Chapter 105: Pregnancy and Lactation

Alicia B. Forinash; Kylie Barnes

KEY CONCEPTS

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1. Complex physiology surrounds the process of fertilization and pregnancy progression.
2. Medication characteristics and physiologic changes modify pharmacokinetics during pregnancy, including changes in absorption, protein binding, distribution, and elimination, requiring individualized pharmacotherapy selection and dosing.
3. Although medication-induced teratogenicity is a serious concern during pregnancy, most medications can be used during pregnancy. Healthcare providers need to evaluate the risk of the medication with the risk of the untreated condition. Informed selection of pharmacotherapy is essential.
4. Healthcare practitioners must know where to find and how to evaluate evidence related to medications used during pregnancy and lactation.
5. Acute pregnancy issues, such as nausea and vomiting, can be treated with nonpharmacologic treatment or carefully selected pharmacotherapy.
6. Some acute and chronic illnesses pose additional risks during pregnancy, requiring treatment with appropriately selected and monitored pharmacotherapies to minimize risk to the fetus and pregnant individual.
7. Management of the pregnant individuals during the peripartum period not only can encompass uncomplicated pregnancies/deliveries, but can also include a wide variety of potential complications that require the use of evidence-based treatments to maximize positive outcomes.
8. Understanding the physiology of lactation and pharmacokinetic factors affecting medication distribution, metabolism, and elimination can assist the clinician in selecting appropriate medications during lactation.

BEYOND THE BOOK

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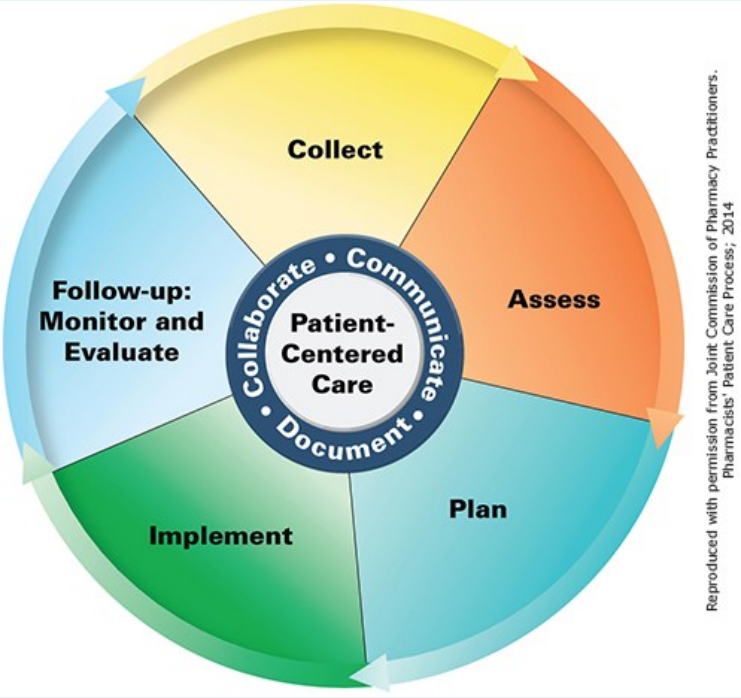
Search the Food and Drug Administration (FDA) Website (https://tinyurl.com/2ujhjm) for "Pregnancy and Lactation Labeling Rule." Choose one link to review and then summarize the key points about the new pregnancy and lactation labeling requirements. How do they differ from pregnancy categories? Do pregnancy categories still exist? This activity is useful to enhance understanding about what type of pregnancy and lactation information to expect in medication product labeling.

PATIENT CARE PROCESS

Patient Care Process for the Management of Gestational Diabetes



Collect

- Patient characteristics (eg, age, race, gender identity, biological sex, pregnancy status)
- Characteristics of the pregnancy (eg, gestational age, gravidity and parity, weight gain to date)
- Characteristics of previous pregnancy(ies) (eg, prior gestational diabetes, birth weight of previous children, unexplained fetal demise)
- Patient history (eg, past medical, family, social habits, physical activity habits, and dietary discretion)
- Current medications (including complementary or alternative therapies) and adherence to medication schedules
- Social and cultural issues: preferences, values, and beliefs; health literacy
- Physical exam: height, weight, body mass index (BMI), blood pressure, heart rate
- Labs (eg, urine dipstick results for glucose, protein, and albumin)

