage I abruption and managed expectantly, if undelivered after 34 weeks and stable, they are given the option to continue expectant management until 37 weeks. These pregnancies are followed with close surveillance, with serial growth scans and fetal monitoring. Data are not available to allow for evidence-based delivery decisions [83].

Preterm abruption: <34 weeks

- Delivery is most often indicated with maternal and/or fetal compromise (stage II and III).
- Expectant management: For patients with stage I abruption, with no evidence of maternal or fetal compromise, expectant management may allow time for glucocorticoid administration and appears to be a safe option [1, 20, 82].
  - Tocolytic use, in particular magnesium sulfate, is discouraged, as it did not improve outcomes [57].
  - Antepartum testing should be frequent, and at least initially, continuous fetal monitoring and ultrasound should be employed.
  - Ultrasound surveillance of fetal growth, as FGR has been associated with chronic abruption, presumably due to placental dysfunction [86, 87].
  - Magnesium for neuroprotection may be considered if delivery prior to 32 weeks expected.

Mode of delivery

Deciding on the method of delivery is dependent primarily on the condition of the mother and fetus. Level I evidence is not available [88].

Stage I abruption: No evidence of maternal or fetal compromise. With close monitoring of the mother and fetus, vaginal delivery may be accomplished. In studies of women with the equivalent of stage I abruption, those who delivered vaginally had a similar perinatal mortality rate compared with those with a cesarean delivery [84].

Stage II abruption: Evidence of fetal compromise.

Nonreassuring fetal testing: Rapid delivery, typically cesarean delivery, is indicated. In a study of placental abruption complicated by fetal bradycardia, a decision-to-delivery interval of ≤20 minutes was associated with substantially reduced neonatal morbidity and mortality [89].

Fetal death: Vaginal delivery is preferred in this group, as a cesarean delivery may exacerbate maternal hemorrhage [90].

Stage III abruption: Maternal stabilization is paramount (treatment of shock and correction of coagulopathy, etc.). Mode of delivery is dependent on maternal status. If present, DIC will typically improve with evacuation of the uterus, with possible improvement in clotting parameters even prior to delivery [21, 90].

Anesthesia

No specific suggestions. Anesthesia support is particularly important with DIC, hemorrhagic shock, and massive transfusion cases.

Postpartum

Attention should be paid to hemodynamic state and possible late hemorrhage from uterine atony after abruption.

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31

POSTPARTUM CARE

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Early postpartum care after vaginal delivery

Repair of obstetric lacerations

Key points

- Obstetric lacerations are very frequent, affecting **53%–79%** of all vaginal deliveries.
- **Forceps** delivery followed by vacuum delivery, regardless of the use of episiotomy, is the **strongest risk factor** for obstetric anal sphincter injuries (OASIS) and repeated OASIS, with subsequent anal and fecal incontinence.
- A first-degree laceration may heal by secondary intention if it is not bleeding or if it does not distort the anatomy. When the first-degree laceration is repaired, the use of adhesive glue achieves cosmetic and functional results equal to traditional suturing.
- Second-degree lacerations (as well as higher order) involving the perineal muscles need to be repaired. The **continuous suturing techniques and rapidly absorbing synthetic materials** are recommended.
- The two methods for repairing the external anal sphincter (EAS) are the end-to-end method and the overlap.
- **Prophylactic antibiotic therapy** prevents perineal wound infections **in third- and fourth-degree lacerations** (single-dose, second-generation cephalosporin—cefotetan or cefoxitin, 1 g intravenously).
- **Postoperative laxative regimens** (e.g. oral lactulose) following the primary repair OASIS are suggested to avoid constipation.
- Limited data support the effectiveness of local cooling treatments for treating perineal pain.

Epidemiology/Incidence

Obstetric lacerations are very frequent, affecting **53%–79% of all vaginal deliveries**. They usually involve the perineum and, less commonly, the labia, clitoral area, and vaginal walls.

Classification

Perineal lacerations are generally classified into four grades according to the severity of the lesion: First-degree lacerations involve the perineal skin only, second-degree lacerations involve the perineal muscle as well, while third- and fourth-degree lacerations involve the anal sphincter complex and are referred to as obstetric anal sphincter injuries (OASIS) (Table 31.1).

Risk factors

Forceps delivery followed by vacuum delivery, regardless of the use of episiotomy, is the **strongest risk factor** for OASIS and repeated OASIS, with subsequent anal and fecal incontinence (AI and FI) [1–3]. Other risk factors for severe perineal lacerations during childbirth include high birth weight, median episiotomy, primiparity, Asian ethnicity, labor induction, labor augmentation, epidural anesthesia, and persistent occiput posterior presentations [4].

Workup

Careful physical examination of the obstetric laceration is central to define the anatomic defect, its right depth, and degree. A **digital rectal examination** is also recommended if an occult anal sphincter injury is suspected [5]. There is some evidence to suggest that the **use of endoanal ultrasound (EAUS) prior to perineal repair is associated with reduced risk of severe anal incontinence** but an increase in the incidence of perineal pain at 3 months postpartum. However, more research is needed to fully evaluate the intervention before the routine use of EAUS on the labor ward could be supported [6].

A first-degree laceration may heal by secondary intention if it is not bleeding or if it does not distort the anatomy. When the first-degree laceration is repaired, the use of **adhesive glue** achieves cosmetic and functional results equal to traditional suturing [7].

Higher-order lacerations must be repaired. The repair of a second-degree laceration requires approximation of the vaginal tissue identifying the apex of the laceration, the perineal muscles (transverse perineal muscles and bulbocavernosus muscle), and the perineal skin [8]. Use of **continuous suturing techniques and rapidly absorbing synthetic materials** for repair of second-degree lacerations is recommended [9, 10].

There are currently no controlled studies that compare the various techniques or various suture materials for anal mucosa repair. Traditionally, the anal mucosa is approximated using closely spaced interrupted or running sutures with delayed absorbable materials 4/0 or 3/0 polyglactin. The indications on the injury repair technique of the internal anal sphincter (IAS) are limited. The IAS is identified as a glistening, white, fibrous structure placed between the rectal mucosa and the external anal sphincter (EAS). The IAS may be retracted laterally, and placement of Allis clamps on the muscle ends facilitates repair with continuous 2/0 polyglactin sutures [8].

Two methods for repairing the EAS are recognized. In the **end-to-end method**, the torn ends of the EAS are approximated and sutured. In the **overlap method**, the torn ends of the EAS are brought together and sutured by overlapping one end of the muscle over the other in a double-breasted fashion [11]. The **overlapping** repair results in a larger surface area of tissue contact between the two torn ends, and it is only possible when a full-length and full-thickness disruption and 1–1.5 cm of torn muscle on either end are present. Therefore, the overlap method should not be used to repair grade 3a tears and partial grade 3b tears, as these should be repaired by the end-to-end technique. There is no consensus on which technique to use to repair the EAS, and the choice is currently left to the preference of the physician [12]. Neither the repair method nor the suture material used (polyglactin 2/0 versus polydioxanone 3/0) seem to affect overall morbidity, which instead is reduced if anal sphincter repair is performed by appropriately trained staff [13].

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TABLE 31.1: Perineal Lacerations

First degree	Injury to perineal skin only
Second degree	Injury to perineum involving perineal muscles but not involving anal sphincter
Third degree	Injury to perineum involving anal sphincter complex 3a: Less than 50% of external anal sphincter thickness torn 3b: More than 50% external anal sphincter thickness torn 3c: Both external anal sphincter and internal anal sphincter torn
Fourth degree	Injury to perineum involving anal sphincter complex (external anal sphincter and internal anal sphincter) and anal epithelium

Source: Adapted from American College of Obstetricians and Gynecologists. *Obstetric Data Definitions* (version 1.0). Washington, D.C.: American College of Obstetricians and Gynecologists; 2014. http://www.acog.org/-/media/Departments/Patient-Safety-and-Quality-Improvement/2014reVITALizeObstetricDataDefinitionsV10.pdf.

Therapy

If antibiotics are unnecessary for repair of first- and second-degree lacerations, in the case of **third- or fourth-degree lacerations, prophylactic antibiotic therapy may reduce the incidence of perineal wound infections associated with them**. The only randomized controlled trial (RCT) that compared the effect of prophylactic antibiotic (single-dose, second-generation cephalosporin—cefotetan or cefoxitin, 1 g intravenously) with placebo found a rate of postpartum perineal wound complications (wound disruption and purulent discharge) in third- or fourth-degree perineal tears at 2 weeks of 8% and 24% in the treatment and the control groups, respectively [14]. Although the data derive from a small trial with high rate of loss to follow-up, they are the best available data on which to base a recommendation. The Royal College of Obstetricians and Gynaecologists (RCOG) and the American College of Obstetricians and Gynecologists (ACOG) support the use of broad-spectrum antibiotics to reduce the incidence of postoperative infection for third- and fourth-degree lacerations [15, 16].

Postoperative laxative regimens (e.g. oral lactulose) are suggested to avoid constipation and the potential risk of perineal laceration breakdown, and when compared with a constipating regimen, are associated with a significantly earlier and less painful bowel motion, as well as discharge [17]. Routine prescribing of a stool-bulking agent in addition to a laxative in the immediate postnatal period for women who have sustained anal sphincter injury at vaginal delivery is not recommended because of more frequent incontinence in the immediate postnatal period compared with laxative alone [18]. Evidence for the effectiveness of topically applied local anesthetics for treating perineal pain is not compelling, and there are limited data that support the effectiveness of local cooling treatments (ice packs, cold gel pads, cold/iced baths) [19, 20].

Episiotomy

Key points

- **Episiotomies should be avoided** if at all possible. A policy of **selective episiotomy** results in 30% fewer women experiencing severe perineal/vaginal trauma.
- Episiotomies, like obstetric lacerations, that involve the muscle layer need to be stitched by continuous suturing techniques and preferably with rapidly absorbing synthetic sutures.

An episiotomy is performed to enlarge the vaginal orifice by a controlled incision in the perineum and facilitate difficult deliveries. Since 2006 in the United States the percentage of episiotomies is declining, when the ACOG recommended a **restrictive episiotomy use**. The episiotomy rate dropped from 17.3% to 11.6% from 2006 to 2012 [21]. **The current evidence does not justify routine episiotomy**. A meta-analysis including 12 RCTs (6177 women) compared selective versus routine use of episiotomy. Women in labor, for whom a vaginal birth was intended, were evaluated in 11 RCTs (5375 women). **In this group, a policy of selective episiotomy resulted in 30% fewer women experiencing severe perineal/vaginal trauma** (relative risk [RR] 0.70, 95% confidence interval [CI] 0.52–0.94). Both selective and routine episiotomies have little or no effect on neonatal outcome (Apgar score less than 7 at 5 minutes), perineal infection, dyspareunia, and long-term urinary incontinence (UI). Subgroup analyses by parity (primiparas versus multiparas) and by surgical method (midline versus mediolateral episiotomy) did not identify any modifying effects. One trial examined selective episiotomy compared with routine episiotomy in women where an operative vaginal delivery was intended in 175 women and did not show a clear difference in severe perineal trauma between the restrictive and routine use of episiotomy, but the analysis was underpowered. This review thus demonstrates that in women where no instrumental delivery is intended, selective episiotomy policies result in fewer women with severe perineal/vaginal trauma [22]. Episiotomies, like obstetric lacerations, that involve the muscle layer need to be stitched by continuous suturing techniques and preferably with rapidly absorbing synthetic sutures [9, 10]. There are no clear indications that prophylactic antibiotics reduce the incidence of episiotomy wound dehiscence with infection or without infection, and therefore no recommendation can be made [23].

Pelvic floor disorders

Key points

- Pelvic floor disorders (PFDs) define a variety of interrelated clinical entities that include pelvic organ prolapse (POP), UI, and FI.
- Increasing parity is strongly associated with UI.
- There is no evidence that labor alone, in the absence of vaginal delivery, represents a risk factor for UI, FI, or POP.
- Vaginal delivery is associated with an increased risk of PFDs, particularly with UI.
- There is no evidence to recommend episiotomy for the prevention of PFDs.
- Operative vaginal delivery with forceps, but not vacuum delivery, is associated with POP and UI, while both forceps and vacuum are risk factors for AI.
- There is no evidence to recommend planned cesarean delivery for the prevention of PFDs.
- **Antenatal pelvic floor muscle training (PFMT) prevents UI in late pregnancy and in the mid-postnatal period**, while its role to reduce UI in incontinent women (treatment) appeared uncertain.

Definition

Pelvic floor disorders (PFDs) define a variety of interrelated clinical entities that include pelvic organ prolapse (POP), UI, and FI. They are more common in adult women and strongly associated with pregnancy and childbirth [24].

Epidemiology/Incidence

The mean prevalence of **UI during pregnancy is approximately 41%**, whereas this disorder affects **one-third of women during the first 3 months of postpartum** [25, 26].

Symptoms related to altered **anal continence after pregnancy are reported in 3%–4% of women, with FI reported in up to 25% of primiparous women at 6 weeks postpartum** [27]. Although the data about POP among pregnant women are limited, in nulliparous pregnant women, the Pelvic Organ Prolapse Quantification (POP-Q) stage appears to increase during pregnancy and does not change significantly following delivery. In the postpartum period, POP-Q stage may be higher in women delivered vaginally compared to women delivered by cesarean [28].

Risk factors/Associations

Parity

A national survey of 1261 women in the United States reported that the impact of increasing parity is strongly evident in **UI**: **Nulliparous (6.5%)**, **one birth (9.7%)**, **two births (16.3%)**, **and three or more births (23.9%)**. Regarding **POP, parity is associated with a small but significant increase**: **Nulliparous (0.6%)**, **one birth (2.5%)**, **two births (3.7%)**, **and three or more births (3.8%)**. However, **the increase of FI according to parity is not significant**: Nulliparous (6.3%), one birth (8.8%), two births (8.4%), and three or more births (11.5%) [29].

Labor

Although data on the role of labor in the development of PFDs are controversial, **there is no evidence that labor alone, in the absence of vaginal delivery, represents a risk factor for UI** [30, 31] **or FI** [32, 33]. No difference in prolapse between women who had undergone cesarean before or after labor have been reported [34].

Vaginal delivery

Vaginal delivery is associated with an increased risk of PFDs, particularly with UI. A meta-analysis investigating the long-term impact of delivery mode on **stress urinary incontinence (SUI) and urgency urinary incontinence (UUI)** showed that vaginal delivery compared with cesarean delivery is associated with an almost **twofold increase in the risk of long-term SUI, with an absolute increase of 8%, and an effect that is largest in younger women** [35]. Furthermore, a registry-based national cohort study of 5236 women who had one singleton delivery 20 years previously reported that vaginal delivery, compared with cesarean delivery, was associated with a 67% increased risk of UI and with an almost doubled risk of symptomatic POP (14.6% versus 6.3%) [36, 37]. The role of vaginal delivery in the development of AI has not yet been clarified; the current evidence is based only on conflicting observational data [38–40].

Episiotomy

There is **no evidence to recommend episiotomy for the prevention of PFDs** [41].

Operative vaginal delivery

There is some evidence that **operative vaginal delivery with forceps, but not vacuum delivery, is associated with POP and UI** [42, 43]. Forceps and other instrumented delivery represent a risk factor for AI according to the available data. A comparative systematic review of 12,237 women found that instrumental delivery compared with spontaneous vaginal delivery is significantly associated with an increase of AI symptoms [44]. The only available RCT that compares vacuum- and forceps-assisted delivery to determine the effects of either mode of delivery on anal sphincter function found that **significantly more women complained of altered continence following forceps-assisted delivery compared with vacuum-assisted delivery** [45].

Cesarean delivery

There is no evidence to recommend elective cesarean delivery for the prevention of PFDs [46].

Management

PFMT is commonly recommended during pregnancy and after the birth to prevent or treat UI. A recent Cochrane review of 38 trials involving 9892 women showed that compared with usual care, **continent pregnant women performing antenatal PFMT (for prevention) may have had a lower risk of reporting UI** in late pregnancy (62% less) and in the mid-postnatal period (more than 3–6 months postpartum) (29% less), while there was insufficient information available for the late (more than 6–12 months) postnatal period to determine effects at this point. In the same meta-analysis, compared with usual care, the role of antenatal PFMT to reduce UI in incontinent women (treatment) appeared uncertain in late pregnancy, in the mid and late postnatal periods. When a mixed population was considered (women with or without UI), antenatal PFMT appeared to decrease UI risk in late pregnancy and the mid-postnatal period but not in late postpartum. Regarding AI, the few data available showed considerable uncertainty about the efficacy of PFMT. It is possible that the effects of PFMT might be greater with targeted rather than mixed prevention and treatment approaches and in certain groups of women [47].

Pain control

Key points

- **Nonsteroidal antiinflammatory drugs (NSAIDs)**, including aspirin, are better than placebo for relief of pain due to uterine cramping after vaginal birth.
- **Aspirin and acetaminophen are both effective as perineal pain relievers, although NSAIDs are more effective compared to acetaminophen**.
- **Local cooling pain relievers, such as ice packs,** have been shown to be associated with a significant reduction of perineal pain at 24–72 hours, compared with no treatment.
- When a standard dose of an NSAID is insufficient, a multimodal approach including NSAIDs, acetaminophen, and a milder opioid (if needed) can be considered as a reasonable next step.
- Pain after vaginal delivery might be caused by contractions of the uterus or by perineal injuries.

Nonsteroidal antiinflammatory drugs (NSAIDs), including aspirin, are better than placebo and probably even better than opioids for relief of pain due to uterine cramping after vaginal birth. [48].

When considering perineal pain, **aspirin and acetaminophen are both effective as pain relievers, although NSAIDs are more effective** to achieve pain control at 4 and 6 hours when compared to acetaminophen [49–51].

Some nonpharmacologic methods have been suggested to control postpartum pain, and in particular perineal pain, after

TABLE 31.2: Recommendations for Early Post-Vaginal Delivery Care

- Continuous suturing techniques and rapidly absorbing synthetic materials for second-degree (or high-order) lacerations
- Prophylactic antibiotic therapy in third- and fourth-degree lacerations
- Avoidance of episiotomy, unless absolutely necessary
- Pelvic floor muscle training before delivery to prevent urinary incontinence
- Nonsteroidal anti-inflammatory drugs or acetaminophen to reduce postpartum pain
- Local cooling pain relievers for perineal pain

vaginal delivery. Among them, **local cooling pain relievers, such as ice packs**, have been shown to be associated with a significant reduction of perineal pain at 24–72 hours, compared with no treatment. However, this evidence to support the effectiveness of local cooling treatments (ice packs, cold gel pads, cold/iced baths) for the perineum following vaginal delivery to relieve pain is limited [20].

When a standard dose of an NSAID is insufficient, a multimodal approach including NSAIDs, acetaminophen, and a milder opioid (if needed) can be considered as a reasonable next step [52].

In summary, for early post–vaginal delivery care, we suggest the interventions in Table 31.2.

Early postpartum care after cesarean delivery

Enhanced recovery after surgery strategies

Key points

- **Early ambulation should start about 4 hours after cesarean** delivery and should last approximately 5–10 minutes several times a day to hasten intestinal recovery and prevent venous thromboembolism.
- **Early oral feeding with both fluids or food within 6–8 hours after cesarean** delivery improves the return of gastrointestinal function and does not increase the occurrence of gastrointestinal complications.
- **Chewing gum three times a day immediately after cesarean** delivery is a well-tolerated intervention that enhances early recovery of bowel function.
- If used, immediate removal of the bladder catheter after cesarean should be encouraged to reduce urinary discomfort and infections.

Enhanced recovery after surgery (ERAS) is a clinical approach towards perioperative care that has been utilized for about 30 years in many surgical fields in order to achieve at least three main objectives: Increasing patient satisfaction, improving quality, and reducing costs for the health care system [53].

ERAS strategies have also been successfully applied to obstetric care, and in particular after cesarean delivery, thus resulting in shorter length of hospital stay, reduced opioid consumption, and unchanged visual analog pain scores at the time of hospital discharge when these policies are properly accomplished [53].

ERAS procedures after cesarean delivery usually involve multimodal analgesia (see "Pain Control"), early ambulation, early oral feeding, and expeditious removal of the bladder catheter, if used.

Early ambulation—preferably after sitting up for a few minutes in bed to prevent hypotension—should start about **4 hours after cesarean** delivery and should last approximately **5–10 minutes**, according to the woman's feelings, **three times a day**. Early ambulation, particularly when involved in a broader spectrum of ERAS policies, has been associated with earlier intestinal sounds, gas passage, and bowel movements, but is also strongly recommended to prevent venous thromboembolism [54–56].

Early oral feeding with both fluids and food **within 6–8 hours after cesarean** delivery improves the return of gastrointestinal function (shorter passage of flatus, bowel movements, and sounds) and does not increase the occurrence of gastrointestinal complications (no nausea, vomiting, diarrhea, abdominal distension, mild ileus symptoms) compared with delayed oral intake [57, 58].

Likewise, **chewing gum in the immediate postoperative** period and then at least **three times per day for about 15 minutes** after cesarean delivery is a well-tolerated intervention that enhances early recovery of bowel function, as it has been associated with early recovery of bowel motility and significantly less incidence of ileus, fewer number of episodes of nausea or vomiting, lower mean time to first flatus or first bowel sounds, shorter length of stay, and therefore significantly higher maternal satisfaction [59, 60].

Lastly, a bladder catheter is usually used during cesarean deliveries, although it is a common cause of discomfort in the early postoperative period. There is **insufficient evidence to assess the routine use of indwelling bladder catheters in women undergoing cesarean delivery** so far. However, as many institutions still use a bladder catheter during cesarean delivery, **immediate removal after surgery, at least in women undergoing elective cesarean delivery, should be encouraged** to reduce postoperative bacteriuria, dysuria, urinary frequency and urgency, and to hasten postoperative ambulation time, time until the first voiding, and length of hospital stay [61, 62].

Pain control

Key points

- **NSAIDs** are associated with lower pain scores at 12 and 24 hours, lower pain with movement at 24 hours, significantly less opioid consumption, and less drowsiness/sedation. Scheduled NSAIDs should be given initially **around the clock**, starting during cesarean, and not as desired by the woman.
- Scheduled **acetaminophen** for 48 hours **around the clock** after cesarean delivery is effective in reducing opioid use compared to as-needed administration.
- **Epidural morphine—and neuraxial opioids in general**—are significantly associated with a reduction in pain scores and postoperative morphine request during the first 24 hours compared to systemic opioid analgesia.
- **A transverse abdominis plane (TAP) block** could be effective for women not receiving neuraxial morphine.
- Perioperative administration of **gabapentin** is associated with lower pain scores at 24-hour movements and with a higher pain control satisfaction at 12 and 24 hours.
- Systemic opioids should be reserved for treating breakthrough pain when pain control obtained by the combination of neuraxial opioids and nonopioid adjuncts becomes inadequate.

Pain after cesarean delivery might significantly affect the early hours of a woman's motherhood experience. In the 2018

guidelines on postpartum pain management, the ACOG recommends a stepwise, multimodal strategy to provide individualized pain control for women in the postpartum period.

In the United States, 1 in 300 opioid-naive patients exposed to opioids after cesarean delivery will become persistent users of opioids, thus highlighting the importance of a proper and timely approach to control postpartum pain [52].

NSAIDs are among the most common pain relievers, usually administered as part of multimodal pain control after cesarean delivery.

A **meta-analysis** of 22 RCTs comparing NSAIDs to control showed that women in the NSAID group had lower pain scores at 12 and 24 hours (when NSAIDs were administered via the intravenous/intramuscular route, but not via oral or rectal routes), lower pain with movement at 24 hours, significantly less opioid consumption, and less drowsiness/sedation, while no difference was reported in terms of nausea or vomiting [63]. Scheduled NSAIDs should be given initially **around the clock**, starting during cesarean (e.g. ketorolac, then ibuprofen) and not as desired by the woman.

Scheduled acetaminophen around the clock for 48 hours after cesarean delivery has been reported to be effective in reducing opioid use compared to as-needed administration in women who received spinal anesthesia containing intrathecal morphine [64], and these data were confirmed also in an RCT of 104 women that showed that compared to placebo, intravenous acetaminophen after cesarean delivery was associated with a significant decrease in oral narcotic consumption for pain control [65].

Epidural morphine—and neuraxial opioids in general—are significantly associated with a reduction in pain scores and postoperative morphine request during the first 24 hours compared to systemic opioid analgesia, but it also increased the incidence of nausea and pruritus compared with systemic opioids [66].

The **transverse abdominis plane block** (**TAP block**) involves using a blunt-tip needle to inject anesthetic in the plane between the internal oblique and transversus abdominis muscles to target the peripheral nerves innervating the lower abdomen, usually performed under ultrasound guidance. After cesarean delivery, TAP block is effective, but the evidence is currently stronger only for women not receiving neuraxial morphine [67].

Due to the lack of robust evidence of efficacy, the ACOG does not recommend **gabapentin** as a first-line treatment for pain management after cesarean delivery, although it might be reasonable in case of a history of chronic pain or uncontrolled pain [52]. Moreover, perioperative administration of 600 mg of gabapentin has been shown to be associated with a lower pain score at 24-hour movements and with a higher pain control satisfaction at 12 and 24 hours in healthy pregnant women undergoing spinal anesthesia for cesarean delivery at term [68].

When focusing on systemic opioids, the ACOG guidelines on postpartum pain management suggest reserving parenteral or oral opioids for treating breakthrough pain when pain control obtained by the combination of neuraxial opioids and nonopioid adjuncts becomes inadequate [52].

Dressing removal

Key points

- **Dressing removal at 6 hours after** a scheduled cesarean delivery is not associated with an increased risk of wound complications.
- **Women's satisfaction is higher with early dressing removal**, allowing them to care for their personal hygiene earlier.

It is **uncertain whether covering surgical wounds that are healing by primary intention with wound dressings reduces the risk of surgical site infections (SSIs)** [69]. Studies on the timing of the wound dressing removal after cesarean delivery are also limited. Epithelialization is an essential component of wound healing and typically occurs in the 48 hours after surgery. Data from three small RCTs showed no significant differences between early (up to 48 hours after surgery) and delayed dressing (beyond 48 hours) removal from non-Cesarean surgical wounds in terms of incidence of SSIs, wound dehiscence, or serious adverse events within 30 days [70]. Additionally, a recent RCT of 320 women observing postsurgery dressing removal showed no increased wound complications with removal at 6 hours instead of 24 hours after a scheduled cesarean delivery. In this same study, **women's satisfaction was significantly increased when dressings were removed at 6 hours after the cesarean** delivery, allowing them to care for their personal hygiene earlier [71].

A multicenter RCT of 869 low-risk obstetric women compared wound dressing removal at 24 hours versus 48 hours post–caesarean delivery with a modified 1-day ASEPSIS score. Higher scores were associated with more severe disruption of healing. The wound scoring was similar in the groups at discharge and first-week evaluation, while at 6 weeks postsurgery, the wound scoring was significantly less in the 48-hour (3.9%) versus the 24-hour group (9%; $p = 0.002$) [72]. Further studies targeting wound complications are necessary to define the timing of dressing removal after cesarean.

The proper technique for the removal of adhesive dressings in obstetrics and gynecology has also been studied. By **using a slow rate of removal in the direction of hair growth, the proper angle of traction (an ideal angle of 150–180 degrees to the skin), countertraction with an index finger, and adhesive solvents when necessary, patients experience much less pain with dressing removal, and skin injury can be avoided** [73].

There is currently **no evidence of harm from early (within 48 hours of surgery) postoperative bathing or showering in women with closed surgical wounds**, because clinically significant increases or decreases in SSIs cannot be ruled out [74].

Sutures

Key points

- **Absorbable subcuticular sutures**, when compared with staples, are associated with fewer wound complications and therefore **should be preferred to reapproximate the skin** at cesarean delivery.
- If staples are used nonetheless for skin closure of a transverse incision, they should be removed at least 4 or more days after the cesarean to reduce the risk of skin separation and the need for reclosure.
- In women with risk factors for wound complications, such as those with diabetes mellitus or obesity, and in vertical incisions, staple removal timing should increase up to 7–10 days.

Absorbable subcuticular sutures, when compared with staples, is associated with **fewer wound complications** and therefore should be **preferred to reapproximate the skin** at cesarean delivery [75]. A planned secondary analysis of an RCT of 746 women in which sutures and staples were compared for transverse skin closure after cesarean showed that more women appear to prefer sutures, as they are less painful, are considered

to have a better appearance, and are associated with fewer wound complications [76]. If staples are used nonetheless for skin closure of a transverse incision, **they should be removed at least 4 days after the cesarean** to reduce the risk of skin separation and the need for reclosure [77]. In **women with risk factors for wound complications**, such as those with diabetes mellitus or obesity, and in vertical incisions, **staple removal timing should increase up to 7–10 days**, as the wound is under more tension. In an RCT including 295 obese women with subcutaneous wound depth ≥2.0 cm and skin staple closure of a transverse incision, the rate of superficial wound dehiscence was 15.2% in the early skin staple removal group (after 3 postoperative days) versus 11.5% in the delayed skin staple removal group (between postoperative day 7 and postoperative day 10), although this difference was not statistically significant. Until other trials can establish the noninferiority of early staple removal, delayed removal should remain the standard in the obese patient [78].

High-risk conditions, such as women with a body mass index (BMI) of more than 35 kg/m^2, urgent cesarean delivery, preterm prelabor rupture of the membranes (PPROM), and chorioamnionitis, **are associated with wound healing complications, regardless of timing of both the dressing and staple removal** (see also Chap. 14) [79].

Postpartum thromboprophylaxis

Key points

- **Venous thromboembolism (VTE) risk in the first week postpartum is 100-fold higher than during pregnancy.**
- **Pneumatic compression devices are recommended for all postpartum women, independent of mode of delivery, until the patient is fully ambulatory.**
- **Low-molecular-weight heparin (LMWH) is recommended over heparin for postpartum pharmacologic anticoagulation.**
- **When a patient meets criteria for postpartum anticoagulation, it should in general not be started prior to 4–6 hours after vaginal delivery or 6–12 hours after cesarean delivery.**
- **Insufficient evidence exists to guide recommendations about the duration of postpartum thromboprophylaxis.**

Epidemiology/Incidence

Venous thromboembolism (VTE) occurs in 0.5–2/1000 pregnancies, with half of those occurring postpartum [80, 81]. **VTE risk in the first week postpartum is 100-fold higher than during pregnancy** [82].

A history of VTE or thrombophilia confers the biggest risk of VTE. In women without these two risk factors, most data suggest that no single risk factor increases the risk more than 1% [83]. However, when women present with multiple risk factors, the cumulative risk may suggest the need for postpartum thromboprophylaxis. All of the following other factors have been associated with an adjusted odds ratio (aOR) of >4 for VTE in the postpartum period: Immobility for >1 week in the antepartum period (aOR 40.1), postpartum infection after vaginal delivery or cesarean delivery (aOR 20.2 and 6.2, respectively), postpartum hemorrhage with or without surgery (aOR 12.0 and 4.1 respectively), pre-eclampsia with fetal growth restriction (aOR 5.8), maternal lupus (aOR 8.7), blood transfusion (aOR 7.6), maternal sickle cell disease (aOR 6.7), multiple gestation (aOR 4.2), and BMI >30kg/m^2 (aOR 5.3) [83].

Extensive discussion of indications for anticoagulation during pregnancy is beyond the scope of this section. Similarly, management of these women in the postpartum period also is beyond the scope. Finally, evaluation and management of acute VTE is covered in Chaps. 29 and 30 in *Maternal-Fetal Evidence Based Guidelines.* However, in this section we will review evidence for postpartum thromboprophylaxis among women without prior VTE history and without known thrombophilia.

Thromboprophylaxis

Pneumatic compression devices should be used for all postpartum women, independent of mode of delivery, until the patient is fully ambulatory. However, this is based on expert opinion and extrapolated from gynecology and general surgery literature [84]. Evidence is limited in pregnancy. However, the Society for Maternal-Fetal Medicine (SMFM) and ACOG do recommend their use starting at the time of cesarean delivery and until the patient is fully ambulatory [85, 86]. These can be continued to be used while the patient is in bed for the duration of the postpartum stay.

Low-molecular-weight heparin (LMWH) is recommended over heparin for postpartum pharmacologic anticoagulation by the Society of Obstetricians and Gynecologists of Canada (SOGC), RCOG, SMFM, and the American College of Chest Physicians, while ACOG notes both are safe [84–88]. While neither compound crosses the placenta, LMWH has a better safety profile, lower incidence of bleeding, and lower rates of heparin-induced thrombocytopenia, as well as having less frequent dosing requirements [89, 90]. Both are compatible with breastfeeding. In the setting of postpartum prophylactic pharmacologic anticoagulation, agents such as warfarin and other newer oral anticoagulants are generally not used, nor well studied. In general, though, warfarin is compatible with breastfeeding, while other newer oral agents such as fondaparinux are not recommended with breastfeeding.

For a patient where pharmacologic anticoagulation is indicated, the optimal time between delivery and initiation is unclear. However, increased bleeding has been shown when anticoagulation is started between 5 and 24 hours after vaginal delivery and 12 and 36 hours after cesarean delivery [91]. ACOG suggests in general **waiting 4–6 hours after vaginal delivery and 6–12 hours after cesarean delivery prior to starting any anticoagulation** [86].

The presence of an epidural catheter can also affect the timing of initiation. The American Society of Regional Anesthesia and Pain Medicine recommend **waiting at least 2 hours after the removal of an epidural catheter prior to initiation of prophylactic pharmacologic anticoagulation** [92]. SOGC and RCOG recommend waiting 4 hours prior to initiation of prophylactic pharmacologic anticoagulation after removal of a neuraxial catheter [84, 87, 93].

Candidates for postpartum pharmacologic thromboprophylaxis

A Cochrane review from 2014 including 840 women attempted to assess the safety and efficacy of VTE prophylaxis in the early postpartum period. The authors of that review concluded that more rigorous and larger RCTs were needed [94]. A more recent placebo-controlled RCT was attempted but had to be stopped early due to futility recruiting [95]. Thus, while no high-quality, large-scale trials exist, it is clear that universal postpartum pharmacologic intervention is likely to cause harm [96].

TABLE 31.3: Risk-Based Recommendations for Postpartum Pharmacologic Thromboprophylaxis

High-Risk Factors (Need ≥1)	Moderate-Risk Factors (Need ≥2)	Low-Risk Factors (Need ≥3)
Postpartum infection[a]	BMI >30[a,b]	Age >35[a,c]
Blood loss >1 L and surgery[a]	Smoking >10 cigarettes per day[a,b]	Parity >2[a]
BMI >40[b]	Pre-eclampsia[a,b]	Multiples[a,c]
	Growth restriction[a]	Abruption[a]
	Cesarean in setting of labor[a]	Assisted reproductive technology[a]
	Blood loss >1 L[a,b]	PPROM[a]
	Maternal lupus[a,b]	Cesarean delivery[ac]
	Sickle cell disease[a,b]	Maternal cancer[a]
	Stillbirth[a,b]	
	Preterm delivery[a,b]	
	Gestational diabetes[a]	
	Inflammatory bowel disease[a,b]	
	Heart failure/maternal cardiac disease[a,b]	

[a] Based on SOCG guidelines.
[b] Based on RCOG guidelines.
[c] Considered moderate risk factor by RCOG.
Abbreviations: BMI, body mass index; PPROM, preterm prelabor rupture of the membranes.

At this time, some experts suggest that the decision for postpartum pharmacologic thromboprophylaxis be an opportunity for shared decision-making among women without prior or current VTE [83]. In contrast, SOGC and RCOG have given specific risk-based guidelines for recommending postpartum pharmacologic thromboprophylaxis (Table 31.3). However, SMFM does recommend the institution develop their own protocols with respect to postpartum pharmacologic thromboprophylaxis for women undergoing cesarean delivery [85].

Insufficient evidence exists to guide recommendations about the duration of postpartum thromboprophylaxis for women without prior VTE or known thrombophilia. Expert opinion suggests anywhere from only while hospitalized to 6 weeks postpartum [84, 87]. Prophylactic LMWH dosing is 40 mg daily. However, this is often weight-based, and doses of 60 mg daily can be considered for women weighing 100–150 kg, and 80 mg daily for those weighing more than 150 kg [97]. Alternatively, subcutaneous heparin can be considered at a dose of 10,000 units twice a day.

Postpartum wound complications

Key points

- Wound complications include hematoma, seroma, dehiscence, infection, and rarely, necrotizing fasciitis and occur in 1%–2% of primary cesarean deliveries.
- Characteristic signs of wound infection are erythema, edema, heat, discharge, and induration of the incision; fever and leukocytosis may be systemic evidence of this condition.
- In the first 24–48 hours, the most common pathogens associated with wound infections are group A or B beta-hemolytic *Streptococcus*.
- **Effective interventions to decrease SSI include prophylactic antibiotic use before skin incision, no hair removal or hair removal using clippers, use of preoperative vaginal cleansing, suture closure of subcutaneous tissue if the wound thickness is >2 cm, and skin closure with sutures**.
- **Mild, nonpurulent cellulitis** without systemic signs of infection should be treated with **antistreptococcal antimicrobial agents**; **if purulent drainage or exudates accompany cellulitis**, empiric therapy should include a**dequate coverage for methicillin-resistant *Staphylococcus aureus***.

Diagnosis/Definition

Wound complications include several surgical morbidities that can prolong postoperative pain and convalescence, lead to readmission, and contribute to rising health care costs. Complications that can affect the wound after a cesarean delivery include hematoma, seroma, dehiscence, infection, and rarely, necrotizing fasciitis. The diagnosis of wound complications is clinical and posted in the presence of the classical signs of infection.

Symptoms/Signs

Characteristic signs of wound infection are erythema, edema, heat, discharge, and induration of the incision; fever and leukocytosis may be systemic evidence of this condition. Hematoma and seroma present as a collection of blood and serum, respectively, both of which can cause dehiscence and act as a nidus for the development of wound infection [98]. Necrotizing fasciitis is a rare but serious infection of the deep soft tissue that results in progressive destruction of the muscle fascia and overlying subcutaneous fat. Severe pain, wooden-hard induration of the subcutaneous tissues, bullous lesions, skin necrosis or ecchymosis, and elevated serum creatine kinase level are usually observed [99]. Computed tomography or magnetic resonance imaging may help in the diagnosis of necrotizing fasciitis, which will be confirmed at the time of repeat surgery.

Epidemiology/Incidence

The rate of postpartum wound complications in the literature ranges from 2.8% to 26.6% [100] with a percentage of **1%–2% for primary cesarean delivery** [101] **and a higher percentage for repeat cesarean deliveries**.

Microbiology

In the first 24–48 hours, the most common pathogens associated with wound infections are group A or B beta-hemolytic *Streptococcus*, while later infections usually involved *Staphylococcus epidermidis* or *aureus*, *Enterococcus faecalis*, *Escherichia coli*, and *Proteus mirabilis* [102].

Risk factors

Risk factors for the development of SSIs following cesarean delivery in decreasing order of significant risk are listed in Table 31.4 [103].

Workup

Examination of the surgical site is central when a woman presents with signs and symptoms possibly related to wound complication. The area of the wound should be carefully examined and potentially marked to assess for spread over time. A sterile swab can be used to investigate any open areas and the dimensions of the separation of tissues. **Superficial infection such as cellulitis can be treated with antibiotics alone and does not require incision and drainage**. If the wound has purulent drainage, exudate or separation, incision and drainage to remove abscess, exudate, and hematoma is needed [103].

TABLE 31.4: Risk Factors for Surgical Site Infection

Variables	Relative Risk or Odds Ratios
Subcutaneous hematoma	11.6
Chorioamnionitis	5.6–10.6
American Society of Anesthesiologists class 3 or greater	5.3
Tobacco	5.3
Incision length >16.6 cm	4.9
Prenatal visit <7	4
Body mass index >35 kg/m^2	3.7
Corticosteroid	3.1
Body mass index >30 kg/m^2	2.0–2.8
Subcutaneous tissue thickness >3 cm	2.8
Second stage (vs. first stage)	2.8
Teaching service	2.7
No antibiotic prophylaxis	2.6
Pregestational diabetes	1.4–2.5
Operating time ≥38 minutes	2.4
Hypertensive disease/pre-eclampsia	1.7–2.3
Duration of labor >12 hours	2.0
Nulliparity	1.8
Twin	1.6
Premature rupture of membrane	1.5
Gestational diabetes	1.5
Blood loss (every 100 mL)	1.3
Previous cesarean delivery	1.3
Emergency delivery	1.3
Rupture of membranes (each hour)	1.02

Source: From Ref. [103] under Creative Commons License.

Prevention

Effective interventions to decrease SSI include **prophylactic antibiotic use before skin incision** [104], **no hair removal or hair removal using clippers instead of razors** [105], **use of preoperative vaginal cleansing especially in women with ruptured membranes** [106], **suture closure of subcutaneous tissue if the wound thickness is >2 cm** [107], **and skin closure with sutures instead of with staples** [108]. Evidence-based bundles in women who undergo cesarean delivery are associated with a significant reduction in SSI [109].

Therapy

Wound infection needs **early antibiotic intervention**. **Mild, nonpurulent cellulitis** without systemic signs of infection should be treated with **antistreptococcal antimicrobial agents**, such as cephalexin, dicloxacillin, penicillin VK, amoxicillin/clavulanate, or, in cases of penicillin allergy, clindamycin [110]. **If purulent drainage or exudate accompanies cellulitis**, empiric therapy should include a**dequate coverage for methicillin-resistant *S. aureus*** [111]. Options for oral antibiotics include clindamycin, trimethoprim–sulfamethoxazole, and tetracycline (doxycycline or minocycline). Reclosure of disrupted laparotomy wounds can be accomplished with a high likelihood of success (>80%) and a small number of recurrent abscesses, seromas, and minor wound separations. Compared with healing by secondary intention, reclosure results in a faster healing time (16–18 days versus 61–72 days) and fewer number of postoperative visits [112].

Postpartum endometritis

Key points

- Postpartum endometritis refers to an infection of the decidua, typically polymicrobial, that occurs in about 1%–3% of vaginal births and up to 27% of cesarean deliveries.
- The diagnosis is clinical and suspected if the patient develops puerperal fever, usually accompanied by abdominopelvic pain and purulent or foul-smelling lochia.
- Cesarean delivery is the most important risk factor for postpartum maternal infection, especially when performed after a prolonged labor with ruptured membranes.
- Routine blood cultures in women with uncomplicated endometritis are not recommended, since empiric treatment with a broad-spectrum antibiotic is usually effective.
- Effective prevention measures able to reduce the incidence of postpartum endometritis in women who are undergoing cesarean delivery include vaginal preparation with antiseptic solution and antibiotic prophylaxis within 60 minutes prior to making the skin incision.
- **The gold standard for the treatment of postpartum endometritis is the combination of clindamycin 900 mg IV every 8 hours plus gentamicin 5 mg/kg IV every 24 hours**.

Diagnosis/Definition

Postpartum endometritis refers to an infection of the decidua, typically polymicrobial, that may extend into the myometrium or involve the parametrial tissues. The diagnosis is clinical and suspected if the patient develops fever in the absence of any other cause. Puerperal febrile morbidity is defined as an oral temperature ≥38°C (100.4°F) on any 2 of the first 10 days postpartum or a single oral temperature of 38.7°C (101.6°F) in the first 24 hours [113].

Symptoms/Signs

Puerperal fever is usually accompanied by abdominopelvic pain and purulent or foul-smelling lochia. Additional findings observed in some women are chills, headache, malaise, and/or anorexia. Uterine involution can be delayed in the case of endometritis, particularly if the myometrium is involved (endomyometritis), and excessive bleeding can occur.

Epidemiology/Incidence

It is the most common postpartum infection, occurring in 1%–3% of vaginal births and in up to 27% of cesarean births [114. Data derived from a review of Maternal-Fetal Medicine Unit Network publications involving over 70,000 cesarean deliveries reported a rate of endometritis of around 6% for primary cesarean delivery performed before labor and around 11% for primary cesarean delivery performed during labor [101].

Etiology/Basic pathophysiology/Microbiology

Infections are usually polymicrobial and related to a mixture of two to three aerobes and anaerobes that ascend from the lower genital tract to the uterus, colonizing the decidua, within 6 weeks of the birth. The most common pathogens isolated from the endometrium include *E. coli* and other aerobic gram-negative organisms such as *Klebsiella pneumoniae, Enterobacter*, and *Proteus* species; aerobic gram-positive organisms, including group B *Streptococcus* and other *Streptococcus* species such as *Enterococcus* and *S. aureus*; and coagulase-negative anaerobes such as *Bacteroides* and *Prevotella* species, *Peptostreptococcus* species, and the gram-variable *Gardnerella vaginalis* [115, 116].