Assess*

- Risk factors and need for early screening and diagnosis (see Table105-2)
- Screening and diagnostic testing between 24 and 28 weeks gestation for all; first trimester testing for high-risk patients (see Table 105-2)
- Achievement of target fasting and 1- or 2-hour postprandial glucose goals
- Efficacy and adherence to dietary modifications and current antihyperglycemic regimen and alternative therapies
- Achievement of goals for comorbidities (eg, blood pressure)
- Assess for depression, anxiety regarding treatment, dietary habits

- Screen for psychosocial problems and barriers to diabetes self-management

Plan*

- Set appropriate blood glucose goals based on age, comorbidities, and other factors
- Tailored lifestyle modifications (eg, diet, exercise)
- Medication therapy regimen including specific antihyperglycemic agent(s), dose, route, frequency, and duration
- Monitoring parameters including efficacy (eg, self-monitored blood glucose), safety (eg, medication-specific adverse events, hypoglycemia), and time frame
- Patient education (eg, potential maternal and fetal adverse events, self-monitoring parameters, risks of uncontrolled blood glucose levels, purpose of treatment, medication administration, dietary and lifestyle modifications)
- Encourage screening at 4 to 12 weeks postpartum visit and periodically throughout life
- Encourage follow-up with primary care provider postpartum if not already established for continued care

Implement*

- Provide patient education regarding all elements of the treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence to the treatment plan
- Schedule follow-up clinic visits to adjust the treatment plan and monitor and evaluate adverse effects

***Collaborate with patients, caregivers, and other healthcare professionals.**

INTRODUCTION

As medication use in pregnancy and lactation is a controversial and emotionally charged subject, due to medicolegal and ethical implications, it is often a topic underemphasized in the education of health professionals. However, clinicians are responsible for ensuring appropriate therapy before conception, during pregnancy and parturition, and after delivery. Optimal treatments for illnesses during pregnancy sometimes differ from those used in the nonpregnant patient, and active patient participation in this process is essential.

In many cases, medication dosing recommendations for acute or chronic illnesses in pregnant individuals are the same as for the general population. However, some cases require different dosing and selection of medications. Principles of medication use during lactation, although similar, are not the same as those applicable during pregnancy.

Within this chapter, the text has been written to reduce the use of gendered terms as recommended by the American College of Obstetricians and Gynecologists (ACOG) and International Lactation Consultants Association. Thus, all included gendered terms refer to biological sex and not gender.

PHYSIOLOGY OF PREGNANCY

[1] Fertilization and progression of pregnancy are complex, resulting in the survival of only approximately 40% to 50% of embryos. Because most losses occur early, usually in the first 2 weeks after fertilization, many individuals do not realize they were pregnant. Spontaneous loss of pregnancy later in gestation (ie, after 12 weeks) accounts for less than 20% of miscarriages.

Fertilization occurs when a sperm attaches to the outer protein layer of the egg, the zona pellucida, and renders the egg nonresponsive to other sperm. The attached sperm releases enzymes that allow the sperm to fully penetrate the zona pellucida and contact the egg's cell membrane. The membranes of the sperm and egg then combine to create a new, single cell called a *zygote*. Male and female chromosomes join in the zygote, fuse to create a single

nucleus, and organize for cell division.

Fertilization usually occurs in the fallopian tube. The fertilized egg begins cell division and travels down the fallopian tube reaching the uterus by day 3. Cell division continues for another 2 to 3 days in the uterine cavity before implantation. Approximately 4 to 5 days after fertilization, the cell mass is termed a *blastocyst*. Implantation begins with the blastocyst sloughing the zona pellucida to rest directly on the endometrium, allowing initiation of growth into the endometrial wall. Human chorionic gonadotropin (hCG) becomes detectable in serum or urine by pregnancy testing, as early as 7 or 9 days after ovulation; however, sensitivity may vary by brand of test. Approximately 6 to 7 days after fertilization, the blastocyst is implanted under the endometrial surface and receives nutrition from the pregnant individual's blood. On the first day of the third week postfertilization, it is called an *embryo*.

After the embryonic period (between weeks 2 and 8 postfertilization), the embryo is renamed a *fetus*. Most body structures are formed during the embryonic period, and they continue to grow and mature during the fetal period. The fetal period continues until the pregnancy reaches term, approximately 40 weeks after the last menstrual period.