TABLE 31.5: Risk Factors for Postpartum Endometritis

Maternal Conditions	Intrapartum and Postpartum Conditions
Malnutrition	Multiple vaginal examinations
Severe anemia	Prolonged rupture of the membranes
Diabetes	Severe meconium staining in liquor
Obesity (body mass index >30 kg/m^2)	Cesarean delivery
HIV infection	Manual extraction of placenta
Altered vaginal microflora (e.g. bacterial vaginosis, vaginal group B streptococci colonization)	

Source: Data from Refs. [122–124].

Risk factors/Associations

Cesarean delivery is the most important risk factor for postpartum maternal infection, especially when performed after a prolonged labor with ruptured membranes [117, 118]. An increased incidence of endometritis following cesarean delivery has also been reported in association with bacterial vaginosis [119]. For vaginal birth, the presence of bacterial vaginosis, prolonged rupture of membranes, and multiple vaginal examinations during labor are associated with an increased risk of endometritis [118, 120]. The most common maternal, intrapartum, and postpartum conditions associated with an increased risk of postpartum endometritis are listed in Table 31.5 [121–123].

Complications

Endometritis is still an important cause of maternal deaths worldwide, although the use of antibiotics has considerably reduced its incidence [114]. Serious complications of postpartum endometritis include peritonitis, pelvic abscess, and septic thrombophlebitis, which can be associated with septic pulmonary emboli.

Workup

The white blood cell (WBC) count is elevated, but this can be a normal finding in postpartum women secondary to the physiologic leukocytosis of pregnancy and the effects of labor, while a rising, rather than falling, neutrophil count postpartum is suggestive of an infectious process [124]. **Routine blood cultures in women with uncomplicated endometritis are not recommended**, since empiric treatment with a broad-spectrum antibiotic is usually effective. However, in some selected cases, such as endometritis complicated by sepsis or failure of the initial antibiotic therapy, women with an increased risk for bacterial endocarditis, or immunocompromised women, the detection of bacteremia with blood cultures can be useful to tailor antibiotic treatment [125]. Endometrial bacterial cultures are challenging to obtain without contamination through the cervix and rarely provide information that affect treatment decisions [126]. There are no characteristic sonographic findings associated with postpartum endometritis [127]. In the differential diagnosis it is necessary to consider other postpartum febrile episodes such as SSI, engorgement, mastitis, breast abscess, and less frequently, a viral syndrome, appendicitis, pyelonephritis, atelectasis, or pneumonia.

Prevention

Effective prevention measures able to reduce the incidence of postpartum endometritis in women who undergo cesarean delivery include vaginal preparation with an antiseptic solution (iodine-based solutions or chlorhexidine-based solutions) immediately before cesarean delivery [106], antibiotic prophylaxis within 60 minutes prior to making the skin incision [128], and spontaneous placental extraction [128].

TABLE 31.6: Recommendations for Early Post-Cesarean Delivery Care

- Early ambulation 5–10 minutes several times a day starting from 4 hours after CD
- Early oral feeding within 6–8 hours after CD
- Chewing three times a day immediately after CD
- Immediate removal of catheter, if used
- Postoperative analgesia with scheduled NSAIDs or acetaminophen for 48 hours given around the clock
- Dressing removal at 6 hours after a scheduled CD
- Absorbable subcuticular suture to reapproximate the skin
- Pneumatic compression devices during postpartum, regardless of mode of delivery, until the woman is fully ambulatory
- LMWH for postpartum pharmacologic anticoagulation 6–12 hours after CD in women meeting criteria for anticoagulation
- Early antibiotic therapy for postpartum wound infection and postpartum endometritis

Abbreviations: CD, cesarean delivery; LMWH, low-molecular-weight heparin.

Therapy

Antibiotic treatment that includes coverage for aerobic and anaerobic pathogens likely to be causing endometritis should be administered promptly. **The gold standard for the treatment of postpartum endometritis is the combination of clindamycin 900 mg IV every 8 hours plus gentamicin 5 mg/kg IV every 24 hours** [114]. The combination of ampicillin-sulbactam (3 g every 6 hours) and gentamicin (1.5 mg/kg every 8 hours) is as effective and well tolerated as a combination regimen using clindamycin plus gentamicin and therefore could be used in case of clindamycin resistance [129]. **The treatment should be continued until the woman is afebrile for (usually) 24–48 hours** and the pelvic pain disappears. In case of persistent fever for more than 48 hours of antibiotic therapy, the addition of ampicillin or penicillin to the regimen can be an effective approach because of the presence of resistant organisms, such as enterococci, in about 20% of cases [130]. If the woman has not improved despite the adjustment of the initial antibiotic therapy, other etiologies of fever should be considered. Ultrasound may demonstrate the retained tissue fluid collection such as pelvic abscess or infected hematoma [131]; computed tomography (CT) or magnetic resonance imaging are helpful if septic pelvic thrombophlebitis or ovarian vein thrombosis is suspected. For women with negative imaging, the likelihood of a drug fever should be considered [132].

In summary, for early post–cesarean delivery care, we suggest the interventions in Table 31.6.

Other postpartum issues for both vaginal and cesarean delivery

Postpartum ultrasound

Key points

- The upper limit of **normal for endometrial thickness was 25 mm up to 7 days postpartum** and continued to

decrease during the puerperium period, as all other uterine measurements gradually do.
- Endometrial stripe thickness and ultrasound presence of echogenic material in the uterine cavity should not be used as clinical predictors for abnormal bleeding complications, since they may be common findings in the early postpartum period.

Postpartum ultrasound is not routinely performed in every institution, although it is considered a useful tool when a suspicion for placental pathology arises during the postpartum course. A recent, large systematic review including 3106 women undergoing transabdominal and/or transvaginal ultrasound from day 1 to a maximum of 6 weeks postpartum provided clinical guidance for the sonographic evaluation of women with an uncomplicated postpartum course. **The upper limit of normal (95th percentile) for endometrial thickness was 25 mm up to 7 days postpartum** and continued to decrease (18 mm at 14 days, 12 mm at 4 weeks, and 9 mm at 6 weeks) similarly, regardless of parity or mode of delivery. All other uterine measurements also gradually decreased during the puerperium period similarly, regardless of parity or mode of delivery [133]. Endometrial stripe thickness and ultrasound presence of echogenic material in the uterine cavity should not be used as clinical predictors for the development of abnormal bleeding complications, since they may be normal findings in the early postpartum ultrasound [134].

Breastfeeding

Key points

- In normal reproductive physiology, lactation follows pregnancy. For the infant, use of artificial breast milk substitutes is associated with increased acute and chronic disease risk. For mothers, never or curtailed (e.g. short-term) breastfeeding is associated with increased risks of malignancy and metabolic disease.
- All major medical organizations recommend **6 months of exclusive breastfeeding, with continued breastfeeding through 1–2 years**, or longer as mutually desired by mother and infant.
- Infant demand drives maternal milk supply. To ensure adequate milk production, **encourage frequent, on-demand feeding in response to infant cues, continuing until the infant is satisfied**.
- Prenatal and postnatal lay and/or professional support and evidence-based physician training improve breastfeeding duration and exclusivity.
- Maternity care practices affect breastfeeding initiation and duration. Implementation of the United Nations International Children's Emergency Fund (UNICEF)/World Health Organization (WHO) Baby Friendly Hospital Initiative (BHI) improves breastfeeding duration, intensity, and infant health outcomes.
- Prenatal treatment of inverted nipples does not increase breastfeeding success.
- Distribution of formula company marketing materials and samples adversely affects breastfeeding outcomes. Formula company materials should not be distributed in health care facilities.
- **At birth, early skin-to-skin contact increases breastfeeding duration**. Healthy infants should be placed skin-to-skin on the mother's chest and remain there, undisturbed, until the first feeding is accomplished.
- **Treatment for mastitis begins with frequent removal of milk, hydration, and analgesia**. **Healthy term infants can continue to feed on the affected side**. **Antibiotics are used if conservative management is ineffective or the patient is acutely ill**.
- There is limited evidence that galactagogues increase milk production in placebo-controlled trials. Optimal breastfeeding education can increase milk supply among women with low production.
- **Most medications are compatible with breastfeeding, or a safe alternative medication exists**. The physiology of the placenta differs from the breast, and providers should not extrapolate drug safety information from pregnancy to lactation.
- Breastfeeding is contraindicated in the setting of an infant with classic galactosemia, active maternal use of illicit drugs, maternal medications that are contraindicated in breastfeeding, or maternal infection with T-cell lymphotropic virus type I or II (e.g. HTLV). Recommendations for breastfeeding in the setting of maternal HIV or tuberculosis vary by region. Women with HIV in the United States are advised not to breastfeed because of the risk of maternal-infant transmission and the availability of safe artificial feeding. Breastfeeding is temporarily contraindicated during perinatal maternal *Varicella* infection or from a breast with an active herpetic lesion.

Definition

Breastfeeding is the physiologic form of infant nutrition. It is defined as the infant receiving any amount of human milk. Exclusive breastfeeding is defined as receiving human milk alone for nutrition while mixed feeding is defined as receiving both human milk and infant formula. It should be noted that breastfeeding is synonymous with nursing, but also includes bottle-feeding pumped breastmilk to the baby.

Breastfeeding physiology

Secretory differentiation occurs during pregnancy, as placental hormones stimulate development of mammary alveoli. After birth, secretory activation occurs as progesterone levels fall and milk production increases from 50 mL/day to approximately 500 mL/day in the first 2–3 days after birth. Positive feedback via infant stimulation of the breast causes secretion of prolactin from the anterior pituitary and oxytocin from the posterior pituitary. Prolactin stimulates continuous milk synthesis, whereas oxytocin stimulates intermittent milk secretion, when myoepithelial cells contract to transfer milk from the alveoli to the areola. If milk is not removed regularly, negative feedback downregulates prolactin receptors and reduces production. Frequent, on-demand feeding is essential to establish and maintain lactation [135].

Health effects of infant feeding

Infants who are artificially fed face higher risks of infectious morbidity and chronic disease than infants who are breastfed. An Agency for Healthcare Research and Quality (AHRQ) meta-analysis of outcomes in developed countries found that **artificially fed infants** faced a 2.0-fold risk of **otitis media**, a 3.6-fold risk of **pneumonia**, and a 2.8-fold risk of **gastrointestinal infection** compared with infants who were exclusively breastfed [136].

Artificial feeding is also associated with a 1.8- to 3.7-fold risk of sudden infant death syndrome (**SIDS**), a 1.1- to 1.4-fold risk of **child obesity**, and a 1.5-fold risk of **type 2 diabetes** compared with breastfeeding. Artificial or mixed feeding is also associated with higher risks of **asthma** compared with exclusive breastfeeding. Among preterm infants, artificial feeding is associated with a 5% absolute increased risk of **necrotizing enterocolitis** compared with being fed mother's milk [136].

For mothers, artificial feeding is similarly associated with increased health risks. **Compared with women who have breastfed, parous women who have never breastfed or weaned early** face higher rates of **breast cancer** [137, 138], particularly triple-negative breast cancer, **ovarian cancer, retained gestational weight** gain [139], **type 2 diabetes** [140–143], **hyperlipidemia** [144], **metabolic syndrome** [145, 146], **hypertension** [142, 147], **and myocardial infarction** [142, 148].

Optimal duration of exclusive breastfeeding

Six months of exclusive breastfeeding, compared with 3–4 months of exclusive breastfeeding with mixed feeding through 6 months, reduces infant risk of gastrointestinal and respiratory tract infections without any adverse effect on infant growth. For mothers, longer exclusive breastfeeding was associated with delayed resumption of menses and, in one small study, with greater maternal weight loss [149].

Infant feeding recommendations

All major medical organizations [150–153] recommend **exclusive breastfeeding for the first 6 months of life**. The World Health Organization (WHO) recommends continued breastfeeding up to 2 years of age or beyond [153]. The American Academy of Pediatrics (AAP) recommends continued breastfeeding for **at least the first year of life**, continuing for as long as mutually desired by mother and child.

Promoting breastfeeding

Antenatal interventions can increase breastfeeding initiation and duration (Table 31.7) [154]. **Breastfeeding education** improves initiation rates among low-income U.S. populations. In subgroup analyses, one-on-one, needs-based, informal education sessions were more effective than generic, formal antenatal sessions [155]. Both lay and professional support for mothers after birth improves breastfeeding duration and exclusivity, with the strongest effects found with proactive, face-to-face, lay support involving four to eight contacts. A U.S. Preventative Services Task Force (USPSTF) review similarly found that interventions to promote and support breastfeeding increase initiation, duration, and exclusivity of breastfeeding, and interventions that include both prenatal and postnatal components may be most effective [156]. Proactive, integrated prenatal and postnatal support for breastfeeding mothers improves breastfeeding duration and intensity.

Training of providers

Breastfeeding education and knowledge among health care providers is inconsistent [157–159]. A meta-analysis found that **training breastfeeding support personnel** using the WHO/UNICEF breastfeeding training course [160] increases the duration of exclusive breastfeeding. In a cluster-randomized trial, implementation of a breastfeeding training curriculum for residents improved provider knowledge, practice patterns, and confidence and increased exclusive breastfeeding rates at 6 months (odds ratio [OR] 4.1) compared with control sites [161]. Interventions for hospital staff are similarly associated with improved breastfeeding outcomes. Health care providers who work with mothers and infants should receive comprehensive breastfeeding training.

TABLE 31.7: Successful Breastfeeding Recommendations

Offer additional breastfeeding support to women who have had a narcotic/general anesthetic, a caesarean, or delayed contact with their baby.
Ensure breast pumps are available for women who have been separated from their babies, and give instruction on how to use them.
Encourage unrestricted breastfeeding frequency and duration.
Reassure women about breast milk supply and help them gain confidence.
Advise women that babies will stop feeding when satisfied.
Advise women of the signs that a baby is successfully feeding: • Swallowing is audible and visible. • There is a sustained rhythmic suck. • The arms and hands are relaxed. • The mouth is moist. • Regular soaked/heavy nappies.
Reassure women that they may feel the following: • Brief discomfort at the start of feeds in the first few days; this is not uncommon but should not persist. • Softening of their breast during the feed. • No compression of the nipple at the end of the feed. • Relaxed and sleepy.
Attachment and Positioning
Advise women of the following signs of good attachment and positioning: • The baby's mouth is wide open. • There is less areola visible underneath the chin than above the nipple. • The baby's chin is touching the breast, the lower lip is rolled down, and the nose is free. • There is no pain.
If the baby is not attaching effectively, advise teasing the baby's lips with the nipple to open the mouth.

Source: Adapted from Ref. [156].

The Baby Friendly Initiative

Maternity care affects breastfeeding outcomes. The Baby Friendly Initiative (BFI) is WHO-developed set of maternity care recommendations designed to increase initiation and duration of breastfeeding. The BFI requires maternity centers to implement the **Ten Steps to Successful Breastfeeding** (Table 31.8) [162]. Each country is responsible for establishing processes and procedures for a maternity center designation as baby friendly [162]. In a cluster-randomized trial in Belarus, BFI implementation improved breastfeeding exclusivity at 3 months (43.3% versus 6.4%, $p < 0.001$) and 6 months (7.9% versus 0.6%, $p = 0.01$) and increased any breastfeeding rates at 12 months (19.7% versus 11.4%). Infants born in intervention hospitals had lower rates of gastrointestinal illness and atopic eczema in the first year of life [163]. Observational studies in the United States have found a dose–response association between implementation of BFI steps and maternal achievement of breastfeeding goals [164, 165]. Cohort studies suggest that the Ten Steps are particularly effective among women with lower education, suggesting that BFI maternity care can reduce socioeconomic disparities in breastfeeding [166].

TABLE 31.8: The Ten Steps to Successful Breastfeeding

Every facility providing maternity services and care for newborn infants should:

1. Have a written breastfeeding policy that is routinely communicated to all health care staff.
2. Train all health care staff in skills necessary to implement this policy.
3. Inform all pregnant women about the benefits and management of breastfeeding.
4. Help mothers initiate breastfeeding within a half-hour of birth.
5. Show mothers how to breastfeed and how to maintain lactation even if they should be separated from their infants.
6. Give newborn infants no food or drink other than breast milk unless medically indicated.
7. Practice rooming in—allow mothers and infants to remain together 24 hours a day.
8. Encourage breastfeeding on demand.
9. Give no artificial teats or pacifiers (also called dummies or soothers) to breastfeeding infants.
10. Foster the establishment of breastfeeding support groups and refer mothers to them on discharge from the hospital or clinic.

Source: From Declercq E, Labbok MH, Sakala C, et al. Hospital practices and women's likelihood of fulfilling their intention to exclusively breastfeed. Am J Pub Health. 2009;99(5):929–935. Ref. [164], with permission.

The National Institute for Health and Clinical Excellence (NICE) postnatal care guideline recommends that all health care providers implement a structured program that encourages breastfeeding, using the BFI as a minimum standard (Table 31.7) [154].

Breastfeeding in clinical care

Antenatal breast exam

Clinical guidelines recommend evaluation of breast anatomy as part of prenatal care [151, 167]. However, there are no RCTs regarding the effects of an antenatal breast exam on breastfeeding outcomes or maternal satisfaction [168]. There is no evidence that antenatal manipulation for inverted nipples improves breastfeeding outcomes [169, 170].

Avoiding commercial infant feeding materials

In randomized trials, provision of formula company materials and gift packs during prenatal care [171] or during the maternity hospitalization [172–174] reduces exclusive breastfeeding. In a time-series design study, changing from formula marketing discharge packs to noncommercial packs was associated with higher breastfeeding rates, but more than one-third of women in the noncommercial cohort received formula samples, demonstrating that policy implementation is challenging [175]. **Formula company marketing materials should not be distributed in the health care setting**.

Skin-to-skin contact at birth

Early skin-to-skin contact improves breastfeeding outcomes. Skin-to-skin contact is defined as placing the naked infant prone on the mother's bare chest, with the infant's back covered with a warm blanket, ideally beginning immediately after birth. In a Cochrane meta-analysis, **early skin-to-skin contact increased breastfeeding** at 1–4 months after birth (RR 1.27) and increased the duration of total breastfeeding by about 6 weeks [176]. Based on these data, the NICE [177], AAP [178], and ACOG [151] recommend that all healthy infants be placed skin-to-skin at birth. **Infants should remain with their mothers for at least 1 hour**, and providers should encourage mothers to recognize when the infant is ready to feed and offer help if needed [162]. **Routine procedures, such as weighing, bathing, and vitamin K and eye prophylaxis, should be avoided during the first hour, or be performed on the mother's chest**. Skin-to-skin care during procedures, such as a heel lance, appears to reduce infant pain. Skin-to-skin is also feasible following cesarean section.

Anticipatory guidance to support normal physiology

Human milk production is driven by infant demand. Therefore, frequent feeding, on demand in response to infant feeding cues, continuing until the infant is satisfied, is a cornerstone of breastfeeding success [179], although a recent meta-analysis did not identify trials comparing baby-led feeding with scheduled breastfeeding [180]. NICE clinical guidelines have outlined anticipatory guidance for successful breastfeeding. A small pilot study found that early, limited supplementation with hydrolyzed formula for infants with ≥5% weight loss increased exclusive breastfeeding rates at 1 week and 3 months postpartum [181]; several trials to test whether these findings can be replicated are underway (NCT02313181 and NCT02221167).

Management of breastfeeding complications

Engorgement

Breast engorgement typically occurs between 2 and 5 days postpartum. A meta-analysis found insufficient evidence to support any single treatment strategy for engorgement [182]. **Cold packs and cabbage leaves may be helpful, and acupuncture was associated with some improvement** in symptoms. NICE guidelines recommend **breast massage, continued breastfeeding, and analgesia for symptom relief** [154].

Mastitis

Mastitis is defined as acute inflammation of connective tissue within the breast, which may or may not be accompanied by infection [183]. Interventions to prevent mastitis have not proven effective [184]. A Cochrane meta-analysis (2 RCTs, $n = 125$ patients) concluded that there is insufficient evidence to support treatment with antibiotics. An RCT suggests that *Lactobacilli* strains isolated from breast milk may be effective for the treatment of mastitis [185].

Clinical guidelines emphasize **effective milk removal, hydration, and analgesia** as key elements of clinical management of mastitis. Healthy term infants may continue to breastfeed on the affected breast. **If symptoms do not improve with conservative management or the woman is acutely ill**, antibiotics are recommended. **Penicillinase-resistant penicillins (e.g. dicloxacillin) are preferred** [186].

Breastfeeding and maternal medications

Most medications are compatible with breastfeeding, or a safe alternative medication exists. The physiology of the placenta differs from that of the maternal breast and infant gut, so the provider should not assume that a drug's pregnancy safety profile applies to breastfeeding. Many drug databases utilized by commercial pharmacies do not contain accurate information on drug safety in lactation [187]. The National Library of Medicine's LactMed database (https://www.ncbi.nlm.nih.gov/books/NBK501922/) provides a comprehensive set of monographs on medication safety in lactation. Decisions about medication use in lactation should consider the risks and benefits of maternal treatment or nontreatment, the risk of drug transfer to the infant, and the risks to mother and infant

of discontinuing breastfeeding [188]. Maternal providers should collaborate with the pediatric provider regarding counseling about medication use in breastfeeding.

Milk expression

If mothers and infants are separated, milk expression is necessary to maintain supply and provide milk to the infant. Evidence suggests that early initiation of milk expression, simultaneous pumping of both breasts, breast massage, relaxation techniques, and expressing milk after kangaroo (i.e. skin-to-skin) mother care improve milk production among neonatal intensive care unit (NICU) mothers [189–194].

Galactagogues

There is limited evidence to support pharmacotherapy for low milk supply [195, 196]. Two small randomized, placebo-controlled, blinded studies have found that domperidone increases milk supply among mothers of preterm infants [197, 198]. Domperidone is not approved by the U.S. Food and Drug Administration (FDA) for any indication. Routine use of metoclopramide in the early postpartum period does not improve milk production [199, 200]. In two studies among women with low milk supply who received education on optimal breastfeeding [201, 202], metoclopramide provided no additional benefit compared with placebo. The AAP notes that galactagogues have a limited role in facilitating lactation; mothers experiencing milk production difficulties should undergo assessment by a lactation specialist and be offered nonpharmacologic measures to increase supply [188].

Maternal diet during lactation

In two small trials, maternal dietary restrictions during lactation did not reduce the incidence of atopic eczema or the severity of existing disease [203]. Maternal supplementation with long-chain polyunsaturated fatty acids (LCPUFAs) during lactation does not improve infant neurodevelopmental outcomes. In two studies, LCPUFA supplementation increased infant head circumference [204]. A meta-analysis found limited evidence for LCPUFA supplementation during pregnancy and/or lactation to reduce allergic diseases in children [205]. There is insufficient evidence to recommend LCPUFA supplementation during breastfeeding.

Contraindications

Breastfeeding is contraindicated in the setting of the following:

- Infant with classic galactosemia (galactose-1-phosphate uridyltransferase deficiency)
- Maternal medications:
  - Mothers with current, active illicit drug use, in the absence of a coordinated treatment plan among maternal and infant providers [206]
  - Mothers requiring medications that are contraindicated in breastfeeding
- Maternal infectious disease:
  - Mothers who are human T-cell lymphotropic virus type I or II positive (e.g. HTLV)
  - Mothers with untreated brucellosis
  - Mothers with active herpetic lesions on the breast(s). Mothers can continue to breastfeed on the unaffected breast and provide expressed milk from the affected breast.
  - Mothers with *Varicella* onset within 5 days before until 48 hours after delivery should be separated from their infants, but expressed milk can be provided to the infant.
  - Mothers with HIV infection in settings where safe artificial feeding is available (see later).

Tuberculosis

The AAP lists active, untreated tuberculosis as a contraindication to breastfeeding. According to AAP guidelines, the infant may continue to receive expressed milk while the mother is treated, but mother and infant should be separated until the mother is treated for a minimum of 2 weeks and is documented to be no longer infectious. The WHO recommends continued breastfeeding in the setting of maternal tuberculosis. The infant should be treated with 6 months of isoniazid preventive therapy, followed by immunization with bacillus Calmette-Guerin (BCG) [207].

HIV

Artificial infant feeding is efficacious in preventing maternal-child transmission of HIV, but RCTs in regions of the world where access to clean water is limited demonstrate similar mortality and malnutrition among breastfed and artificially fed infants. If infants are breastfed, early exclusive breastfeeding and extended antiretroviral prophylaxis reduce the risk of HIV transmission [208].

Women with HIV in the United States are advised not to breastfeed because of the risk of maternal-infant transmission and the availability of safe artificial feeding [26].

The WHO recommends that national or subnational health authorities determine recommendations regarding infant feeding for HIV-positive mothers, balancing HIV prevention with protection from other causes of child mortality [209]. In countries where breastfeeding is recommended, antiretroviral prophylaxis for mothers and infants reduces HIV transmission. Exclusive breastfeeding is recommended for the first 6 months, continuing through 1 year. When mothers decide to stop breastfeeding, they are advised to wean gradually, over 1 month, and mothers or infants receiving antiretroviral prophylaxis should continue for 1 week after breastfeeding is fully stopped.

Contraception

Key points

- **Postpartum educational interventions can increase contraceptive use and delay repeat pregnancy**.
- **Intrauterine device (IUD)** placement <48 hours postpartum is not associated with infectious morbidity, but expulsion rates are higher than with placement >4 weeks. Since many women do not present for postpartum follow-up, overall IUD **use is highest when inserted in the immediate postpartum period**.
- Postpartum tubal ligation (PPTL) is highly effective. However, the risk of regret is higher for PPTL than for interval TL.
- Postpartum placement of the contraceptive implant shows promise as an additional long-acting option for women early in the postpartum period, with potentially less lactogenic effects
- Lactation amenorrhea is an effective, but not perfect, method of contraception, until the infant is 6 months old, begins complementary feeding, or the mother's menses resume.
- Barrier methods are preferred during lactation compared with hormonal contraception because of theoretical effects of hormonal methods on milk supply and hormone exposure for the infant.

Background

Sexual activity is resumed by about 53% of women within 6 weeks postpartum, with 41% attempting vaginal sex. By 8 weeks, about 65% attempt vaginal sex, rising to 8%–95% by 3 months [210]. **Women with uncomplicated vaginal births resume sex earlier** compared to women who had perineal lacerations, assisted vaginal births, or cesarean deliveries [211]. However, by 1 year, sexual function returns to near pre-pregnancy levels independent of mode of delivery [212]. Two-thirds of women have unmet contraceptive needs after childbirth [213]. Educational interventions during the postpartum hospitalization increase contraceptive use compared with no intervention. Home visit programs reduce repeat pregnancies among teenagers [214].

Contraceptive guidelines

A detailed review of contraception is beyond the scope of this book. The WHO has published detailed guidelines regarding timing of initiation of postpartum contraception and other relative and absolute contraindications. Postpartum recommendations for healthy women are summarized in Tables 31.9 and 31.10. The full guidelines are available online [215].

TABLE 31.9: WHO Guidelines for Postpartum Contraception: Hormonal Contraception

	Progestin-Only Methods[a]	Combined Hormonal Contraceptives[b]
Breastfeeding		
<6 weeks postpartum	3/2[c]	4
>6 weeks to <6 months postpartum (primarily breastfeeding)	1	3
>6 months postpartum	1	2
Not Breastfeeding		
<21 days postpartum	1	(i) Without other risk factors for VTE: 3 (ii) With other risk factors for VTE: 3/4
>21 days to 42 days	1	(i) Without other risk factors for VTE: 2 (ii) With other risk factors for VTE: 2/3
>42 days	1	1

Source: From World Health Organization. Medical Eligibility Criteria for Contraceptive Use, 5th ed. Geneva: World Health Organization; 2015. Ref. [217], with permission.

Abbreviation: VTE, venous thromboembolism.

1: A condition for which there is no restriction for the use of the contraceptive method.

2: A condition where the advantages of using the method generally outweigh the theoretical or proven risks.

3: A condition where the theoretical or proven risks usually outweigh the advantages of using the method.

4: A condition that represents an unacceptable health risk if the contraceptive method is used.

[a] Progestogen-only pills, levonorgestrel and etonogestrel implants, depot medroxyprogesterone acetate, and norethisterone enanthate.

[b] Combined oral contraceptives, combined contraceptive patch, combined contraceptive vaginal ring, and combined injectable contraceptives.

[c] 3: Depot medroxyprogesterone or norethisterone enanthate, 2: All other progestogen-only methods.

TABLE 31.10: WHO Guidelines for Intrauterine Devices

	Breastfeeding	Not breastfeeding
Levonorgestrel-releasing (LNG) IUD, <48 hours postpartum	2	1
Copper-bearing (Cu) IUD, <48 hours postpartum	1	1
LNG-IUD or Cu-IUD >48 hours to <4 weeks	3	3
>4 weeks	1	1
Puerperal sepsis	4	4

Source: From World Health Organization. Medical Eligibility Criteria for Contraceptive Use, 5th ed. Geneva: World Health Organization; 2015. Ref. [217], with permission.

1: A condition for which there is no restriction for the use of the contraceptive method.

2: A condition where the advantages of using the method generally outweigh the theoretical or proven risks.

3: A condition where the theoretical or proven risks usually outweigh the advantages of using the method.

4: A condition that represents an unacceptable health risk if the contraceptive method is used.

Intrauterine devices

IUDs are highly effective methods of contraception. Unfortunately, less than 50% of women who express interest in an IUD postpartum actually receive one [216]. **Immediate postpartum placement** has been shown to be safe and allows women to access contraception during the maternity hospitalization, though it is associated with an increased risk of expulsion compared with delayed insertion [217, 218]. In an RCT of postplacental versus delayed insertion, women randomized to postplacental insertion were more likely to have a device inserted (98% versus 90.2%, $p = 0.20$). There were no differences between groups in IUD use at 6 months postpartum (84.3% versus 76.5%). However, among women who were ineligible for the study and were advised to follow up for IUD placement as part of routine postpartum care, only 26.8% were using an IUD at 6 months postpartum [219]. These results were confirmed in a more recent Cochrane review, with IUD use at 6 months twice as likely, though expulsion was four times more likely [220]. These results suggest that **women undergoing postplacental placement are more likely to use an IUD than those advised to follow up for placement during routine postpartum care**. Immediate postplacental IUD placement has been classified as category 1 or 2 by the Centers for Disease Control and Prevention's U.S. Medical Eligibility Criteria for Contraceptive Use [221].

Implants

The contraceptive implant is another highly effective form of long-acting reversible contraception that can be placed **immediately postpartum**. The implant can be placed in the delivery room immediately after delivery. However, unlike the IUD, it can also be placed anytime during the delivery admission. Though theoretical concerns about lactogenesis in the setting of early exposure to exogenous progesterone have been raised, a recent RCT showed women who had the **implant placed immediately postpartum showed no difference in lactogenesis or inability to breastfeed** [222]. Similar to concerns about low attendance, the postpartum visit, and financial barriers mentioned with regard to the IUD, immediate postpartum placement of the implant alleviates those concerns. While an IUD cannot be placed in the

setting of intraamniotic infection, this is not a contraindication to immediate postpartum implant placement.

Postpartum sterilization

Sterilization is the most commonly used form of contraception worldwide. **Postpartum partial salpingectomy has a 1-year failure rate of 0.6/1000** and a **10-year failure rate of 7.5/1000**, which compares favorably with other sterilization methods [223, 224]. In a small RCT, operative times were shorter with postpartum Filshie clip placement compared with the Pomeroy technique, but failure rates were not evaluated [225]. Another larger RCT with 1400 women compared postpartum titanium clips to partial salpingectomy (Pomeroy technique); though this study did not assess operative time, it did find that pregnancy probability at 2 years was 0.017 and 0.004 for clips and salpingectomy, respectively ($p = 0.04$) [226]. Maternal age <30 increases risk of regret and request for tubal reversal [227]. Risk of regret is higher among women undergoing postpartum tubal ligation (PPTL) compared with interval tubal ligation (TL). Other risk factors for regret include ligation at the time of C-section, abrupt decision to undergo PPTL, and sterilization performed for obstetric indications [228].

In a cohort study of women planning postpartum sterilization, one-third did not receive the procedure prior to hospital discharge. Of these women, 47% were pregnant within 1 year, compared with 22% of women who had not planned a postpartum sterilization [229]. Women who desire but do not undergo postpartum sterilization are at high risk for unplanned pregnancy. Among women who desired PPTL but did not receive it, the postpartum implant is an equally efficacious option (though less long acting) that can be placed during the delivery hospitalization.

In recent years, some practices have begun to perform salpingectomy instead of TL. The rationale for this is prevention of future tubal disease, decreased risk of ectopic pregnancy, and opportunity to decrease the risk of ovarian cancer [230]. Additionally, no significant difference in length in hospital stay; readmissions; blood transfusions; or postoperative complications, infections, and fevers have been identified in cases of cesarean with and without salpingectomy [231]. While many have raised concerns about the surgical safety of this procedure, given the increased blood supply, multiple studies, including two RCTs, demonstrated no statically significant difference in blood loss and intraoperative and postoperative complications for opportunistic salpingectomy compared to standard TL at the time of cesarean delivery [232–233]. Based on these data, this approach can be considered in the appropriately counseled patient.

Contraception during breastfeeding

Breastfeeding reduces fertility and prolongs amenorrhea after childbirth. In the first 6 months after birth, cohort studies suggest that 0%–7.5% of women who are fully breastfeeding and amenorrheic become pregnant [234, 235]. To maintain effective protection against pregnancy, another method of contraception must be used as soon as menstruation resumes, the frequency or duration of breastfeeds is reduced, bottle feeds are introduced, or the baby reaches 6 months of age [215].

WHO recommendations regarding hormonal contraception during breastfeeding are listed in Table 31.9. WHO guidelines indicate that **breastfeeding women can generally receive the levonorgestrel intrauterine device (LNG-IUD) at <48 hours postpartum** [215]. In a small RCT [236], immediate postpartum placement of an LNG-IUD decreased exclusive breastfeeding rates at 3 and 6 months postpartum compared with insertion at 6–8 weeks. A study comparing insertion at 6–8 weeks of the LNG-IUD with the **Cu T380A IUD** found no differences in breastfeeding outcomes, infant growth, or development [237]. WHO recommendations regarding timing of IUD insertion are listed in Table 31.10.

The **contraceptive implant** is a progesterone-only option that can be placed immediately postpartum. Theoretical concerns regarding the effect on lactogenesis and lactation exist, but level 1 data have not confirmed them. In a RCT comparing early insertion (1–3 days postpartum) to standard insertion ($n = 69$), there was no difference in hours to lactogenesis (mean difference, –1.4 hours, 95% CI –10.6 to 7.7 hours) or lactation failure (risk difference 0.03, 95% CI –0.02 to 0.08) between the two groups [238]. There was no difference in the percentage of women partially or completely breastfeeding at 3 or 6 months. Women with early insertion were more likely to be contracepting at 3 months. A second small RCT ($n = 24$) used deuterium to index milk ingestion among healthy, term newborns of mothers randomized to immediate postpartum ENG implant placement or 6-week placement [239]. Participation was limited to nonobese women who had previously breastfed for at least 3 months. No differences were found in milk intake. Therefore, the implant is also a good contraceptive choice in women breastfeeding.

Postpartum mood and anxiety disorders

Key points

- See Chap. 21 in *Maternal-Fetal Evidence Based Guidelines* for details of management of mood disorders in pregnancy.
- **One in seven women experience perinatal depression**, making it the most common complication of pregnancy.
- Risk factors include **history of maternal anxiety or depression, lack of social support, traumatic birth experience, infant admission to neonatal intensive care, and breastfeeding problems**.
- Routine screening is recommended **at least once during perinatal care**.
- **Positive screens require additional evaluation**. If depression is diagnosed, referral and follow-up to ensure treatment occurs are essential.

Definition

Perinatal depression (PND) is an episode of moderate or severe major depressive disorder (MDD) beginning either during pregnancy or within 4–6 weeks after delivery [240, 241]. Perinatal generalized anxiety disorder (GAD) is episode of GAD that occurs during pregnancy or 4–6 weeks postpartum.

Symptoms/Signs

In addition to typical depression symptoms of sadness, despair, disrupted sleep and appetite, women with postpartum depression often experience prominent anxiety symptoms. The presentation of GAD during postpartum is similar to GAD symptoms outside of pregnancy.

Epidemiology/Incidence

The prevalence of PND is about 15%, affecting one in seven women [242, 243]. The prevalence of GAD during pregnancy is as high as 29% and about 8%–16% in the postpartum period [244, 245]. It should also be noted that much overlap exists between perinatal anxiety and depression, and in many cases women have both.

Risk factors and associations

Risk factors for PND and anxiety include past history of depression or anxiety, life stressors, lack of social support, unintended pregnancy, lower income or education, domestic violence, and smoking. Additional risk factors for postpartum depression include a traumatic birth experience, infant admission to neonatal intensive care, and difficulties breastfeeding [246].

Complications

During the postpartum period, women with depression are at increased risk of maternal suicide, infanticide, and impaired maternal sensitivity and attachment with the infant [247–250]. Women with depression are also less likely to engage in enriching interactions with the child, such as reading or singing [251]. Anxiety symptoms have been associated with increased maternal health care utilization and reduced breastfeeding duration [252, 253].

Prevention

Psychosocial and psychological interventions are effective at reducing postpartum depression. In a large meta-analysis, both **lay and professional prevention interventions** reduced postpartum depression symptoms (average RR 0.78, 95% CI 0.66–0.93). Effective strategies included **postpartum home visits, telephone support, and interpersonal psychotherapy**. Another recent systematic review of mobile interventions (text messages, apps, etc.) in the prenatal and intraparutm peroid found an improvment in the Edinburgh Postnatal Depression Scale (EPDS), but no difference in anxiety or social support with use of these interventions [254].

Screening

Screening for PND should be performed using a validated instrument, such as the EPDS. Despite the high prevalence and substantial morbidity associated with PND, this condition is underrecognized. Major obstetric and pediatric medical organizations recommend routine screening. Although clinicians are generally supportive of screening for PND, these attitudes do not consistently translate into practice. In the United States, less than half of women are formally screened for PND [255]. Consistent with such efforts, less than 50% of PND cases are detected in routine clinical practice, with antenatal recognition rates reported at 41% and postnatal rates ranging from 29% to 43% [256–258]. Screening alone does not ensure treatment: In a recent review, one in five women who screened positive had at least one mental health visit [259]. Patient engagement strategies increased the chance that women with depression symptoms received mental health care.

Treatment

Both psychotherapy and medications are effective for treating PND. For further details on treatment of postpartum depression, see Chap. 21 in *Maternal-Fetal Evidence Based Guidelines*. As with any patient diagnosed with a health condition, women with postpartum depression should be followed up to ensure adequate engagement with treatment and response to therapy. Monitoring patient symptoms is essential, just as measurement of blood pressure is necessary to guide treatment of hypertension. A stepped care approach with serial measurement of symptoms with a tool such as the PHQ-9 to inform depression management can increase the likelihood that patients receive adequate therapy [260].

TABLE 31.11: Postpartum (Including Post-Cesarean) Advice Regarding Common Daily Life Activities

Advice	Evidence	Suggested Recommendations
Lifting	Lifting increases intraabdominal pressure much less than Valsalva, forceful coughing, or rising from supine to erect position.	1. Patients should continue lifting patterns as before pregnancy. 2. Patients need an adequate postoperative analgesic regimen as necessary.
Climbing stairs	Climbing stairs increases intraabdominal pressure much less than Valsalva, forceful coughing, or rising from supine to erect position.	1. Patients should continue climbing stairs as before pregnancy. 2. Patients need an adequate postoperative analgesic regimen as necessary.
Driving	No consistent prospective or retrospective evidence.	1. Patients need an appropriate postoperative analgesic regimen that does not cause a clouded sensorium when driving. 2. Patients may resume driving when comfortable with hand and foot movements required for driving.
Exercise	Limited retrospective and prospective evidence. Forceful coughing increases intra-abdominal pressure as much as jumping jacks.	1. Patients need an appropriate postoperative analgesic regimen as necessary. 2. Patients may resume pre-pregnancy exercise level. 3. Exercise program may need to be tailored for postpartum women. 4. Preprocedure and postprocedure recommendations should be consistent.
Vaginal intercourse	No retrospective or prospective evidence.	1. Women and their partners should make the decision to resume intercourse mutually. 2. Women should use appropriate contraception after childbirth. 3. There is insufficient evidence as to when to resume vaginal intercourse.
Returning to work	No consistent retrospective evidence; no prospective evidence.	1. Women should be encouraged to return to work relatively soon postpregnancy; the usual times in the United States are 6 weeks after vaginal and 8 weeks after cesarean delivery, but these are not based on level 1 evidence. 2. Consider graded return to work, as tolerated.

Source: Adapted from Ref. [266].

Recommendation at discharge

Women report receiving insufficient guidance from their providers about recovery from birth, and feeling unprepared for postpartum concerns is correlated with postpartum mood symptoms [261]. In a randomized trial, **routine provision of guidance about expected symptoms and coping strategies reduced depression symptoms** [262] **and increased breastfeeding duration** [263] among black and Latina women.

There is insufficient evidence for general postpartum advice on common issues such as lifting, climbing stairs, driving, vaginal intercourse, and return to work. Suggestions based on this limited evidence and mostly expert opinions are shown in Table 31.11 [264, 265]. The U.S. Department of Health and Human Services physical activity guidelines for Americans recommends 150 minutes of moderate exercise for women in the postpartum period, recognizing this may not apply to those immediately after surgery and in consultation with the obstetric provider [266, 267]. Additionally, two recent systematic reviews have found physical activity postpartum to be protective against postpartum mood disorders [268, 269].

Women are routinely counseled to defer intercourse until 6 weeks postpartum, but there are no data supporting this recommendation. The risk of bleeding or infection is minimal after 2 weeks, and **guidelines recommend that women resume intercourse when it is comfortable and desired**, once the perineum has healed and bleeding has decreased [270]. More than half of women resume sexual intercourse by 6 weeks postpartum, and 90% resume by 12 weeks postpartum [271]. Multiple prospective cohort studies have attempted to identify risk factors for persistent dyspareunia after delivery. Though data are mixed, Connolly et al., Serati et al., and Barrett et al. each conducted prospective cohort studies, which failed to implicate mode of delivery, episiotomy, and perineal lacerations as risk factors for postpartum dyspareunia [272–274]. Barrett et al. did note that a history of dyspareunia was a major risk factor for postpartum dyspareunia (OR 4.97) [272].

Finally, more recently, moving the postpartum visit from 6 weeks to 4 weeks after delivery has come into vogue in order to ensure the provider closer follow-up. Increased focus on maternal emotional, mental, and physical health during the "fourth trimester" is a topic of ongoing investigation, as such high-level data do not yet exist to guide provider management [275].

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32

THE NEONATE

Laura De Angelis and Luca Ramenghi

Key points

- **Necessary equipment** for neonatal resuscitation must be available at every delivery.
- **Trained personnel in neonatal resuscitation** should be present at every delivery.
- **An infant ≥37 weeks' gestation, crying or breathing, and with good muscle tone does not require resuscitation. Dry the baby, place the baby skin-to-skin with the mother, and cover the baby with dry linen to maintain temperature**.
- Provide routine care; provide warmth; assure open airway; dry; and continuously evaluate color, activity and breathing.
- **Neonatal resuscitation must be started if the neonate does not proceed through a successful transition, regardless of the Apgar score at any time**. Stimulate the baby and open the airway. **Routine suctioning is no longer suggested**. If further resuscitation is needed, it is frequently due to poor respiratory transition and can usually be resolved with positive pressure ventilation.
- **Initial positive pressure ventilation should be performed with room air**. Oxygen should be titrated according to pulse oximetry to achieve the target oxygen saturations (Table 32.2).
- **Low-risk infants** are born ≥37 weeks' gestation and have a birth weight between 2500 and 4200 g, Apgar score of ≥7 at 5 minutes, normal vital signs, and no signs of congenital anomalies or respiratory distress.
- A difficult transition may be anticipated in infants who are at risk and may be due to hypothermia, hypoglycemia, or congenital anomalies.
- **The preterm infant** (especially <35 weeks) is at **greater risk** for complications in the delivery room and in the nursery. With high-risk infants, there must be immediate access to means of establishing **intravenous (IV) access** and **airway positive pressure support**.
- **Late-preterm infants** are those born at $34^{0/7}$–$36^{6/7}$ weeks. While these infants are often the size and weight of term infants, they are physiologically more immature and at higher risk for complications.
- Every nursery should have preexisting **protocols** to institute the best stabilization practices and should have clear statements of what conditions and degrees of illness are appropriate to be admitted to the well-baby nursery.
- **The majority of cases of cerebral palsy do *not* result from isolated intrapartum asphyxia with resultant hypoxemia and organ damage**.
- The health benefits of circumcision include prevention of urinary tract infections, penile cancer, and transmission of sexually transmitted infections. In the United States, the **benefits are not considered great enough for universal male circumcision**.