Gravidity is the number of times that an individual has been pregnant. A multiple birth is counted as a single pregnancy. *Parity* refers to the number of pregnancies exceeding 20 weeks of gestation and relates information regarding the outcome of each pregnancy. Medical terminology abbreviations are used to indicate an individual's gravidity (G) and parity (P) history. In sequence, the numbers reflect (a) term deliveries, (b) premature deliveries, (c) aborted pregnancies, and (d) the number of living children. For example, in an individual who has been pregnant four times and has experienced two term deliveries, one premature delivery, one ectopic pregnancy and has three living children their designation would be G_4P_{2113}.

Characteristics of Pregnancy

Pregnancy lasts approximately 280 days (about 40 weeks or 9 months) with the time period being measured from the first day of the last menstrual period to birth. *Gestational age* refers to the age of the embryo or fetus beginning with the first day of the last menstrual period, which is about 2 weeks prior to fertilization. For the remainder of the chapter pregnancy information will be described in gestational age. The Naegele rule may be used to estimate due date, by adding 7 days to the first day of the last menstrual period then subtract 3 months. However, early first trimester ultrasounds are the preferred method for determining pregnancy dating, when they are available, due to improved accuracy. Pregnancy is divided into three periods of 3 calendar months, each being called a *trimester*. The first trimester occurs between gestational weeks 1 and 13, the second trimester weeks 14 through 27, and the third trimester weeks 28 to 40, or delivery.

Early signs and symptoms of pregnancy include cessation of menses, breast tenderness and anatomical changes, fatigue, and increased frequency of urination. After the first or second missed menstrual period, nausea and vomiting can occur. While commonly called *morning sickness*, this is a misnomer as it can happen at any time of the day; however, it usually resolves at 14 to 16 weeks gestation. Pregnant individuals may begin to feel fetal movements in the lower abdomen as early as 13 to 16 weeks gestation, with most individuals feeling movement by 18 to 20 weeks gestation.

Pharmacokinetic Changes During Pregnancy

2 Normal physiologic changes that occur during pregnancy may alter medication effects, resulting in the need to more closely monitor and, sometimes, adjust therapy. Physiologic changes begin in the first trimester and peak during the second trimester. For medications that can be monitored by blood or serum concentration measurements, monitoring should occur throughout pregnancy due to the many changes that occur during this time.

During pregnancy, a pregnant individual's cardiac output, and renal clearance both increase by 30% to 50% and plasma volume increases by approximately 40% above baseline. In addition, renal plasma flow increases by up to 80% by the end of the first trimester. This, in combination with increased cardiac output, leads to an overall increase in glomerular filtration rate, which leads to potential lowering in the concentration of renally eliminated medications. With changes in plasma volume and body weight, the volume of distribution of medications may be affected. Plasma albumin concentration decreases by as much as 70% to 80%, which typically increases the volume of distribution of medications that are highly protein bound. Hepatic blood flow is variable during pregnancy. Increases in hepatic blood flow could theoretically increase the hepatic metabolism and elimination of high extraction medications. Additionally, activity of metabolic enzymes and drug transporters changes during pregnancy. Activity of cytochrome P450 3A4, 2C9, and 2D6, as well as UGT1A4 are increased while that of 1A2 is decreased. Nausea and vomiting, as well as delayed gastric emptying, may also alter the absorption of medications.

Transplacental Medication Transfer

Although once thought to be a barrier to medication transfer, the placenta is the organ of exchange between the pregnant individual and fetus for a number of substances, including medications. Most move from the pregnant individual's circulation to the fetal circulation by diffusion. Certain chemical properties impact transplacental medication transfer, such as half-life, lipid solubility, ionization, molecular weight, and degree of protein binding of medications.

Medications with a molecular weight of less than 500 Da readily cross the placenta, whereas larger molecules (600-1,000 Da) cross more slowly. Medications with molecular weight greater than 1,000 Da, such as insulin and heparin, usually do not cross the placenta in significant amounts. Despite the very high molecular weight of monoclonal antibodies, most will cross the placenta and have higher infant levels than maternal levels at the time of delivery. Lipophilic medications, such as opioids and antibiotics, cross the placenta more easily than do water-soluble medications. A pregnant individual's plasma albumin progressively decreases, which may result in higher concentrations of certain protein-bound medications in the fetus. Fetal pH is slightly more acidic than the pregnant individual's pH. Once in the fetal circulation, weak bases (eg, bupivacaine) become more ionized leading to ion trapping, higher fetal levels, and are less likely to diffuse back into the pregnant individual's circulation.