Delivery room management

For management of the normal neonate, see also Chap. 10. For management specific to meconium, see Chap. 25. The perinatal period is the riskiest time in a child's life [1–3]. Every newborn infant has the right to receive a resuscitation performed at a high level of competence. A competent resuscitation means that proper equipment and well-trained personnel must attend every delivery. In addition, in case of prenatal and/or intrapartum conditions which may impair neonatal transition, the presence of an experienced neonatal resuscitation team is required. **Necessary equipment** is shown in Table 32.1.

Initial steps of neonatal resuscitation

Due to the complex cardiorespiratory transition occurring at birth, many newborn infants will experience apnea or bradycardia requiring stimulation, airway suctioning, and respiratory support. The need for advanced resuscitation or medications is rare.

The first steps of neonatal resuscitation include the following:

1. **Thermal management:** Placing the infant under a preheated radiant warmer, gently drying, and frequently replacing wet blankets with dry ones.
2. **Opening the airway:** Positioning the infant supine with the head in midline position and a mild neck extension. As nasopharyngeal suctioning may lead to vagal stimulation and subsequent bradycardia, airway suctioning should be reserved for infants with airway obstruction or needing ventilatory support.
3. **Tactile stimulation:** Gently rubbing the baby's back, trunk, or extremities may occasionally be necessary to stimulate the baby to breathe, thus increasing heart rate. In case of persistent apnea, positive pressure ventilation should be promptly initiated.
4. **Oxygen delivery:** Newborn infants usually have low levels of blood oxygen saturation during the first minutes of life. Normal preductal oxygen saturations within the first 10 minutes after birth are shown in Table 32.2 (preductal pulse oximetry is measured at the upper right limb). As both insufficient and excessive oxygen may be harmful to the newborn infant, oxygen administration should be carefully considered based on the infant's condition and oxygen saturation levels. Resuscitation of infants with a gestational age ≥34 weeks should start using room air, and oxygen concentration should be titrated according to infant response.

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TABLE 32.1: Necessary Equipment for Neonatal Resuscitation in the Delivery Room

1. Suction equipment
   a. Bulb syringe
   b. Mechanical suction and tubing
   c. Suction catheters of various sizes (recommended: 5 or 6, 8, 10, and 12 or 14 Fr)
   d. Feeding tubes (8 Fr with 20-mL syringe)
   e. Meconium aspirator
2. Bag mask equipment
   a. Device for delivering PPV as neonatal resuscitation bag with manometer or T-piece resuscitator
   b. Face masks in newborn and premature sizes
   c. Oxygen and compressed air sources
   d. Oxygen blender with flow meter and tubing
3. Intubation equipment
   a. Laryngoscope with 00, 0, and 1 blades (for preterm and term infants)
   b. Endotracheal tubes (ETTs) (2.5–4.0 mm)
   c. Stylet
   d. CO_2 detector
   e. Laryngeal mask airway (for use in the case of a difficult intubation)
4. Other equipment
   a. Clock (Apgar timer)
   b. Alcohol
   c. Stethoscope
   d. Gloves
   e. Scissors
   f. Tape (for securing ETT and lines)
   g. Stopcocks
   h. Syringes (1–20 mL)
   i. Umbilical artery and vein tray with catheters (3.5 and 5 Fr)
   j. Warmer
   k. Needles (25, 21, and 18 gauge)
   l. Pulse oximeter
   m. Food-grade plastic wrap
   n. Transporter

Abbreviations: PPV, positive pressure ventilation; CO_2, carbon dioxide.

Delivery room resuscitation

The need to start neonatal resuscitation is based on the evaluation of breathing efforts, heart rate, and skin color. The algorithm in Figure 32.1 may be used as a guideline for the resuscitation of a term or late preterm infant. **The Apgar score** (outlined in Table 32.3) **is a useful tool for communicating the infant's adaptation but should not be used to guide resuscitation**.

In case of persistent apnea and/or bradycardia after the first steps of neonatal resuscitation, positive pressure ventilation should be promptly initiated.

Chest compressions may be necessary if bradycardia (heart rate less than 60 beats per minute) persists after breathing is adequately supported. Rarely, medications are necessary and should be readily available (refer to Table 32.4 for the full list). The most commonly used are as follows:

1. Epinephrine 1:10,000: 0.1–0.3 mL/kg IV or via endotracheal tube given rapidly.
2. Volume expanders: 0.9% saline, Ringer's lactate, or whole blood. Dose is 10 mL/kg IV over 5–10 minutes.
3. Sodium bicarbonate 0.5 mEq/mL: 2 mEq/kg IV given over at least 2 minutes.
4. Naloxone hydrochloride 1.0 mg/mL: 0.1 mg/kg IV or IM given rapidly.

TABLE 32.2: Goal Preductal (Right-Hand) Oxygen Saturations after Birth

1 minute	60%–65%
2 minutes	65%–70%
3 minutes	70%–75%
4 minutes	75%–80%
5 minutes	80%–85%
10 minutes	85%–95%

TABLE 32.3: Apgar Score

	0	1	2
Color	Blue/pale	Acrocyanosis	Pink
Heart rate	Absent	<100 per minute	>100 per minute
Reflex/irritability	No response	Grimace	Cry/active withdrawal
Tone	Limp	Some flexion	Active motion
Respirations	Absent	Weak cry/ hypoventilation	Good/crying

Withholding or discontinuing neonatal resuscitation

Resuscitation should always be considered in cases with high rates of survival and acceptable rates of morbidity. There are conditions associated with high mortality and poor outcomes in which withholding resuscitation may be appropriate, particularly when there has been an opportunity for parental agreement. In cases of uncertain prognosis, every single case should be addressed on an individual basis with a consistent and coordinated approach by both the obstetric and neonatology teams according to the parents' desire. Cases in which withholding of resuscitation should be considered are the following:

- Gestational age ≤23 weeks
- Birth weight ≤400 g
- Anencephaly
- Some chromosomal abnormalities (e.g. trisomy 13)

It is appropriate to consider the interruption of resuscitation in infants who are born without a detectable heart rate, if the heart rate remains undetectable at 10 minutes of life.

Altered birth transition

The transition to extrauterine life generally occurs over the first hours after birth. Delay in transition can occur for many reasons—the most common are listed in Table 32.5.

In infants with signs of poor transition (tachypnea, cyanosis, mottled skin or pallor, tremors, and/or jitteriness), additional measurements of the child's vital signs should be considered. These include temperature, blood glucose, and arterial blood saturation (by pulse oximetry or blood gas analysis).

TABLE 32.4: Medications Required for Resuscitation

1. Epinephrine 1:10,000 (0.1 mg/mL)
2. Crystalloid fluids (normal saline or Ringer lactate)
3. Sodium bicarbonate 4.2% (5 mEq/10 mL)
4. Dextrose 10%
5. Normal saline flushes
6. Naloxone hydrochloride

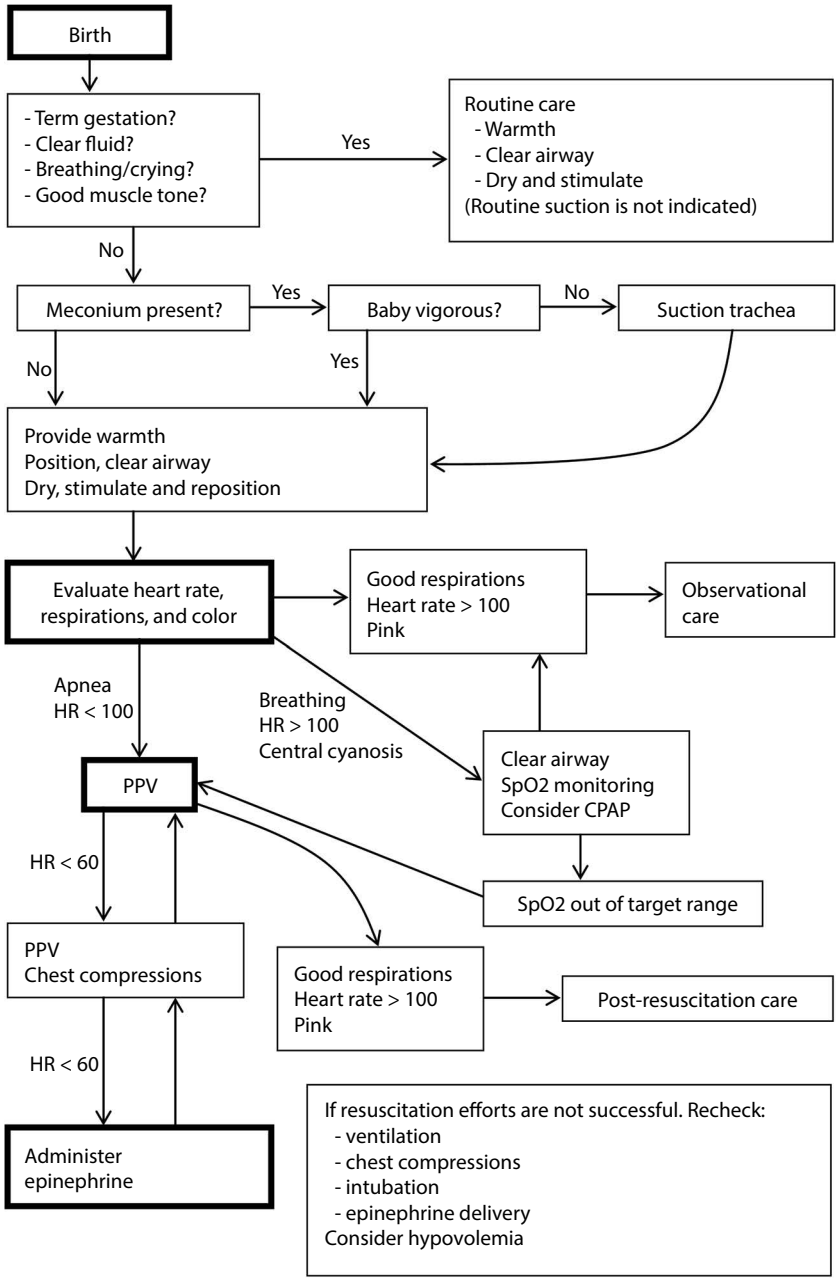


FIGURE 32.1 Neonatal Resuscitation Program (NRP): guidelines for resuscitation. *Abbreviations.* PPV, positive pressure ventilation; HR, heart rate.

Hypoglycemia

Neonatal hypoglycemia is a common condition, often associated with prenatal and perinatal risk factors (e.g. maternal diabetes, large for gestational age [LGA], small for gestational age [SGA], fetal growth restriction [FGR], prematurity), while rarely it may be caused by congenital abnormalities of glucose metabolism. The exact threshold to define hypoglycemia still remains unclear, but according to the 2011 report by the Committee of Fetus and Newborn of the American Academy of Pediatrics (AAP), hypoglycemia is defined as a blood glucose <40 mg/dL in the first 4 hours of life and <45 mg/dL from 4 to 24 hours of life in high-risk neonates [4].

All *symptomatic* and *asymptomatic high-risk infants* should be regularly checked for blood glucose levels in the first 24 hours of life. Routine screening of blood glucose is not needed in asymptomatic term newborns who lack the risk factors for hypoglycemia. The diagnostic and treatment algorithm proposed by the AAP is presented in Table 32.6. In case of neonatal hypoglycemia, treatment should be promptly started. In case of prolonged (beyond the first 48–72 hours of life) and persistent low blood glucose levels, a congenital hypoglycemia disorder must be suspected, and the neonate should be transferred to a third level of care unit. Although persistent and prolonged neonatal hypoglycemia may result in brain injury and adverse long-term

TABLE 32.5: Factors Associated with Delayed Transition

Infant
Hypothermia
Hypoglycemia
Delayed pulmonary fluid absorption
Preterm birth (<37 weeks)
Multiple births
Small or large for gestational age (<2500 g or >4200 g)
Postterm birth (≥42 weeks)
Meconium-stained amniotic fluid
Low Apgar scores (<7 at 5 minutes)
Congenital problems (i.e. chromosomal abnormalities and malformations)
Infection
Mother
Diabetes
Hypertension or preeclampsia
Tocolysis
Licit or illicit drug use
No prenatal care
Maternal age >35 years

neurodevelopmental outcomes, uncertainty exists about the glucose threshold and the duration of hypoglycemia associated with the risk of adverse neurologic consequences, especially in cases of asymptomatic infants [5].

Meconium aspiration syndrome

Meconium is the first intestinal discharge of newborn infants, normally expelled within the first 24 hours from birth. It is a thick, dark-greenish mass composed of substances ingested during the intrauterine life, including intestinal epithelial cells, lanugo, mucus, amniotic fluid, bile, and water. Intrauterine or intrapartum stress may cause the meconium to be expelled before birth. Meconium-stained fluid is present in 8%–20% of deliveries, and it is almost exclusively found in term or postterm infants. Meconium aspiration syndrome occurs intrapartum when a newborn infant breathes a mixture of meconium or meconium-stained amniotic fluid. The presence of meconium in the lungs may cause bronchial obstruction and lung inflammation, leading to a moderate to severe respiratory insufficiency. The treatment is based on the infant's conditions at birth. If the baby is vigorous and cries immediately, routine neonatal care should be administered. If the infant is floppy or lethargic, prompt intubation and direct suction of the trachea are warranted. Intrapartum endotracheal intubation and tracheal suction before the shoulder's delivery is no longer recommended in case of meconium-stained amniotic fluid (see Chap. 25) [6].

Respiratory distress syndrome and other causes of respiratory insufficiency

Respiratory distress syndrome is the most common respiratory disorder in preterm infants, primarily caused by inadequate pulmonary surfactant production. Pulmonary surfactant is composed of a mixture of phospholipids and specific proteins, and its reduction/absence in the alveolar bed leads to compromised lung compliance and a significant tendency to atelectasis with resultant hypoxemia and hypercarbia.

Signs of respiratory distress syndrome appear within the first hours from birth and include tachypnea (>60 breaths per minute), intercostal and subcostal retractions, nasal flaring, grunting, and cyanosis. A progressive worsening for 48–72 hours is often followed by a slow recovery. Other clinical features include hypotension, acidosis, and hyperkalemia. Treatment consists of exogenous surfactant administration and respiratory support as needed. In the last three decades, introduction of antenatal steroids and exogenous surfactant has greatly improved neonatal outcomes [7].

In term neonates, signs of respiratory distress may be caused by a number of conditions, including congenital lung anomalies, infections, pneumothorax, airway malformations (e.g. choanal atresia, tracheal-esophageal fistula), cardiovascular system anomalies (e.g. congenital heart disease, congestive heart failure, pulmonary hypertension), neurologic anomalies (e.g. central nervous system infections, hypoxic injury, hydrocephalus), blood dyscrasia (anemia or polycythemia), or exposure to maternal drugs. Specific diagnostic tests and treatments should address the underlying etiology.

Transient tachypnea of the newborn

Transient tachypnea of the newborn (TTN) is a benign, self-limiting condition affecting term or near-term infants soon after birth, and it is characterized by the development of tachypnea (60–120 breaths per minute) associated with other signs of mild to moderate respiratory distress, including nasal flaring, grunting, and retractions. Risk factors for TTN include cesarean delivery, precipitous delivery, fetal polycythemia, and maternal diabetes. This condition is caused by a delayed resorption of fetal lung fluid. Oxygen administration and support therapy are usually enough to resolve this condition, but severe cases may require continuous positive airway pressure (CPAP). If the infant's condition does not

TABLE 32.6: Hypoglycemia Management in Infants with Gestational Age ≥34 Weeks with Known Risk Factors for Hypoglycemia[a] According to the AAP

Symptomatic[b] Infant with BG <40 mg/dL	Asymptomatic Infant (Birth to 4 hours of Age)	Asymptomatic (4–24 hours of life)
Use IV glucose (2 mL/kg dextrose 10% IV and/or continuous infusion of dextrose 10% at 80–100 mL/kg per day). Maintain BG between 40 and 50 mg/dL.	Initial feed within 1 hr after birth. BG screening 30 min after the first feed. If BG is <25 mg/dL, feed and recheck in 1 hr. If BG persists <25 mg/dL, start IV dextrose, if BG is 25–40 mg/dL, refeed and use IV dextrose as needed.	Continue feeds every 2–3 hours. BG screening before each feed. If BG <35 mg/dL, feed and recheck in 1 hr. If BG persists <35 mg/dL, start IV dextrose, if BG is 35–45 mg/dL, refeed and use IV dextrose as needed.
TARGET GLUCOSE ≥45 mg/dL PRIOR TO ROUTINE FEEDINGS		

[a] Risk factors for hypoglycemia: Maternal diabetes, large-for-gestational-age and small-for-gestational-age infants, prematurity.

[b] Symptomatic hypoglycemia: Irritability, tremors, jitteriness, exaggerated reflexes, high-pitched cry, seizures, lethargy, floppiness, cyanosis, apnea, and poor feeding.

Abbreviations: BG, blood glucose; IV, intravenously; hr, hour; min, minute.

quickly resolve, other diagnoses should be ruled out, including early-onset sepsis, pulmonary hypertension, congenital heart disease, pneumonia, pneumothorax, central hyperventilation, and congenital malformations.

Common malformations affecting transition

Some congenital abnormalities may affect neonatal transition, thus requiring resuscitation maneuvers in the delivery room. Common malformations with stabilization procedures before transferring the infant to a tertiary care center are the following:

1. Choanal atresia (blockage of the nasal passageway): Secure an oral airway.
2. Pierre-Robin sequence (small mandible with relatively large tongue): Secure an oral airway, consider intubation if inadequate.
3. Congenital diaphragmatic hernia: Insertion of a nasogastric tube to decompress the stomach and intubation of the airway are required immediately after birth.
4. Abdominal wall defects (omphalocele and gastroschisis): Cover the defect with a silo as soon as possible after birth. Gastroschisis may require prompt surgical correction; therefore, a surgical team should attend the delivery.
5. Neural tube defects: The optimal management is controversial, but the goal is to keep the area moist and free of contamination. The area may be covered with sterile plastic wrap, or the baby may be placed in a sterile plastic bag to just above the lesion.

Type of nursery: Low- versus elevated-risk neonates

Minimal intervention is needed for healthy infants following an uncomplicated delivery. Therefore, it is important to distinguish which infants are at low risk and can be admitted to the nursery and which infants are at high risk and require further evaluation and treatment.

Low-risk infants

These infants can be admitted without pediatric specialist consultation. Low-risk infants are ≥37 weeks of gestation and have all of the following characteristics: Birth weight between 2200 and 4200 g, Apgar scores of ≥7 at 5 minutes, normal vital signs, and no signs of congenital anomalies or respiratory distress.

Elevated-risk infants

Elevated-risk infants require pediatric specialist consultation before being admitted to the nursery. The following conditions should be evaluated: Infants at risk for neonatal abstinence syndrome, suspected sepsis, rupture of membranes longer than 16 hours, maternal vaginal/rectal swab positive for group B streptococcus (GBS) inadequately treated with maternal prophylaxis before birth, maternal temperature higher than 100.4°F (38°C) within 24 hours from delivery, infants of diabetic mothers, infants born outside the hospital, infants of uncertain gestation, gestational age <37 weeks, and birth weight <2200 g or >4200 g.

Late-preterm infants (gestational age 34^{+0}–36^{+6}) weeks are often the size of a term infant but have an increased risk of hypothermia, hypoglycemia, dehydration, and poor feeding. The AAP recommends that late-preterm infants should receive special attention prior to discharge and close outpatient follow-up in order to prevent rehospitalization.

Care of the well newborn after L&D care

All infants must be observed until they complete transition to extrauterine life. A skilled staff member must assess vital signs every 30 minutes for at least 2 hours from birth and observe that the newborn is completely stable on its own. Completion of transition includes thermostability, respiratory rate less than 60 breaths per minute, heart rate greater than 100 beats per minute, and good muscle tone and sucking reflex.

Newborn screening

Newborn screening identifies conditions that can affect a child's long-term health or survival. Early detection, diagnosis, and intervention can prevent death or disability and enable children to reach their full potential. The newborn screening program varies across countries and should be performed after 24 hours from birth (a list of suggested tests is shown in Table 32.7) [8–10].

Circumcision

Over 60% of the world male population is *not* circumcised, as this procedure is elective and tied in the past to religious practices and not scientific benefit or considerations. The health benefits to circumcision include prevention of urinary tract infection (from approximately 7–14/1000 to 1–2/1,000), penile cancer (about 1000 circumcisions needed to prevent one penile cancer), and transmission of sexually transmitted infections (about 15% decrease in lifetime HIV risk). In the United States, the benefits are not considered great enough to offer universal male circumcision. The AAP recommends that circumcision be chosen by parents after having received all the information about the risks and benefits associated with the procedure [11]. The World Health Organization suggests circumcision as a means to reduce the risk of acquiring HIV infection in high-risk populations [12]. Complications of the procedure have been reported to range from 0.3% to 20% and include excessive bleeding (1/100–1/1,000), infection (1–6/10,000), and penile injury (4/10,000).

Circumcision should be delayed in the following cases:

- Suspected sepsis or bacteremia
- Family history of bleeding problems (until the child is fully assessed by a hematologist)
- Genital abnormalities, including ambiguous genitalia, genital tract anomalies (micropenis hypospadias, epispadias, or chordae)

Performing a circumcision

Prior to circumcision, infants should have completed transition, voided at least once, and been fasting for 1 hour prior to the procedure. Pain control should be utilized and can include dorsal penile nerve block, topical analgesic, or subcutaneous ring block. Sucrose solution and pacifier sucking may be used to reduce pain perception. Techniques for circumcision include the Mogen, Plastibell, and Gomco. After the procedure, breastfeeding or bottle feeding is an excellent pain control method. If needed, acetaminophen (12–15 mg/kg/dose) may be administered. A gauze wrap is no longer recommended after the procedure. The area should be kept clean with plain water and covered with lubricant for up to 1 week until completely healed. The parents should be told to expect a white-yellow discharge for 5–7 days.