PHARMACOTHERAPY SELECTION DURING PREGNANCY

Many misconceptions exist regarding the association between medications and birth defects. Although some have the potential to cause teratogenic effects, most medications required to manage acute and chronic conditions during pregnancy can be used.

The baseline risk (also known as background risk) for congenital malformations is approximately 3% to 5%. It is imperative when selecting medications to compare the baseline risk to the potential risk of medication exposure. Medication exposure is estimated to account for less than 1% of all birth defects; instead 80% are related to unknown causes, and of those with a known cause, 95% have chromosomal or genetic cause.

Factors such as the stage of pregnancy during exposure, medication route of administration, and dose can also affect outcomes. In the first 4 weeks of gestation, exposure to a teratogen may result in an "all-or-none" phenomenon, which could either destroy the embryo or cause no problems. Organogenesis occurs during the embryonic period when organ systems are developing; therefore, teratogenic exposures during this period may result in structural anomalies. After organogenesis, exposure to teratogens may result in growth restriction, central nervous system abnormalities, impaired organ function, and fetal demise. Examples of medications associated with teratogenic effects in the period of organogenesis include some chemotherapy agents (eg, methotrexate and cyclophosphamide), some sex hormones (eg, androgens), lithium, retinoids, thalidomide, warfarin, and certain antiseizure medications. Other medications, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and tetracycline derivatives, are more likely to exhibit effects in the second or third trimester.

Medications are often necessary during pregnancy for the treatment of acute and chronic conditions. Identifying medication use before conception, eliminating nonessential medications, discouraging self-medication, minimizing exposure to medications known to be harmful, and adjusting doses are all strategies to optimize the pregnant individual's health while minimizing fetal risk. In summary, a small number of medications have the potential to cause congenital malformations, and many can be avoided during pregnancy. In situations where a medication may be teratogenic but is necessary for the pregnant individual's care, considerations related to route of administration, dosage form, and dosing may lessen the risk.

Methods and Resources for Determining Medication Safety in Pregnancy

When assessing the safety of using medications during pregnancy, evaluation of the quality of the evidence is important. Ideally, safety data from randomized, controlled trials are most desirable, but pregnant individuals are not usually eligible for participation in clinical trials. Other types of data commonly used to estimate the risk associated with medication use during pregnancy include animal studies, case reports, case–control studies, prospective cohort studies, historical cohort studies, and voluntary reporting systems (eg, registries). Information can be found from the FDA (https://www.fda.gov/science-research/womens-health-research/list-pregnancy-exposure-registries) and package inserts, and patients should be encouraged to enroll in medication registries when medications are used throughout pregnancy to increase information on medication exposure.

Animal studies are a required component of medication testing, but extrapolation of the results to humans is not always valid, and 75% of the time animal medication exposure does not demonstrate a similar response in humans. Additionally relying on animal data is often limited due to species differences, issues with poor study methodology, concerns for publication bias, study or data inconsistency, and lack of clinical translation. A prime

example of this is thalidomide, which was regarded as safe in some animal models, but proved to have significant teratogenic effects in human offspring. The value of case reports is limited because birth defects in the offspring of pregnant individuals who used medication during pregnancy may occur by chance. It is important to also consider other factors that can influence pregnancy outcomes, such as exposure to tobacco, alcohol, recreational substances, environmental factors, and infection or uncontrolled disease states in a pregnant individual, as these factors are not always accounted for in literature and each can impact pregnancy outcomes. Case–control studies identify an outcome (congenital anomaly), match subjects with or without that outcome, and report how often exposure to a suspected agent occurred. Recall bias is a concern, with retrospective design, as individuals with an affected pregnancy may be more likely to remember medications used during the pregnancy than those with a routine pregnancy.

Cohort studies that evaluate the intervention (use of a particular medication) in a group of persons and compare outcomes in a similar group of subjects without the intervention are also possible. Prospective studies eliminate some of the problems with recall bias, but require time and large numbers of participants and may not adequately account for potential confounding variables. Despite these disadvantages, cohort studies are often used for evaluating the effects of medication exposure on pregnancy outcomes.

Teratology information services provide pregnant individuals and healthcare providers with information about potential exposures during pregnancy. Many also offer additional resources including patient education materials (eg, https://mothertobaby.org/fact-sheets/). These services may publish pooled data to facilitate information sharing about medications used during pregnancy. Some pharmaceutical companies have organized voluntary reporting systems (also called pregnancy registries) for medications used during pregnancy.

4 Computerized databases (eg, LactMed [https://ncbi.nlm.nih.gov/books/NBK501922/]), guidelines, and textbooks with information regarding medication use during pregnancy and lactation offer valuable assistance.

The FDA-approved product-labeling requirements for medications approved after June 20, 2015 include a subsection for pregnancy that provides information about pregnancy exposure registries, a risk summary, clinical considerations, supporting data, lactation, and if there are concerns for reproductive health. Prescription medications approved after June 30, 2001 are required to have updated product labeling to meet the new requirements and use of the new requirements has been phased in gradually. Medications approved before June 30, 2001 do not have to implement the new labeling requirements, but were required to remove the pregnancy category (ie, A, B, C, D, and X) from product labeling due to the multiple limitations of this system including categories oversimplifying risk and causing confusion. Of note, the FDA product labeling update only applies to prescription medications including biologic agents, and pregnancy risk categories remain in product labeling for over-the-counter (OTC) medications.

In summary, determining medication safety during pregnancy is limited by the quality of data and the types of study designs that can be used. While information from product labeling may provide a rough estimate of risks for medication-related adverse fetal outcomes, careful evaluation of other available information sources is necessary to make decisions about medication use in pregnant individuals.

PRECONCEPTION PLANNING

Pregnancy outcomes are influenced by the pregnant individual's health status, lifestyle, and history prior to conception. The goal of preconception care is to optimize the patient's health and well-being, improve pregnancy outcomes, and the future child's health. Key components of preconception planning include both health promotion and patient education. Information supporting healthy lifestyle choices including maintaining a balanced diet, remaining physically active, stress management, and avoiding alcohol, tobacco, and illicit substances are shared to help empower patients to make informed decisions to support overall health and improve the likelihood of a healthy pregnancy. Almost half of all pregnancies in the United States are unintended. Preconception planning is important, since some behaviors and exposures impart risk to the fetus during the first trimester, often before prenatal care is begun or even before pregnancy is detected. Table 105-1 lists selected preconception risk factors, the potential adverse pregnancy outcomes, and management or prevention options.

TABLE 105-1

Selected Preconception Risk Factors for Adverse Pregnancy Outcomes

Preconception Risk Factor	Potential Adverse Pregnancy Outcomes	Management or Prevention Options

Use of Known Teratogens		
Antiseizure medications	• Some are known teratogens; increased risk for craniofacial, NTD, cardiac, and limb defects[a] • Fetal hydantoin syndrome	• Optimize to lower risk therapy while maintaining control prior to conception • Avoid valproic acid[b] • Use monotherapy if possible • Start folic acid at least 0.4 mg daily preferably at least 1 month prior to conception
Retinoids	• Spontaneous abortion • Known teratogen; increased risk for CNS, craniofacial, and cardiac defects[a]	• Discontinue at least 1 month (isotretinoin, bexarotene) or 3 years (acitretin) before attempting conception • Enrolled in iPLEDGE (isotretinoin), Education and Pregnancy Prevention for Acitretin (EPPA) (acitretin). Follow manufacturer recommendations for contraception (isotretinoin, acitretin, bexarotene)
Warfarin	• Fetal warfarin syndrome	• Switch to nonteratogenic anticoagulant (eg, LMWH) before becoming pregnant • Patients with mechanical valves may remain on warfarin for some or all of the pregnancy
Lifestyle Factors		
Alcohol use	• Fetal alcohol syndrome	• Cease alcohol intake before conception
Obesity	• Malformations (eg, NTD and orofacial) • Preterm delivery • Spontaneous abortion • Stillbirth • Macrosomia • Impaired growth • Cesarean section	• Weight loss with appropriate nutritional intake before pregnancy
Tobacco use	• Preterm birth • Low birth weight • Spontaneous abortion • Increased perinatal mortality • Orofacial clefts • Intrauterine growth restriction • Sudden infant death syndrome	• Ideally, cease tobacco use before conception • Individualize approach with nonpharmacologic therapies (including psychosocial and behavioral interventions like CBT, motivational interviewing, and counseling) and can consider NRT products, bupropion, varenicline. Discuss risks and benefits with the patient
Cannabis use	• Intrauterine fetal demise • Low birth weight[c] • Preterm delivery[c]	• Ask about medical and nonmedical use of marijuana in all patients • Educate about potential risks • Encourage to discontinue use ideally prior to conception

CBT, cognitive behavioral therapy; CNS, central nervous system; HTN, hypertension; NRT, nicotine replacement therapy; NTD, neural tube defect; VTE, venous thromboembolism.