TABLE 32.7: Disorders Recommended by the American College of Medical Genetics Task Force for Inclusion in Newborn Screening[a]

Disorders of Organic Acid Metabolism
Isovaleric acidemia
Glutaric aciduria type 1
3-hydroxy-3-methylglutaric aciduria
Multiple carboxylase deficiency
Methylmalonic acidemia, mutase deficiency form
3-methylcrotonyl-CoA carboxylase deficiency
Methylmalonic acidemia, Cb1 A and Cb1 B forms
Propionic acidemia
Beta-ketothiolase deficiency
Disorders of Fatty Acid Metabolism
Medium-chain acyl-CoA dehydrogenase deficiency
Very long-chain acyl-CoA dehydrogenase deficiency
Long-chain L-3-hydroxy acyl-CoA dehydrogenase deficiency
Trifunctional protein deficiency
Carnitine uptake defect
Disorders of Amino Acid Metabolism
Phenylketonuria
Maple syrup urine disease
Homocystinuria
Citrullinemia
Argininosuccinic acidemia
Tyrosinemia type 1
Hemoglobinopathies
Sickle cell anemia
Hemoglobin S-beta-thalassemia
Hemoglobin sickle cell disease
Other Disorders
Congenital hypothyroidism
Biotinidase deficiency
Congenital adrenal hyperplasia
Galactosemia
Hearing deficiency
Cystic fibrosis

[a] The American College of Medical Genetics task force also recommends reporting an additional 25 disorders ("secondary targets") that can be detected through screening but that do not meet the criteria for primary disorders [6]. At this time, there is state-to-state variation in newborn screening; a list of the disorders that are screened for by each state is available at http://genes-r-us.uthscsa.edu.

Abbreviations: CoA, coenzyme A; Cb1 A, cobalamin A; Cb1 B, cobalamin B.

Care of the preterm infant

Infants born at gestational age <36 weeks are at high risk of preterm-related complications. If a preterm delivery is anticipated, the delivery should be attended by a team of neonatal intensive care unit (NICU) personnel (physician, nurse, and respiratory therapist). Management of the infant includes accentuated attention to drying and maintaining thermal stability and close observation of blood glucose, fluid requirements, and respiratory function. Infants with a gestational <29 weeks should be wrapped in a polyethylene bag in order to prevent evaporative heat loss. In high-risk infants, the prophylactic placement of an umbilical venous line should be considered. In addition, early institution of positive airway pressure support may be necessary to prevent respiratory failure, facilitating lung recruitment. The presence of proper equipment and trained personnel for neonatal stabilization and transport will optimize survival.

TABLE 32.8: Survival to Discharge at Very Early (22–28 Weeks) Gestational Ages

Gestational Age (weeks)	Survival to Discharge (all)	Survival to Discharge without Major Morbidities[a]
22	9%	0%
23	33%	0.75%
24	65%	6%
25	81%	20%
26	87%	26%
27	94%	47%
28	94%	56%

Source: Data from Ref. 11.

[a] No necrotizing enterocolitis, sepsis, meningitis, bronchopulmonary dysplasia, severe intraventricular hemorrhage, periventricular leukomalacia, or retinopathy of prematurity grade 3 or higher.

A detailed review of the topic of neonatal care of the preterm infant is beyond the scope of this book. Table 32.8 shows recent data on survival rates at early gestational ages (22–28 weeks) that may be considered for prenatal counseling [13].

Neonatal encephalopathy and cerebral palsy

Neonatal encephalopathy

Neonatal encephalopathy is defined as a pathologic neurobehavioral state with altered level of consciousness and other signs of neurologic and motor dysfunction. It is caused by many conditions, both transitory (e.g. hypoglycemia, maternal drugs) and permanent (e.g. hypoxic-ischemic encephalopathy, neonatal stroke), which may result in a permanent neurologic impairment [14, 15].

Hypoxic-ischemic encephalopathy

Hypoxic-ischemic encephalopathy (HIE) is a neonatal encephalopathy caused by altered gas exchange with hypoxia and/or a reduction in blood flow occurring in the perinatal period. A comprehensive assessment of neonatal status, maternal history, obstetric antecedents, intrapartum factors, and placental pathology is required in order to determine if hypoxic-ischemia occurred in close temporal proximity to labor and delivery. The following conditions increase the likelihood that hypoxia-ischemia played a role in causing neonatal encephalopathy [16]:

- Apgar score ≤6 at 5 minutes (a 5 minute-Apgar score ≥7 renders HIE unlikely)
- Need for resuscitation with ventilatory support for longer than 10 minutes and/or fetal umbilical artery pH <7.0 or base deficit ≥12 mmol/L
- Magnetic resonance (MR) imaging or MR spectroscopy showing hypoxic-ischemic pattern of cerebral imaging (deep nuclear gray matter or watershed cortical injury)
- Multisystemic organ failure
- Sentinel hypoxic/ischemic event immediately before or during labor and delivery (uterine rupture, umbilical cord prolapse, maternal cardiovascular collapse, fetal exsanguination)

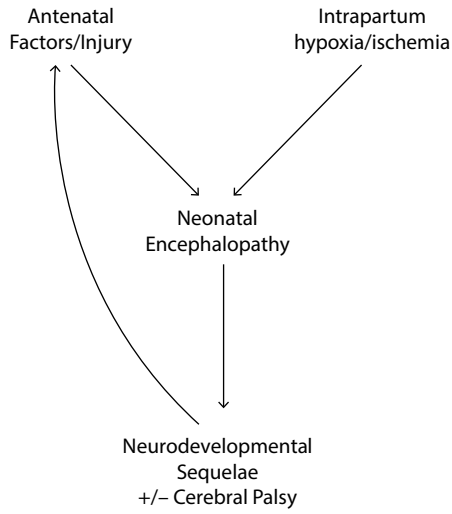
- Fetal heart rate pattern suggesting an acute peripartum or intrapartum event
- Lack of other contributing factors such as infection, feto-maternal hemorrhage, or chronic placental lesions
- Development of spastic quadriplegia or dyskinetic cerebral palsy (other types of cerebral palsy are less likely to be associated with acute intrapartum hypoxic-ischemic events)

Therapeutic hypothermia is recommended for infants ≥35 weeks' gestation with evidence of moderate-to-severe HIE. Several randomized controlled trials have demonstrated lower mortality and an improved neurodevelopmental outcome at 18 months. Therapeutic hypothermia should be performed in a third-level neonatal care center [17].

It is important when considering fetal heart rate to distinguish between patients who present with an abnormal tracing and those who develop an abnormal tracing during delivery. A heart rate pattern that converts from a category I tracing to a category III tracing is suggestive of a hypoxic-ischemic event.

HIE can be a result of antenatal factors alone, intrapartum factors alone, or both in combination. Around 25% of surviving infants will have long-term neurologic sequelae [15].

The usual progression of events is as follows:



Timing of neonatal encephalopathy

Estimating the time when neonatal encephalopathy occurred is extremely difficult. Some studies [12] reported the incidence of risk factors related to this condition:

- 69%: Only antepartum risk factors
- 25%: Both antepartum risk factors and evidence for intrapartum hypoxia
- 4%: Intrapartum hypoxia without antepartum risk factors
- 2%: No recognized risk factors

Therefore, the incidence of neonatal encephalopathy attributed to intrapartum hypoxia in the absence of other preconception or antepartum abnormalities is about 1.6/10,000 infants [14, 15].

Cerebral palsy

Cerebral palsy is a chronic neuromuscular disability affecting 2/1000 live births, characterized by aberrant control of movement or posture, appearing early in life and not as a result of a recognized progressive disease.

Prevention is elusive. Most cases of cerebral palsy do *not* result from isolated intrapartum asphyxia with resultant hypoxemia and organ damage [15]. Risk factors associated with cerebral palsy and/or neonatal encephalopathy are as follows:

- Increasing maternal age
- Family history of seizures or neurologic disease
- Maternal history of infertility treatment or previous neonatal death
- Severe preeclampsia
- FGR
- Congenital malformations or genetic abnormalities
- Autoimmune and coagulation disorders
- Infections

Apgar scores and cerebral palsy

0–3 at 5 minutes:	0.3–1.0% of babies with cerebral palsy
0–3 at 10 minutes:	10% of babies with cerebral palsy (but rates drop to 5% if scores improve at 15 and 20 minutes)
<3 at 15 minutes:	53% mortality, 36% of survivors with cerebral palsy
<3 at 20 minutes:	60% mortality, 57% of survivors with cerebral palsy

Seventy-five percent of children with **cerebral palsy** had **normal Apgar scores** at birth [12].

Criticism of the management of labor should not be confused with cerebral palsy causation because the two often may not be linked.

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33

THE ADNEXAL MASS

Connie D. Cao and Norman G. Rosenblum

Key points

- There are **no randomized trials** on interventions for adnexal masses in pregnancy.
- **Ultrasound**, with transvaginal and Doppler capabilities, **is the mainstay of diagnosis and prognosis**.
- **Most adnexal masses are simple cysts and will resolve**. The **most common** persistent adnexal mass in pregnancy is a **mature teratoma**.
- **The risk of an adnexal mass representing malignancy is 0.93%–4.5%**. Half of all ovarian cancers in pregnancy are epithelial, and two-thirds of those are of low malignant potential.
- For a **suspicious adnexal mass in pregnancy**, early preoperative **consultation with a gynecologic oncologist, anesthesiologist, and neonatologist** is recommended.
- **Complications** related to the persistent adnexal mass in gravid patients may include **severe pain** (5%–26%), **ovarian torsion** (7%–12%), **cyst rupture** (9%), **pelvic impaction and obstruction of labor** (17%), and **ovarian cancer** (<5%).
- **CA-125 is nonspecific and can be elevated simply due to pregnancy**; however, between 15 weeks and delivery, levels between 1000 and 10,000 units/mL cannot be attributed to pregnancy alone.
- Most adnexal masses can be safely followed with **serial ultrasounds**. Management in the **first trimester** is almost uniformly **expectant** unless the clinical presentation is acute or malignancy is suspected. Although there are no strict guidelines, **surgery** is appropriate for adnexal masses that persist in the second trimester and are **≥10 cm, symptomatic, or have sonographic features concerning for malignancy** (i.e. complex masses consisting of both solid and cystic components with nodularity, thick septations, irregular borders, irregular echoes, or papillary projections).
- When necessary and feasible, **surgery should be scheduled in the early second trimester** (e.g. 14–18 weeks) when organogenesis is complete, most spontaneous abortions have occurred, and the risk for preterm delivery is low.
- **Intervention** should be considered **at any point** in gestation **if a mass is complex or suspicious for malignancy and increases in size**. If a suspicious **adnexal mass** is **identified incidentally at the time of cesarean section**, it should be **removed** and not simply aspirated.
- If a **malignant neoplasm of the ovary** is found at the time of exploration, the surgeon should consult a gynecologic oncologist to properly **stage the disease**. For more advanced ovarian cancer, the degree of cytoreductive surgery and the timing of initiation of chemotherapy will depend on fetal viability and maternal choice.

Definition/Diagnosis

An adnexal mass is any mass in the ovary or tube or attached to them (adnexa). There is an increase in the detection of asymptomatic adnexal masses in pregnancy due to the increase in prenatal ultrasounds. The vast majority (>90%) of adnexal masses in pregnancy are ovarian. Most are benign simple cysts under 5 cm. The diagnosis is most accurately made **by ultrasound**, even if it is possible to diagnose an adnexal mass by bimanual physical exam. A persistent adnexal mass is one that does not resolve by the second trimester.

Epidemiology/Incidence

In earlier studies, approximately 1%–4% of women were diagnosed with an adnexal mass in pregnancy with persistence of only 1 in 200 to 1 in 600 into the second trimester [1, 2]. A recent study looked at ultrasounds of asymptomatic women during nuchal translucency evaluation (11–14 weeks) and found an **incidence of 25%, with 85% of those resolving during the pregnancy without intervention** [3]. This dramatic increase in incidence is likely secondary to the early prevalence of functional cysts that spontaneously resolve during the pregnancy. A separate study looking at over 7.7 million deliveries from 2003 to 2011 showed the incidence of ovarian masses to be 0.25% at the time of delivery [4].

The majority of the adnexal masses are simple cysts such as corpus luteal or other functional cysts. **Most of them** (up to 90%), **when identified during pregnancy, will spontaneously regress prior to the second trimester**. Characteristics found to be predictive of persistence of adnexal mass in pregnancy include complex sonographic appearance and larger size of the mass [5]. Two adnexal conditions are specifically associated with pregnancy and spontaneously regress in the postpartum period requiring no further treatment: Luteomas of pregnancy and theca lutein cysts. About **0.93%–4.5% of adnexal masses found in pregnancy are malignant ovarian tumors** [6, 7]. The incidence of ovarian cancer in pregnancy is rare: ˜1 per 56,000 deliveries [6]. It is the fifth most common cancer diagnosed in pregnancy and the second most common gynecologic cancer, following cervical cancer [4, 8].

Classification

It is important to generate a differential diagnosis guided by ultrasound characteristics (Figure 33.1) of the mass and clinical presentation. The differential includes functional cysts, cystadenomas, corpus luteum, teratomas, endometriomas, theca lutein cysts, and malignant ovarian cancers (Table 33.1). **Among persistent adnexal masses** diagnosed during pregnancy (age group 18–35 years), **mature teratomas are the most common** (Table 33.2). Of note, ovarian malignancies are more commonly germ cell tumors among pregnant women (30%) compared to the general population (<5%), likely reflecting the younger age of women in the former group [6, 9].

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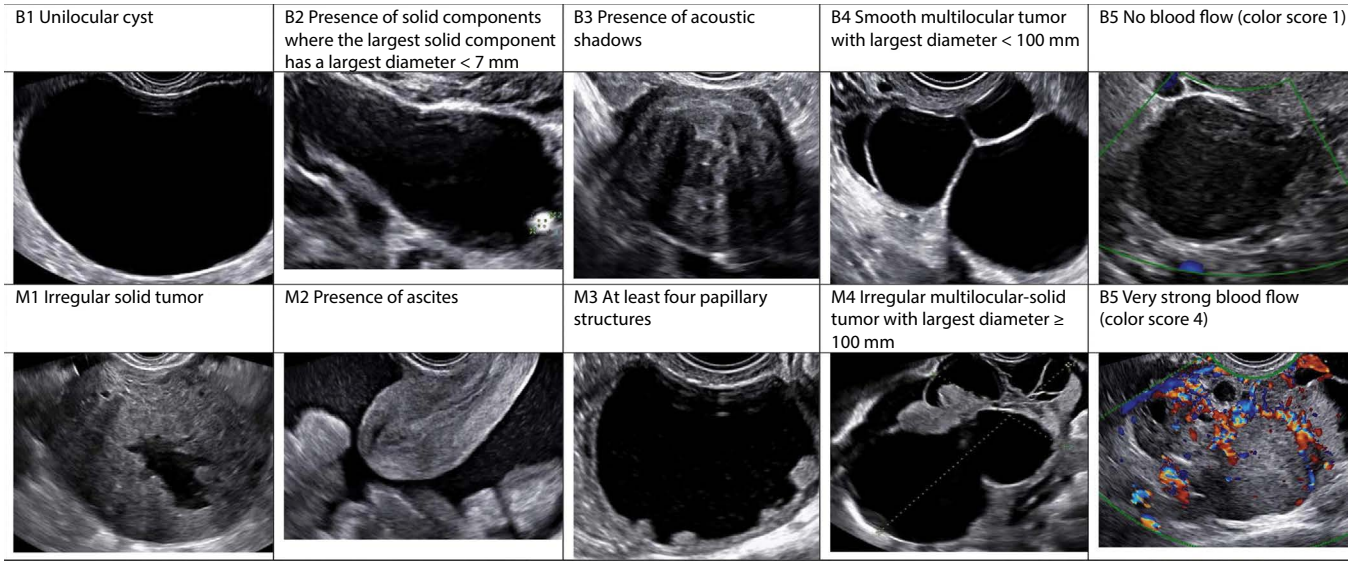


FIGURE 33.1 Simple rules: Sonographic images for features of ovarian masses. (From Abramowicz JS, Timmerman D. Ovarian mass-differentiating benign from malignant: The value of the International Ovarian Tumor Analysis ultrasound rules. *Am J Obstet Gynecol*. 2017;217(6):652–660. [III] Ref. [19], with permission.)

Risk factors/Associations

Maternal age is a risk factor for malignancy, but ovarian malignancies can occur at any reproductive age. Sonographic scoring systems have been proposed to optimize ultrasound examination as a diagnostic test for ovarian malignancies, but these scoring systems require validation in pregnancy [10]. One study among nonpregnant women found several factors associated with an increased risk of malignancy: **Age >55, postmenopausal status, weight ≤200 lb, complex or solid morphology (versus cystic), presence of ascites, tumor bilaterality, tumor diameter >10 cm, and CA-125 ≥35**. None of the cystic tumors in that study were malignant [11]. Furthermore, a large study in postmenopausal women with unilocular cystic masses <10 cm found none to have malignancy [12]. **Assisted reproductive technologies** increase the incidence of enlarged ovaries and cysts, and therefore adnexal masses.

Complications

Complications related to the persistent adnexal mass in gravid patients include **severe pain** (26%), **ovarian torsion** (1%–22%), **cyst rupture** (0%–9%), **pelvic impaction and obstruction of labor** (2%–17%), and **ovarian cancer** (<5%) [13–16]. Ovarian torsion, the most common significant complication in pregnancy, occurs usually in less than 15% of the cases and is most common in adnexal masses with sizes between 6 and 8 cm. Approximately 60% of torsions occur between 10 and 17 weeks of gestation, and less than 6% occur after 20 weeks of gestation [15]. Of the ovarian malignancies diagnosed in pregnancy, the majority represent

TABLE 33.1: Differential Diagnosis for Adnexal Masses in Pregnancy

Benign	Malignant
Corpus luteum	Germ cell tumor (e.g. dysgerminoma)
Simple cyst	Cystadenocarcinoma
Hemorrhagic cyst	Borderline tumors of low malignant potential
Benign mature cystic teratoma (dermoid)	Sex-cord stromal tumor (e.g. granulosa cell or Sertoli-Leydig cell tumors)
Endometrioma	Metastatic cancer to ovary (Krukenberg)
Myoma (pedunculated)	
Luteoma	
Hyperstimulated ovary	
Hydrosalpinx	
Theca-lutein cyst/Hyperreactio luteinalis	
Ectopic/heterotopic pregnancy	
Cystadenoma	
Peritoneal cyst	
Paraovarian/paratubal cyst	

Source: From McMinn E, Schwartz N. Adnexal masses in pregnancy. Clin Obstet Gynecol. 2020;63(2):392–404. [Review; III] Ref. [36], with permission.

TABLE 33.2: Frequency of Adnexal Masses Diagnosed in Pregnancy

Diagnosis	Percentage
Benign Mass (95%)	
Dermoid	37
Cystadenoma	24
Corpus luteum	17
Endometrioma	5
Leiomyoma	5
Other (paraovarian, luteoma, theca-lutein)	12
Malignant (5%)	
Epithelial	50
Low malignant potential	66
Invasive	33
Germ cell tumor	30
Sex-cord stromal tumor	20

Source: From Horowitz NS. Management of adnexal masses in pregnancy. Clin Obstet Gynecol. 2011;54(4):519–527. [Review; III] Ref. [9], with permission.

epithelial tumors of low malignant potential, germ cell tumors, or sex cord stromal tumors [9].

Management

Principles

No randomized trials are available to guide the management of adnexal masses in pregnancy. **As about 90% of these masses resolve, expectant management with serial ultrasounds is usually appropriate in the vast majority of clinical situations** [17]. If malignancy is suspected, the best gestational age for surgery is about 16–18 weeks, as the risk of loss is lowest [9].

Workup

Ultrasound

Highly skilled ultrasonographers may be able to accurately diagnose complications of adnexal masses in pregnancy (e.g. cancer and torsion) without surgical intervention. Suspicious characteristics of an adnexal mass include **complex** masses consisting of both **solid and cystic components** with nodularity, thick septations, irregular borders, irregular echoes, or papillary projections [10, 16]. In one study in pregnant women, ultrasound correctly diagnosed 95% of dermoids, 80% of endometriomas, and 71% of simple cysts. Of 14 masses with suspicious sonographic features, only 1 was a malignancy [16]. Even unilocular cysts <10 cm in postmenopausal women can be safely followed by serial ultrasounds until they resolve or develop solid and/or wall abnormalities prompting surgical intervention secondary to a high suspicion of malignancy [12]. In addition to routine ultrasonography, color **Doppler** studies may be used to distinguish between malignant and benign adnexal masses [18]. Low pulsatility index of <1.0 and low impedance are associated with ovarian neoplasms. **Transvaginal** ultrasound may also help to better visualize the adnexal mass. Recently, the International Ovarian Tumor Analysis (IOTA) group described the Simple Rules (Table 33.3 and Figure 33.1) that are based on a set of ultrasound features indicative of benign tumors and malignant tumors (M-features), which has been shown to have an area under the curve (AUC) of 0.917 [10, 19]. After 20 weeks, adnexal masses are more difficult to see by ultrasound, given the larger uterine size. However, definitive diagnosis requires pathologic confirmation.

Magnetic resonance imaging

Although ultrasound is the primary imaging modality, magnetic resonance imaging (MRI) has been used to characterize adnexal masses. There are insufficient data to assess the effect of MRI on management of adnexal masses in pregnancy, but a review of the topic with respect to each type of adnexal mass and the usefulness of MRI has been published [20]. The conclusions are that **MRI can assist ultrasound** in distinguishing exophytic leiomyoma, degenerating leiomyoma, endometrioma, dermoid cyst, and decidualized endometrioma from other masses. Furthermore, it supports the value of MRI to detect massive ovarian edema and distant findings such as widespread ascites, peritoneal implants, and lymphadenopathy that can help distinguish benign from malignant masses.

Laboratory

Most tumor markers may be elevated in normal pregnancy and are generally **not helpful** in distinguishing between a benign or malignant ovarian mass in pregnancy. For example, up to 16% of pregnant patients may have an elevated CA-125 [21]. Levels of CA-125 peak in the first trimester (range, 7–251 units/mL) and decrease consistently thereafter. Low-level elevations in pregnancy are typically not associated with malignancy [22]. However, **CA-125 levels from 1000 to 10,000 units/mL after 15 weeks of gestation are more likely to be cancer** [9].