[a]List is not all-inclusive.

[b]See 2024 American Academy of Neurology guidelines for additional information.

[c]When stratified by frequency of use (risk at least weekly use).

The most common major congenital abnormalities are neural tube defects (NTDs), cleft palate and lip, and cardiac anomalies. Each year in the United States approximately 3,000 pregnancies are affected by an NTD. Folic acid supplementation in individuals of childbearing potential substantially reduces the incidence of NTDs in their offspring. This is also true in individuals who have previously delivered babies with NTDs, as they occur within the first month of conception due to neural tube closure occurring by gestational week 6. Folic acid supplementation of at least 0.4 to 0.8 mg daily is recommended throughout the reproductive years, since many pregnancies are unplanned and may not be recognized until after the first month. Additionally, 4 mg of folic acid per day starting 3 months prior to conception and continued until 12 weeks gestation is recommended for individuals at high risk for NTD, which includes those with a personal, partner, or previous pregnancy history of an NTD.

Use of alcohol and substances during pregnancy is also associated with risk (see Table 105-1). In 2012 in the United States, alcohol use, cannabis use, and cigarette use were reported in 10%, almost 4%, and 7% of pregnant individuals, respectively. ACOG recommends that patients be educated about the risks of smoking and the potential risks of using nicotine replacement therapy, and should be closely monitored while on therapy. Nicotine replacement therapy during pregnancy may help improve cessation rates and theoretically imparts less risk than exposure to the over 4,000 chemicals found in cigarettes. Although bupropion is not associated with risk during pregnancy, a Cochrane review found that bupropion did not improve cessation rates in pregnancy. Varenicline has limited safety and efficacy data in pregnancy, but available data has not demonstrated teratogenic effects.

ACUTE PREGNANCY ISSUES

Pregnancy causes or exacerbates conditions that pregnant individuals commonly experience, including nausea and vomiting, constipation, hemorrhoids, and gastroesophageal reflux. Individuals with pregnancy-influenced gastrointestinal issues can be treated with lifestyle modification or medications, many of which are nonprescription.

Nausea and Vomiting

5 Nausea and vomiting of pregnancy (NVP) impacts 50% to 80% of pregnant individuals. NVP usually begins between weeks 4 and 6 of gestation and resolves by weeks 14 to 16 with peak symptoms occurring between weeks 8 and 12. Hyperemesis gravidarum (ie, unrelenting vomiting causing weight loss of more than 5% prepregnancy weight, dehydration, electrolyte imbalance, and ketonuria) occurs in 0.3% to 3% of pregnant individuals. Healthcare providers should educate patients with NVP on nonpharmacological interventions. Dietary modifications, such as eating frequent, small, bland, or dry meals every 1 to 2 hours, consuming crackers before getting out of bed in the morning, snacking on high-protein foods, and eliminating fatty or spicy foods, may be helpful. Applying pressure at acupressure point P6 on the volar aspect of the wrist (between the two tendons on about three fingers below the wrist) may be beneficial. Avoiding triggers such as odor, heat, humidity, noise, and flickering lights may help. Additionally, ACOG recommends ginger 250-mg capsules four times daily. If pharmacologic therapy is needed, ACOG recommends pyridoxine 10 to 25 mg with or without doxylamine 12.5 mg up to four times daily, depending on the formulation selected, as the first-line therapy. Immediate release tablets for both agents are available over the counter; however, adverse events such as sedation with doxylamine may limit use. Both extended and delayed release combination tablets are available by prescription, but cost may limit use. If symptoms persist, second line add-on therapies include dimenhydrinate, diphenhydramine, prochlorperazine, and promethazine. Both prochlorperazine and promethazine are available as suppositories if patients are struggling to keep oral products down. For continued symptoms in patients without dehydration, recommended therapies include metoclopramide, ondansetron, and trimethobenzamide as third-line agents. Although metoclopramide has not been associated with a risk of malformations, it carries a boxed warning for tardive dyskinesia. Additionally, the combination of dopamine antagonist therapies such as metoclopramide and phenothiazines may also increase the risk for extrapyramidal symptoms. Conflicting data exist regarding ondansetron use and the risk for malformations such as cardiovascular defects and oral clefts. Ondansetron use prior to 10 weeks gestation should be individualized by patient, after careful consideration of