Therapy

Treatment planning is dependent upon the timeliness of detection of an adnexal mass in pregnancy. When an adnexal mass is diagnosed in the first trimester, the likelihood of a functional etiology is high, as is the probability of spontaneous resolution. Two adnexal conditions are specifically associated with pregnancy and spontaneously regress in the postpartum period requiring no further treatment: Luteomas of pregnancy and theca lutein cysts. In pregnant women, most simple cysts <6 cm have been shown to spontaneously resolve [5, 23–25]. Women who are identified via sonography as low risk for malignancy may be safely followed [14, 25].

Although there are no strict guidelines, **surgery is appropriate for adnexal masses that persist in the second trimester and are ≥10 cm, or are symptomatic, or have sonographic features concerning for malignancy** (i.e. mixed solid and cystic components) (Figure 33.2 and Table 33.4) [9]. When necessary and feasible, **surgery should be scheduled in the early second trimester** (e.g. 14–28 weeks) after most functional cysts have resolved, organogenesis is complete, most spontaneous losses have occurred, and the risk for preterm delivery is low. Additionally, surgical intervention at any point may be indicated if torsion, rupture, or hemorrhage is identified, or if an already suspicious mass rapidly increases in size. Progesterone supplementation is necessary if the corpus luteum is removed prior to 8 weeks [9].

TABLE 33.3: Simple Rules

Benign Features	Malignant Features
Unilocular cyst	Irregular solid tumor
Solid component <7 mm in diameter	Ascites
Presence of acoustic shadows	≥4 papillary structures
Smooth multilocular tumor with largest diameter <10 cm	Irregular, multilocular mass>10 cm in diameter
No detectable color Doppler signal	Strong color Doppler signal

Source: From Abramowicz JS, Timmerman D. Ovarian mass-differentiating benign from malignant: The value of the International Ovarian Tumor Analysis ultrasound rules. Am J Obstet Gynecol. 2017;217(6):652–660. [III] Ref. [19], with permission.

TABLE 33.4: Sonographic Features That Have Been Associated with an Increased Risk of Malignancy

Size >7 cm
Solid components or heterogeneous/complex appearance
Excrescences/papillary structures
Internal septations (especially if thick or vascular)
Irregular borders
Increased vascularity
Low-resistance blood flow
Ascites
Persistence or progression on follow-up imaging

Source: From McMinn E, Schwartz N. Adnexal masses in pregnancy. Clin Obstet Gynecol. 2020;63(2):392–404. [Review; III] Ref. [36], with permission.

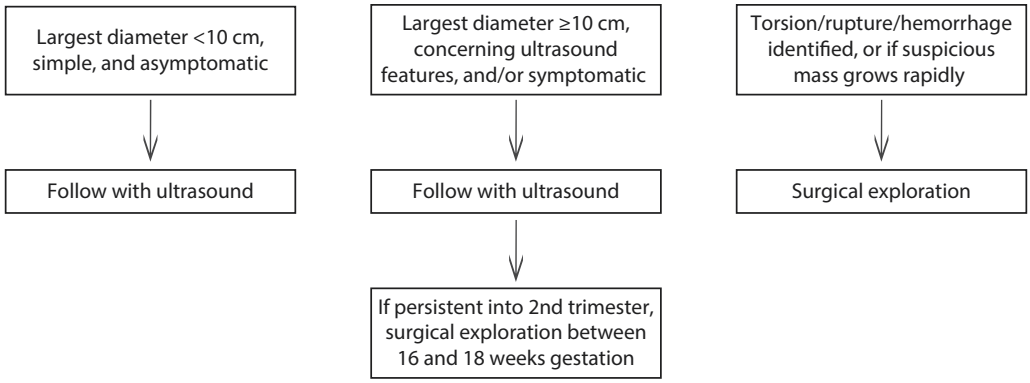


FIGURE 33.2 Management of the ovarian mass in pregnancy.

For adnexal masses suspicious for malignancy in pregnancy, the management is similar to that in premenopausal women**. Early preoperative consultation with a gynecologic oncologist, anesthesiologist, and neonatologist is recommended** [22]. Consultation at <15 weeks is recommended for better operative planning.

Surgery

Many studies have shown that planned abdominal surgery in pregnancy is safe [14, 15, 26]. Removal of adnexal masses can be accomplished via laparoscopy, laparotomy, or at the time of cesarean section. When exploration is necessary, all efforts should be made to **avoid unnecessary manipulation of the uterus** to minimize premature uterine contractions. While traditionally a laparotomy was the standard recommendation used to explore the abdomen of a pregnant patient with an adnexal mass, **laparoscopy** is currently not only an acceptable alternative (in experienced hands) but also is **preferred in cases with low suspicion of malignancy**, as it offers the benefit of a more expeditious recovery [27–29]. In a Cochrane review on laparoscopy for adnexal tumors in pregnancy, the available case series were too limited for conclusions to be drawn on risks and benefits of laparoscopy [30]. Nevertheless, laparoscopy has been demonstrated as safe in all trimesters of pregnancy, and adjustments should be made accordingly depending on the size of the gravid uterus (i.e. using nonintrauterine retractors), location of abdominal entry, and patient positioning in the left lateral decubitus position [17].

Other intraoperative and postoperative considerations should be kept in mind when performing laparoscopy on a pregnant patient (Table 33.5). Preoperative and postoperative fetal doptones are recommended if the fetus is considered previable, and continuous electronic fetal heart monitoring can be considered when the fetus is viable [31, 32], it is physically possible to perform monitoring, and the nature of the planned surgery will allow for the interruption or alteration of the procedure to perform an emergent cesarean section if needed [9, 33].

If a suspicious adnexal mass is identified incidentally **at the time of cesarean section**, it should be **removed** and not simply aspirated [34]. With aspiration and cytologic evaluation, malignancy could be missed [35].

TABLE 33.5: Guidelines for Laparoscopy in Pregnancy from SAGES June 2017

Patient Selection	
Preoperative decision-making	Laparoscopic treatment of acute abdominal disease offers similar benefits to pregnant and nonpregnant patients compared to laparotomy
Laparoscopy and trimester of pregnancy	Laparoscopy can be safely performed during any trimester of pregnancy when surgery is indicated
Treatment	
Patient positioning	Gravid patients beyond the first trimester should be placed in left lateral decubitus position or partial left lateral decubitus position to minimize compression of the vena cava
Initial port placement	Initial abdominal access can be safely performed with an open (Hasson), Veress needle, or optical trocar technique if the location is adjusted for fundal height
Insufflation pressure	CO_2 insufflation of 10–15 mmHg can be safely used for laparoscopy in the pregnant patient
Intraoperative CO_2 monitoring	Intraoperative CO_2 monitoring by capnography should be used during laparoscopy
Venous thromboembolic (VTE) prophylaxis	Intraoperative and postoperative pneumatic compression devices and early postoperative ambulation are recommended for prophylaxis
Adnexal masses	Laparoscopy is a safe and effective treatment in gravid patients with symptomatic ovarian cystic masses
Adnexal torsion	Laparoscopy is recommended for both diagnosis and treatment of adnexal torsion
Perioperative Care	
Fetal heart monitoring	Fetal heart monitoring of a viable fetus should occur preoperatively and postoperatively in the setting of urgent abdominal surgery
Tocolytics	Tocolytics should not be used prophylactically in pregnant women undergoing surgery, but should be considered perioperatively when signs of preterm labor are present

Source: Adapted from Ref. [17].

TABLE 33.6: FIGO Staging for Cancer of the Ovary, Fallopian Tube, and Peritoneum (2014)

Stage I—Growth limited to the ovaries or fallopian tubes
Stage IA—Growth limited to one ovary or fallopian tube, no ascites, no tumor on external surface, and capsule intact
Stage IB—Growth limited to both ovaries or fallopian tubes, no ascites, no tumor on external surface, and capsule intact
Stage IC—Tumor limited to one or both ovaries or fallopian tubes with any of the following:
Stage IC1— Surgical spill intraoperatively
Stage IC2 —Capsule ruptured before surgery or tumor on ovarian or fallopian tube surface
Stage IC3— malignant cells in the ascites or peritoneal washings
Stage II—Growth involving one or both ovaries, with pelvic extension (below pelvic brim) or peritoneal cancer
Stage IIA—Extension and/or implants to the uterus and/or fallopian tubes and/or ovaries
Stage IIB—Extension to other pelvic intraperitoneal tissues
Stage III—Tumor involving one or both ovaries, fallopian tubes, or peritoneal cancer, with cytologically or histologically confirmed peritoneal implants outside the pelvis and/or metastasis to the retroperitoneal lymph nodes
Stage IIIA—Metastasis to the retroperitoneal lymph nodes with or without microscopic peritoneal involvement beyond the pelvis
Stage IIIA1— Positive retroperitoneal lymph nodes only (cytologically or histologically proven)
Stage IIIA1(i) — Metastasis ≤10 mm in greatest dimension
Stage IIIA1(ii) — Metastasis >10 mm in greatest dimension
Stage IIIA2: Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes
Stage IIIB—Macroscopic peritoneal metastases beyond the pelvic brim ≤2 cm in greater dimension, with or without metastasis to the retroperitoneal lymph nodes
Stage IIIC—Macroscopic peritoneal metastases beyond the pelvic brim >2 cm in greater dimension, with or without metastasis to the retroperitoneal lymph nodes (Note 1)
Stage IV—Distant metastases excluding peritoneal metastases
Stage IVA—Pleural effusion with positive cytology
Stage IVB—Metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside the abdominal cavity) (Note 2)

Source: From Prat J. FIGO's staging classification for cancer of the ovary, fallopian tube, and peritoneum: Abridged republication. *J Gynecol Oncol.* 2015;26(2):87–89, with permission.

Note 1: Includes extension of tumor to capsule of liver and spleen without parenchymal involvement of either organ.

Note 2: Parenchymal metastases are stage IVB.

Abbreviation: FIGO, Federation Internationale de Gynecologie et d'Obstetrique (International Federation of Gynecology and Obstetrics).

If a malignant neoplasm of the ovary is suspected prior to surgery, a vertical incision is preferred, and a frozen section should be sent. The surgeon's obligation is to consult a gynecologic oncologist to properly stage the disease (Table 33.6). Since most present as stage I disease, a unilateral salpingo-oophorectomy, omentectomy, and limited pelvic and paraaortic lymph node dissection is the procedure of choice. All suspicious lesions should be biopsied, with surface excrescences and ascites being suggestive of malignancy. If benign disease is suspected, cystectomy is preferred over a salpingo-oophorectomy.

If the disease appears confined to the pelvis, comprehensive surgical staging is indicated. The staging procedure includes peritoneal cytology, multiple peritoneal biopsies, omentectomy, and pelvic and paraaortic lymph node sampling. Rarely is a hysterectomy indicated. **For more advanced disease, cytoreductive surgery should be attempted**. The timing of initiation of chemotherapy depends on fetal viability and maternal choice and should be managed by a gynecologic oncologist. Returning for staging after completion of pregnancy is not thought to adversely affect survival, though late stage of disease harbors a poor prognosis.

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34

CERVICAL CANCER SCREENING AND MANAGEMENT IN PREGNANCY

Vaidehi Mujumdar and Scott D. Richard

Key points

- Cervical cancer screening guidelines for nonpregnant people with a cervix can be followed in pregnant people. **The American Cancer Society (ACS) published screening guidelines in 2020, which differ significantly from their 2012 guidelines. The 2020 ACS guidelines recommend that people with a cervix ages 25–65 get a primary human papillomavirus (HPV) test every 5 years as the preferred screening method**. They **do not recommend cervical cancer screening in patients less than 25 years of age**.
- **The only cervical diagnosis** that is considered **to alter management in pregnancy** is **invasive cancer**.
- A more **conservative approach should be used to manage cervical intraepithelial neoplasia (CIN)** in pregnancy compared to nonpregnancy.
- Due to risks of bleeding and premature rupture of membranes, **endocervical curettage (ECC)** is **never recommended in pregnancy**.
- **Diagnostic conization** during pregnancy should **only be considered when** either the biopsy or cytology is **suggestive of invasive cancer** and the diagnosis of invasion would result in a modification of treatment recommendations, timing, or mode of delivery.
- **In the diagnosis of invasive cancer with a grossly visible lesion**, **cesarean delivery** is indicated and results in better survival outcomes, as well as a decreased risk of obstetric bleeding in the intrapartum and postpartum periods.
- **If a nonvisible microinvasive lesion** (stage IAI or IA2) is identified, **either cesarean or vaginal delivery is acceptable**, depending on the obstetric and gynecologic circumstances.
- Once the diagnosis of cervical cancer is established, individualized recommendations for the **management of the malignancy**, as well as the **pregnancy**, are formulated **with consideration for the stage of disease, gestational age at the time of diagnosis, and maternal desires regarding the continuation of pregnancy**.
- Fertility-sparing surgery and neoadjuvant chemotherapy for earlier-stage cervical cancer found in pregnancy may be considered without worsening survival.
- **Pregnancies exposed to the HPV vaccine are not associated with a higher risk of adverse pregnancy outcomes** than pregnancies with no exposure.

Historic notes

The cytologic evaluation of the cervix, known as the Pap smear, was developed in the 1940s by George Papanicolaou. The Bethesda System standardized terminology for reporting Pap smear cytology results in 1988 [1] and was subsequently updated in 2014 [2]. In response to the standardization of cytology results, the American Society for Colposcopy and Cervical Pathology (ASCCP) initiated a process that developed comprehensive, evidence-based consensus guidelines to assist clinicians in managing abnormal cervical cytology results. The ASCCP screening guidelines were most recently updated in 2019 [3]. The 2019 guidelines expand on the idea of having equal management for equal risks that was a cornerstone of the 2012 guidelines [3].

Diagnosis/Definition

Microinvasive cervical cancer is defined as cancer spread to no more than 5 mm into the tissue of the cervix. **Invasive cervical cancer** is defined as cancer spread from the surface of the cervix to deeper cervical tissue, possible spread to part of the vagina, to the lymph nodes, to the other tissues surrounding the cervix, within the pelvis, or beyond the pelvic areas into nearby organs.

Epidemiology/Incidence

According to the 2017 Cytopathology Checklist, the median reporting rate of atypical squamous cells– undetermined significance (**ASC-US**) among laboratories in the United States was **5.0%** [4]. **The incidence of biopsy-confirmed cervical intraepithelial neoplasia (CIN) 1 was 1.6%, CIN 2 4.4%, and CIN 3+ 2.2%** [4, 5]. In the United States, **the incidence of cervical cancer cases has dropped to 7.4 per 100,000, while deaths from invasive cervical cancer have dropped to 2.8 per 100,000 women** [6, 7]. The peak age of incidence of cervical cancer is in the **mid-40s** [6]. In low- and middle-income countries, cervical cancer is the second most common cancer among people with a cervix, the third most common cause of cancer-related death, and the most common cause of mortality from gynecologic malignancy. In contrast, in high-income countries, the success of Pap smear screening has greatly reduced the incidence of disease by accurately detecting preinvasive and early-invasive cervical disease. In the United States, **the incidence of cervical cancer ranges from 1.5 to 12 cases in 100,000 pregnancies** [8]. About 1% of people who have cervical cancer are pregnant at the time of diagnosis. The likelihood that a pregnant person with ASC pathology has a detectable high-risk human papillomavirus (HR HPV) is 84% [9].

Classification

The Pap smear report consists of the following [2]:

Specimen type

- Conventional Pap smear: Cells from the transformation zone are sampled and transferred directly onto a slide [10].
- **Liquid-based cytology**: Cells from the transformation zone are placed in a prepared liquid preservative and processed by a laboratory. This is the **method most**

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commonly used in clinical practice in the United States because of the added benefit of using a single sample for *HPV co-testing, using a combination of a Pap smear and HPV test*. The use of liquid-based media can also control for obscuring factors, including blood, inflammation, and other processes [10].
- There is no difference in unsatisfactory rates, cytology classifications, and accuracy between conventional and liquid-based cervical cytology [11].

Specimen adequacy

Satisfactory for evaluation

- Defined as a minimum of 5000 well-visualized squamous cells on a liquid-based preparation or 8000–12,000 well-visualized squamous cells on a conventional smear.
- The presence of endocervical cells indicates that the area at risk for neoplasia—the transformation zone—has been adequately sampled [12].
- **Samples reported as negative but with absent or insufficient endocervical/transition zone components have raised concern about missed pathology**. Prior guidelines have recommended repeat cytology. Recent meta-analysis studies reported that negative cytology (with or without sufficient sampling of the endocervical/transition zone) has both good negative predicative value and good specificity. **Current guidelines do not recommend repeat follow-up Pap smears. People with a cervix age 25 or above are recommended to undergo primary HPV testing, as well as co-testing or cytology alone when primary HPV testing is not available**. This guideline is transitional, as full access to primary HPV testing is not available widely. **Options for screening with co-testing every 5 years or cytology every 3 years are still secondary options**. **Pregnant individuals are recommended to follow the same age-dependent guidelines used for nonpregnant patients**. **Pregnant individuals who screen positive for HPV and/or cytology should be managed in accordance with the 2019 ASCCP risk-based management consensus guidelines for abnormal cervical cancer screening tests** (Figures 34.1–34.3) [3].

Unsatisfactory for evaluation

- Defined as more than 75% of the cells being uninterpretable or an unlabeled specimen.
- Since women with this result are more likely to have intraepithelial lesions or cancer on follow-up than women with satisfactory Pap smears [12], a repeated Pap smear in 2–4 months is recommended. If the subsequent Pap smear is unsatisfactory, evaluation with colposcopy and/or biopsies is appropriate [13].

Interpretation/Result

Squamous epithelial cell abnormalities

- ASC of either of the following:
  - Undetermined significance (ASC-US) or
  - Suspicious for high-grade squamous intraepithelial lesions (HSIL or ASC-H)
- Low-grade squamous intraepithelial lesions (LSIL)
  - Changes consistent with HPV, mild dysplasia, or grade 1 CIN (CIN I)
- HSIL
  - HSIL includes moderate or severe dysplasia, CIN II, CIN III, and carcinoma in situ (CIS) and should indicate if there are features suspicious for invasive disease. When glandular cell abnormalities are present, it should be noted whether there are changes favoring neoplasia.
- Carcinoma

Glandular cell abnormalities

- Atypical glandular cells (AGCs) may be of endocervical, endometrial, or other glandular origin
- Endocervical adenocarcinoma in situ (AIS)
- Adenocarcinoma

Human papillomavirus testing

HPV testing is an integral part of cervical cancer screening. Updated ASCCP Consensus guidelines that were most recently validated in 2019 state **HPV co-testing is recommended for all female patients over the age of 30 and for all patients with ASC-US cytology**.

- HPV infection is the leading etiologic agent in the development of premalignant and malignant lower genital tract disease [14].
- **Co-testing should only detect for the presence of high-risk HPV species**. **There is no role in testing for low-risk genotypes**. **Detecting low-risk genotypes has been proven to cause unnecessary procedures and testing, therefore decreasing clinical specificity**. **It is recommended to use only FDA-approved HPV DNA detection kits** [10].
- The most well-studied HPV test is the Hybrid Capture 2 HPV DNA Assay (Digene Corporation, Beltsville, MD), which uses a probe mix for high-risk HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68 [15].
- A newer assay for detecting high-risk HPV was approved for FDA use in 2009. Cervista HR HPV (Hologic Corporation, Waltham, MA) includes the 13 HPV types noted and adds type 66 [8].
- Cervista HPV 16/18 is another diagnostic test that specifies types 16 and 18. These two represent the most common types found in cervical squamous cell carcinomas and adenocarcinomas, respectively.
- Ongoing research looks promising in improving specificity and positive predictive value of screening for CIN 2+ by looking at mRNA instead of DNA for HR HPV [16].

Management

Pregnancy considerations

Pregnancy-induced changes in the cervix include hyperemia, eversion of columnar epithelium, more prominent glands, and increased production and volume of mucus. The decidual changes may exaggerate the colposcopic appearance of CIN. A biopsy during pregnancy may cause substantial bleeding [3]. In pregnancy, the general philosophy for the treatment of intraepithelial neoplasia of the cervix has become expectant management after careful diagnosis.

Screening in pregnancy

The Pap smear is used to screen for cellular abnormalities that are associated with an increased risk for the development of cervical cancer. It selects those women who should have further evaluation, such as HPV DNA testing, colposcopy, and/or biopsy, which

(1) Recommendations are based on risk, not results.
- Recommendations of colposcopy, treatment, or surveillance will be based on a patient's risk of CIN 3+ determined by a combination of current results and history (including unknown history). The same current test results may yield different management recommendations depending on the history of recent past test results.

(2) Colposcopy can be deferred for certain patients.
- Repeat HPV testing or co-testing at 1 year is recommended for patients with minor screening abnormalities indicating HPV infection with a low risk of underlying CIN 3+ (e.g. low-grade cytologic abnormalities after a documented negative screening HPV test or co-test).

(3) Guidance for expedited treatment is expanded (i.e. treatment without colposcopic biopsy).
- Expedited treatment was an option for patients with HSIL cytology in the 2012 guidelines; this guidance is now better defined.
- For nonpregnant patients 25 years or older, expedited treatment, defined as treatment without preceding colposcopic biopsy demonstrating CIN 2+, is preferred when the immediate risk of CIN 3+ is ≥60%, and is acceptable for those with risks between 25% and 60%. Expedited treatment is preferred for nonpregnant patients 25 years or older with HSIL cytology and concurrent positive testing for HPV genotype 16 (HPV 16) (i.e. HPV 16–positive HSIL cytology) and never or rarely screened patients with HPV-positive HSIL regardless of HPV genotype.
- Shared decision-making should be used when considering expedited treatment, especially for patients with concerns about the potential impact of treatment on pregnancy outcomes.

(4) Excisional treatment is preferred to ablative treatment for histologic HSIL (CIN 2 or CIN 3) in the United States. Excision is recommended for adenocarcinoma in situ (AIS).

(5) Observation is preferred to treatment for CIN 1.

(6) Histopathology reports based on Lower Anogenital Squamous Terminology (LAST)/World Health Organization (WHO) recommendations for reporting histologic HSIL should include CIN 2 or CIN 3 qualifiers, i.e. HSIL (CIN 2) and HSIL (CIN 3).