the associated risks and benefits. Additionally, ondansetron use may prolong the QT interval, particularly in patients with underlying cardiac issues, personal or family history of QT prolongation, use with other medications that can prolong the QT, or electrolyte imbalances. In patients with dehydration, intravenous fluids should be administered, and providers should consider administration of dimenhydrinate, metoclopramide, ondansetron, or promethazine. Intravenous or intramuscular chlorpromazine or methylprednisolone may be added on for patients with persistent symptoms. Corticosteroids may be effective for hyperemesis gravidarum; use should be reserved until after 10 weeks gestation due to a small increase in the risk of oral clefts.

Constipation and Hemorrhoids

5 Constipation affects almost 40% of pregnant individuals and may contribute to the development or exacerbation of hemorrhoids which are more prevalent in pregnant persons compared with the general population. Nonpharmacologic treatment (ie, high dietary fiber intake, maintaining hydration by increasing water intake, and use of sitz baths) or moderate physical activity should be recommended alone or in combination with medication therapy. Bulk-forming agents (eg, psyllium, methylcellulose, and polycarbophil) are considered appropriate for long-term use because they are not absorbed or associated with an increased risk of malformations. However, they are not always effective, can take several days to work, and are associated with unpleasant adverse effects including gas, bloating, and cramping. In addition, bulk-forming agents may lack palatability, especially for patients struggling with nausea and vomiting throughout pregnancy. Osmotic laxatives, specifically polyethylene glycol, are commonly utilized throughout pregnancy. Their use has not been associated with adverse pregnancy outcomes; however, the patient might experience adverse effects such as bloating and increased flatulence. Polyethylene glycol is the preferred medication for patients with chronic constipation during pregnancy. In addition, stool softeners (eg, docusate) may also be used and are well tolerated. Stimulant laxatives (ie, senna and bisacodyl) are associated with a fast onset of action; however, these should be reserved for short-term use. If utilized for long term, use should be limited to 3 days a week. Use of magnesium should be cautioned, as can lead to dehydration secondary to diarrhea, and long-term use may lead to magnesium toxicity. In addition, magnesium may increase the risk for electrolyte imbalances. Castor oil and mineral oil should be avoided because they may cause stimulation of uterine contractions and impairment of fat-soluble vitamin absorption, respectively. Data supporting other management options for hemorrhoids during pregnancy are limited. Hemorrhoids should initially be treated by increasing dietary fiber, increasing hydration, stool softeners, and timed toilet training. Topical anesthetics, skin protectants, and astringents (eg, witch hazel) can be used for prolonged symptoms, including anal irritation and pain. Preparation H products, which contain cocoa butter, phenylephrine, or zinc oxide, serve as a protective barrier and prevent contact with stool, which can cause irritation. Products with phenylephrine reduce inflammation and cause vasoconstriction, which temporarily relieves symptoms of burning, pain, and itching. Steroid creams, including hydrocortisone, are considered second-line topical therapy, and help to reduce inflammation and pruritus.

Gastroesophageal Reflux Disease

5 Up to 80% of individuals experience gastroesophageal reflux disease during pregnancy. Nonpharmacologic therapy with lifestyle and dietary modifications can be recommended alone or with medication therapy (see Chapter 53, “Gastroesophageal Reflux Disease”). Antacids (eg, aluminum, calcium, magnesium preparations) are commonly used to relieve symptoms. Magnesium trisilicate-based antacids (eg, Gaviscon) are less preferred because when used in high doses or for long term have been associated with nephrolithiasis, hypotonia, cardiovascular impairment, and respiratory disease in the fetus. In addition, sodium bicarbonate-based antacids (eg, Alka-Seltzer) are generally not recommended in pregnancy due to the risk of fluid overload and metabolic alkalosis. Additionally, sucralfate is used along with lifestyle modifications because it has minimal systemic absorption. Histamine-2 receptor antagonist (H_2RA), most commonly famotidine, can be used for patients unresponsive to lifestyle changes and antacids or sucralfate. Twice daily dosing with H_2RA therapy is commonly used in pregnancy. The use of proton pump inhibitors (PPIs) during pregnancy is generally reserved for patients who fail H_2RA therapy or who require a PPI prior to pregnancy. PPI therapy does not appear to increase the risk of major birth defects; however, most data come from use of omeprazole. Despite previous concerns regarding omeprazole use during pregnancy, a large cohort study evaluating PPI use during pregnancy did not show an increased risk of birth defects in females who took PPIs, including omeprazole. In instances where delayed gastric emptying is contributing to reflux symptoms, metoclopramide may be considered as an add-on therapy to an H_2RA or PPI.