(7) All positive HPV tests, regardless of genotype, should have additional reflex triage testing performed from the same laboratory specimen (e.g. reflex cytology).
- Additional testing from the same laboratory specimen is recommended because the findings may inform colposcopy practice. For example, those with HSIL cytology and concurrent positive testing for HPV genotype 16 qualify for expedited treatment.
- HPV 16 or 18 infections have the highest risk for CIN 3 and occult cancer, so additional evaluation (e.g. colposcopy with biopsy) is necessary even when cytology results are negative.
- If HPV 16 and 18 testing is positive and additional laboratory testing of the same sample is not feasible, the patient should proceed directly to colposcopy.

(8) Continued surveillance with HPV testing or co-testing at 3-year intervals for at least 25 years is recommended after treatment of histologic HSIL, CIN 2, CIN 3, or AIS. Continued surveillance at 3-year intervals beyond 25 years is acceptable for as long as the patient's life expectancy and ability to be screened are not significantly compromised by serious health issues.
- The 2012 guidelines recommended a return to 5-year screening intervals and did not specify when screening should cease. New evidence indicates that risk remains elevated for at least 25 years, with no evidence that treated patients ever return to risk levels compatible with 5-year intervals.

(9) Surveillance with cytology alone is acceptable only if testing with HPV or co-testing is not feasible. Cytology is less sensitive than HPV testing for the detection of precancer and is therefore recommended more often. Cytology is recommended at 6-month intervals when HPV testing or co-testing is recommended annually. Cytology is recommended annually when 3-year intervals are recommended for HPV or co-testing.

(10) Human papillomavirus assays that are FDA-approved for screening should be used for management according to their regulatory approval in the United States. (Note: All HPV testing in this document refers to testing for high-risk HPV types only.)
- For all management indications, HPV mRNA and HPV DNA tests without FDA approval for primary screening alone should only be used as a co-test with cytology, unless sufficient, exceptionally rigorous data are available to support primary HPV testing in management.

FIGURE 34.1 Essential Changes from Prior ASCCP Management Guidelines. (From Perkins RB, Guido RS, Castle PE, et al. 2019 ASCCP Risk-Based Management Consensus Guidelines for Abnormal Cervical Cancer Screening Tests and Cancer Precursors. *J Lower Genital Tract Dis*. 2020;24(2): 102–131. [Review; III]. Ref. [3], with permission.)

then is used for treatment decisions. The National Comprehensive Cancer Network (NCCN) panel has adopted recommendations set forth by the American Cancer Society on initiation and frequency of Pap smear [17]. Of note, ACS has new 2020 recommendations that include that **people with a cervix ages 25–65 get a primary HPV test every 5 years as the preferred screening method**. They do not recommend cervical cancer screening in patients less than 25 years of age [3]. **The primary HPV test**, **the cobas test**, is manufactured by Roche and **can be used alone for screening**. This test detects 14 "high-risk" HPV types, while also specifically identifying HPV 16 and 18. The rationale remains that invasive cancer is rare in women under 21. **Annual surveillance is recommended for patients with known immunosuppression from HIV or organ transplantation; individuals exposed to diethylstilbestrol in utero; or those who have been previously treated for CIN 2, CIN 3, or cervical cancer** [3]. Pap smears are often obtained at the first prenatal visit by many providers, but the **guidelines for nonpregnant patients (HPV test every 5 years for patients ≥25 years old) can be followed in pregnant patients** [10].

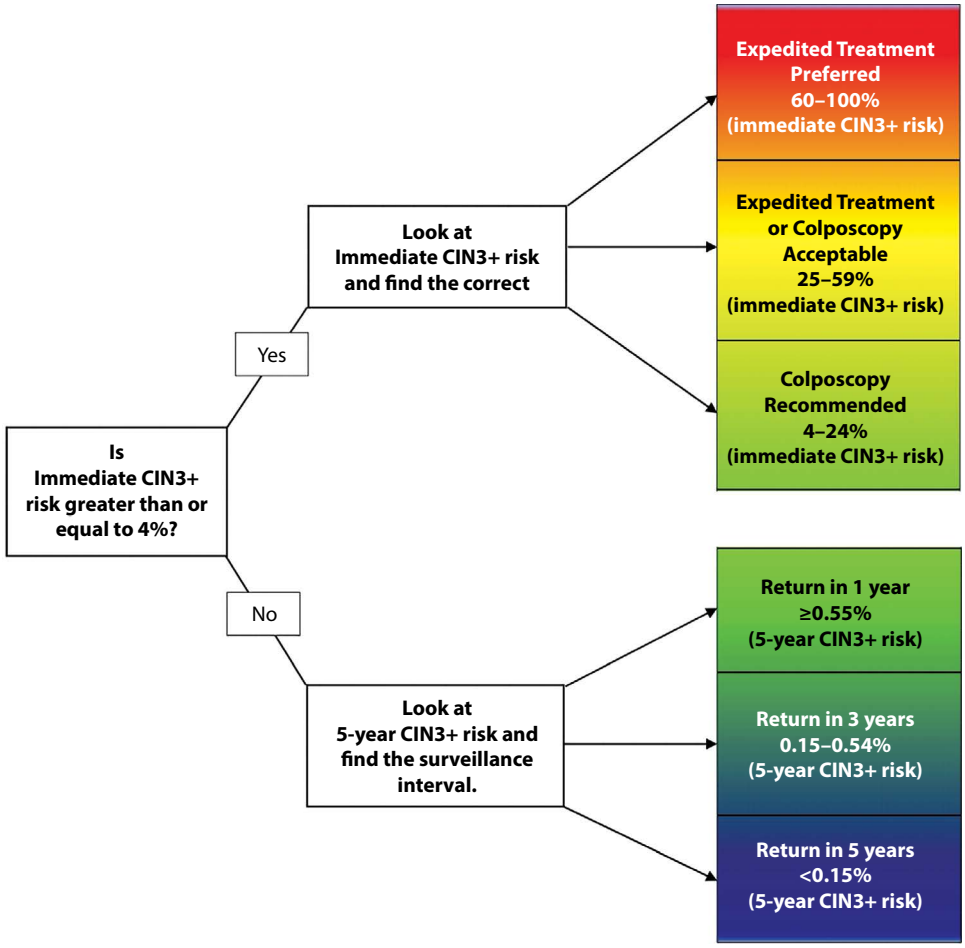


FIGURE 34.2 Evaluation of patient risk for CIN3. For a given current results and history combination, the immediate CIN 3+ risk is examined. If this risk is 4% or greater, immediate management via colposcopy or treatment is indicated. If the immediate risk is less than 4%, the 5-year CIN 3+ risk is examined to determine whether patients should return in 1, 3, or 5 years. (From Perkins RB, Guido RS, Castle PE, et al. 2019 ASCCP Risk-Based Management Consensus Guidelines for Abnormal Cervical Cancer Screening Tests and Cancer Precursors. *J Lower Genital Tract Dis*. 2020;24(2): 102–131. [Review; III]. Ref. [3], with permission.)

Consultations required

Consultation with Gynecologic Oncology and Maternal-Fetal Medicine is recommended in cases of cervical cancer in pregnancy [18]. Consultation with gynecologic oncology should occur as early as possible after the diagnosis of cervical cancer for better therapeutic planning. Collaboration with a maternal-fetal medicine specialist is also recommended for management of obstetric complications and delivery planning.

Indications for colposcopy and cervical biopsy during pregnancy (Figure 34.1)

As in nonpregnant women, **women with abnormal Pap smears during pregnancy should undergo colposcopy with directed biopsies** of suspicious areas to rule out invasive disease [3].

ASC-US, HPV negative

- No indication for colposcopy at any age. Pregnant patients are to follow age-appropriate routine screening.

LSIL and ASC-US, HR HPV positive

- Ages 21–25: Patients are to undergo repeat Pap smear and co-testing in 12 months. Colposcopy is not recommended.
- Ages >25: In pregnant patients, colposcopy is recommended, but it is acceptable to defer colposcopy to 4–6 weeks postpartum.

HSIL or more invasive cytology

- In patients with higher-grade lesions noted on cervical screening exams, necessary colposcopically directed cervical biopsies can be safely performed at any time during pregnancy. Many defer biopsy until the second trimester when the risk of incidental pregnancy loss is minimal. Due to risks of bleeding and premature rupture of membranes, **endocervical curettage (ECC) is never recommended in pregnancy**. Cervical biopsies should only be performed if CIN 2 or above is suspected on colposcopic exam.

CIN 1

- If adequate samples are obtained during colposcopy and invasive disease is not suspected at any point during the pregnancy, it is recommended to defer repeat colposcopy to 6 weeks postpartum.

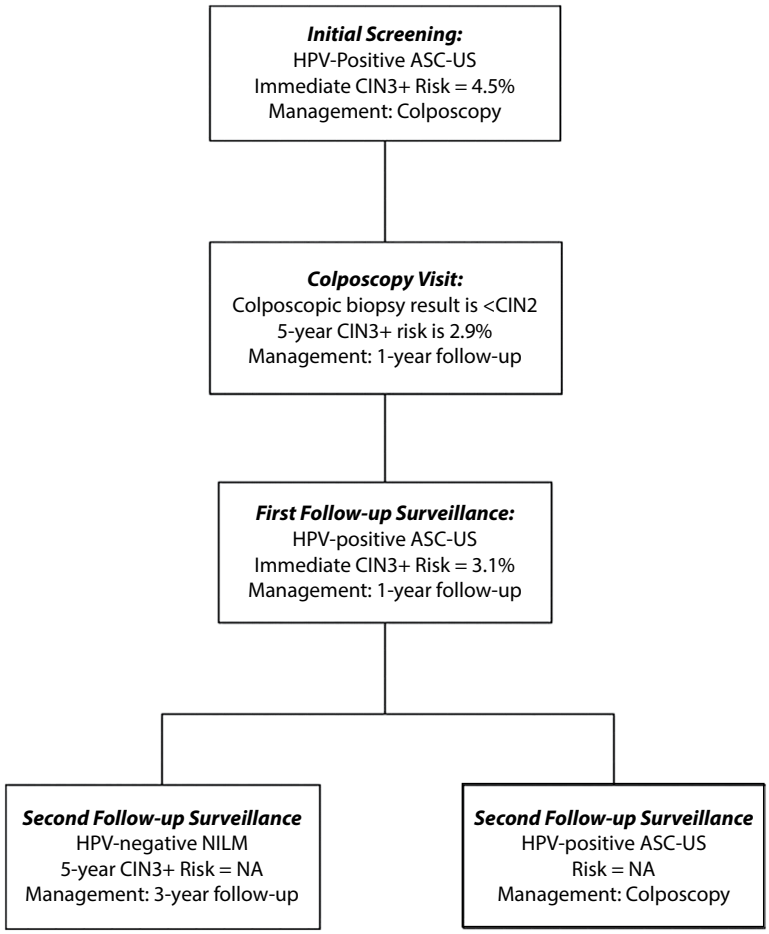


FIGURE 34.3 Management of common low-grade screening abnormality. An initial minimally abnormal screening test result (HPV-positive ASC-US) would lead to colposcopy (immediate risk 4.45%). If colposcopy shows less than CIN 2, the 5-year risk is 2.9% (1-year return). At the 1-year return visit, a second HPV-positive ASC-US result has an immediate risk of 3.1% (1-year return). Note similar management would be recommended if the initial abnormality preceding colposcopy were any minimally abnormal test result (i.e. less severe than ASC-H). If the HPV-based test performed for the second post-colposcopy surveillance test is negative, return in 3 years is recommended. If the second post-colposcopy surveillance test results are either a positive HPV test with any cytology result or a negative HPV test result with a cytology result of ASC-H or higher, colposcopy is recommended. Return in 1 year is recommended for HPV-negative ASC-US or LSIL results. NA, not applicable because stable risk estimates are not available. (From Perkins RB, Guido RS, Castle PE, et al. 2019 ASCCP Risk-Based Management Consensus Guidelines for Abnormal Cervical Cancer Screening Tests and Cancer Precursors. *J Lower Genital Tract Dis*. 2020;24(2): 102–131. [Review; III]. Ref. [3], with permission.)

CIN 2/3 and CIS

- In women with a histologic diagnosis of CIN 2/3 or CIS on initial colposcopy, it is recommended to perform repeat colposcopy and cytology every 12 weeks for the duration of the pregnancy. Repeat biopsy is recommended only if the appearance of the lesions worsens or if cytology is concerning for invasive cancer. It is acceptable to defer tissue biopsy to 4–6 weeks postpartum if no progression of the lesion is noted on colposcopy and cytology [3].

Diagnosis of invasive cancer

Once the diagnosis of cervical cancer is established, individualized recommendations for the management of the malignancy, as well as the pregnancy, are formulated with consideration for the stage of disease, gestational age at the time of diagnosis, and maternal desires regarding the continuation of her pregnancy (see Chap. 44 in *Maternal-Fetal Evidence Based Guidelines*). **The patient should seek consultation by both maternal-fetal medicine and gynecologic oncology.**

Management of the abnormal Pap smear

There are **no randomized controlled trials** assessing any aspect of management of abnormal Pap smear in pregnancy. Most of the recommendations are based on expert opinion and anecdotal experience [18, 19]. **The only diagnosis that is considered to alter management in pregnancy is invasive cancer.**

Management of abnormal Pap smears in pregnancy should follow the new recommendations delineated in Figure 34.1. Recommendations for **colposcopy** in pregnant patients are similar to those in the nongravid state, with certain exceptions, as listed in Table 34.1. Newer guidelines for colposcopy in pregnancy state that colposcopy is preferred for ASC-US associated with positive HR HPV type or LSIL Pap smears, but also that colposcopy can be deferred by the clinician until after pregnancy for these two categories. Colposcopy during pregnancy has as its **primary goal to**

TABLE 34.1: Cervical Screening Considerations during Pregnancy

- Endocervical brush cytology is safe
- Cervical biopsy is safe
- Endocervical curettage (ECC) should be avoided
- For ASC and LSIL, HR HPV–positive, colposcopy is preferred but can be done postpartum
- For CIN 2 or CIN 3, Pap and colposcopy can be repeated postpartum if cancer is not suspected
- Delay treatment of any level of CIN until postpartum period
- Cervical conization is recommended if invasion is suspected

Abbreviations: ASC, atypical squamous cells; LSIL, low-grade squamous intraepithelial lesion; HR HPV, high risk human papillomavirus; CIN, cervical intraepithelial neoplasia.

assess for invasive cancer. Biopsies should only be performed for women with colposcopic impression of **CIN 3/CIS, AIS, or cancer**, with the purpose to exclude invasive cancer [20].

Repeat Pap and colposcopy is recommended if invasive cancer is suspected but not yet proven, specifically with evidence of CIN 2/3 or CIS on cytology or biopsy. Repeat biopsy during pregnancy should only be performed if progression of the lesion is suspected**. ECC** is **not performed** in pregnancy [16, 20].

Conization performed during pregnancy is associated with increased morbidity. **The most common complications include hemorrhage, abortion, premature delivery, and infection** [20]. **Therefore, cervical conization** has **limited indications in pregnancy** (Table 34.2). In general, diagnostic conization during pregnancy should only be considered **when either the biopsy or cytology is suggestive of invasive cancer or AIS** and the diagnosis of invasion would result in a modification of treatment recommendations, timing, or mode of delivery [20].

Unlike standard recommendations for cervical conization in non-obstetric patients with inadequate colposcopy biopsies or discordance between Pap smears and colposcopic biopsies [15], pregnant individuals with these findings can defer further examination until after pregnancy if invasive cancer has been ruled out. If a cervical conization must be performed during pregnancy, this procedure should ideally be performed in the early second trimester.

Management of cervical cancer (Table 34.1)

For staging and management, please refer to Table 34.3 [30] and Chap. 44 in *Maternal-Fetal Evidence Based Guidelines* [1]. Microinvasive cervical cancer is defined as cancer spread to no more than 5 mm deep into the cervical stroma. Microinvasive disease includes stages IA1 and IA2. Invasive cervical cancer is defined as cancer that has invaded deeper than 5 mm into the cervical stroma, is grossly visible, or involves additional structures. Invasive disease includes stage IB1 or greater.

Stage IA1

- **Conization** is recommended for both treatment and diagnosis in patients with evidence of stage IA1 cancer [22]. To minimize the risk of spontaneous abortion, is it optimal to perform conization in the early second trimester [21].
- If conization margins are negative, patients can be managed expectantly for the duration of the pregnancy [21].
- Either abdominal or vaginal delivery routes are expected with these patients. Mode of delivery should be discussed with a maternal-fetal medicine specialist with consideration of other gynecologic and obstetric circumstances. This should be decided on an individual basis [22].

TABLE 34.2: Indications for Conization in Pregnancy

- Histologic presence of microinvasive or invasive disease
- Persistent cytologic impression of invasive cancer (in the absence of histologic confirmation)
- Histologic presence of adenocarcinoma in situ

TABLE 34.3: Staging and Management of Cervical Cancer in Pregnancy

Stage I:
The carcinoma is strictly confined to the cervix uteri (extension to the corpus should be disregarded)
IA Invasive carcinoma that can be diagnosed only by microscopy, with maximum depth of invasion <5 mm

- **IA1** Measured stromal invasion <3 mm in depth
- **IA2** Measured stromal invasion ≥3 mm and <5 mm in depth

IB Invasive carcinoma with measured deepest invasion ≥5 mm (greater than stage IA), lesion limited to the cervix uteri

- **IB1** Invasive carcinoma ≥5 mm depth of stromal invasion and <2 cm in greatest dimension
- **IB2** Invasive carcinoma ≥2 cm and <4 cm in greatest dimension
- **IB3** Invasive carcinoma ≥4 cm in greatest dimension

Stage II:
The carcinoma invades beyond the uterus, but has not extended onto the lower third of the vagina or to the pelvic wall
IIA Involvement limited to the upper two-thirds of the vagina without parametrial involvement

- **IIA1** Invasive carcinoma <4 cm in greatest dimension
- **IIA2** Invasive carcinoma ≥4 cm in greatest dimension

IIB With parametrial involvement but not up to the pelvic wall
Stage III:
The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or nonfunctioning kidney and/or involves pelvic and/or paraaortic lymph nodes
IIIA Carcinoma involves the lower third of the vagina, with no extension to the pelvic wall
IIIB Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney (unless known to be due to another cause)
IIIC Involvement of pelvic and/or paraaortic lymph nodes, irrespective of tumor size and extent (with r and p notations)

- **IIIC1** Pelvic lymph node metastasis only
- **IIIC2** Paraaortic lymph node metastasis

Stage IV:
The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous edema, as such, does not permit a case to be allotted to stage IV

- **IVA** Spread of the growth to adjacent organs
- **IVB** Spread to distant organs

Source: From Bhatla N, Berek JS, Cuello Fredes M, et al. Revised FIGO Staging for Carcinoma of the Cervix Uteri. *Int J Gynaecol Obstet*. 2019;145(1):129–135, with permission.

- If continued fertility is desired, patients can be followed up every 3 months for 2 years and every 6 months for the next 3 years [21].

Stage IA2

- **Conization** with the addition of **pelvic lymphadenectomy** is recommended to rule out high-risk disease. Radical trachelectomy is not recommended, given the risk of significant blood loss and obstetric complications resulting from prolonged surgery [22].
- Given the technical complications performing lymphadenectomy after 25 weeks of gestation, in patients diagnosed after 25 weeks, it is recommended to delay treatment and full surgical staging until after delivery. If disease progression is suspected, it is recommended to obtain an abdominal and pelvic MRI [21].
- As stated earlier, patients can undergo either abdominal or vaginal delivery with consideration of other obstetric circumstances. Delivery can be delayed until fetal maturity at 37 weeks [21].
- Given that IA2 carries a higher risk of nodal metastasis, patients can undergo either classic cesarean delivery with modified radical hysterectomy or surgery can be delayed 6–8 weeks postpartum in the case of vaginal delivery [21].

Stage IB1

- Neoadjuvant **chemotherapy** is recommended until fetal maturity. The goal of therapy is to stabilize the tumor during pregnancy [22]. Postponement of treatment is acceptable if there is no evidence of disease progression. As stated earlier, MRI should be obtained if there is any suspicion. Patients should be examined every 2–4 weeks [21].
- Delivery can be delayed until documented fetal lung maturity with amniocentesis. Testing for fetal lung maturity should begin at 32 weeks [21].
- Patients should undergo classic cesarean delivery with modified radical hysterectomy and pelvic lymphadenectomy [21].

Stage IB2 and higher-stage tumors

- **Termination** of pregnancy is recommended, given the high risk of disease progression during pregnancy [22].
- **If pregnancy is desired**, initiation of neoadjuvant **chemotherapy** is recommended. Chemotherapy allows the pregnancy to be continued to an average of 33 weeks. **Early delivery** is recommended to expedite the initiation of standard-of-care treatment. The practitioner should discuss the initiation of betamethasone therapy for fetal maturity as indicated [22].
- The patient should undergo a cesarean delivery followed by initiation of therapy 6 weeks postpartum [21].

Recurrence and follow-up treatment

Seventy-five percent of patients with CIN diagnosed during pregnancy have persistent or progressive disease at postpartum evaluation [22]. A regression rate of only 12% is found in pregnant women with CIN 3, emphasizing the importance of **reevaluation 6 weeks postpartum** [14, 23, 24].

Routine surveillance can be resumed if there is no recurrence after the first 2 years of follow-up, which includes performing two Pap smears at 6-month intervals or HPV testing at 1-year intervals. Postpregnancy surveillance intervals are modified if the Pap smear or colposcopic biopsies reveal CIN 2, CIN 3, or CIS and are the same as the nonpregnant guidelines [14].

Prevention

The HPV-16 vaccine reduces the incidence of both HPV-16 infection and HPV-16–related CIN [25]. Currently, the three licensed HPV vaccines include Cervarix (two-valent; types 16 and 18), Gardasil (four-valent; types 6, 11, 16, and 18), and most recently, Gardasil-9 (nine-valent; types 6, 11, 18, 19, 31, 33, 45, 52, and 58). The nine-valent vaccine is equivalent to the prior recommended vaccine and as of 2017, it is the only HPV vaccine available in the United States [25–28]. Although the HPV vaccination is not recommended for pregnant women, studies have shown that **HPV vaccine–exposed pregnancies were not associated with a higher risk of adverse pregnancy outcomes** than pregnancies with no such exposures [29, 30].

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