Diabetes in Pregnancy

6 Up to 7% of pregnancies are complicated by any type of diabetes, with gestational diabetes mellitus (GDM) accounting for roughly 86% of cases

overall. Diabetes diagnosed prior to pregnancy is commonly referred to as pregestational diabetes, whereas GDM is most commonly diagnosed between 24 and 28 weeks gestation. GDM is a complex condition characterized by the development of carbohydrate intolerance, pancreatic β-cell dysfunction, and insulin resistance that occurs during pregnancy. Diabetes that develops during the first trimester of pregnancy is most commonly type 2 diabetes that has been previously undiagnosed; however, this condition may be type 1 diabetes or GDM. The most common risk factor for developing GDM is a history of GDM in a previous pregnancy. Additional risk factors include high-risk race (eg, Asian American, American Indian, Pacific Islander, African American, and Latinx populations), BMI greater than or equal to 25 kg/m^2 (or greater than or equal to 23 kg/m^2 for individuals of Asian decent), history of diabetes in a first-degree relative, previous birth of an infant weighing 4,000 g (about 9 pounds) or more, physical inactivity, hypertension or on medication for hypertension, polycystic ovary syndrome, high-density lipoprotein cholesterol less than 35 mg/dL (0.91 mmol/L), triglycerides greater than 250 mg/dL (2.83 mmol/L), A1c greater than 5.7% (0.057; 39 mmol/mol) or impaired fasting glucose on previous testing, other clinical indications of insulin resistance such as prepregnancy BMI greater than 40 kg/m^2 or acanthosis nigricans, and history of cardiovascular disease.

Complications During Pregnancy

Poorly controlled diabetes, regardless of type, can increase the risk for fetal malformations, fetal morbidity and mortality, and morbidity for the pregnant individual. The most common fetal complications include macrosomia (birthweight greater than 4,000 g), neonatal hypoglycemia often requiring neonatal intensive care unit stay, neonatal hyperbilirubinemia, and birth trauma. In individuals with pregestational diabetes, preconception A1c plays an important role in determining the risk for fetal malformations. Patients with a preconception A1c between 5% and 6% (0.05-0.06; or 31-42 mmol/mol) have a fetal malformation rate similar to pregnancies not impacted by diabetes. As a patient's preconception A1c approaches 10% (0.1; 86 mmol/mol) and higher, the fetal malformation rate increases to 20% to 25%. The most commonly observed malformations include cardiac defects, central nervous system anomalies, and skeletal malformations. An increased risk for long-term complications also exists for the child, and include impaired glucose tolerance, type 2 diabetes, hypertension, obesity, and hyperlipidemia. Risks to the pregnant individual include higher incidence of cesarean delivery, hypertension and preeclampsia, metabolic syndrome, and cardiovascular disease. In addition, individuals with GDM are at a 10-fold increased risk for developing type 2 diabetes later in life, and those with pregestational diabetes are at risk for worsening retinopathy and deteriorating renal function.

Screening and Diagnostic Criteria

Due to the risks for the pregnant individual, fetus, and neonate, the American Diabetes Association (ADA) and ACOG recommend universal screening for GDM between 24 and 28 weeks gestation in all patients not previously diagnosed with type 1 or 2 diabetes. Individuals who have a BMI greater than or equal to 25 kg/m^2 (or greater than 23 kg/m^2 in Asian Americans) and have one or more risk factors for GDM as defined previously should be screened in early pregnancy for undiagnosed diabetes. Generally, early screening is recommended at the first pregnancy visit (or before 15 weeks gestation) for those at high risk if the patient is able to tolerate screening; however, screening may be delayed in patients with uncontrolled nausea or vomiting. If GDM is not diagnosed with early screening, screening should be completed again between 24 and 28 weeks gestation. A diagnosis of GDM can be confirmed using two different approaches: a one-step strategy or a two-step strategy (Table 105-2).

TABLE 105-2

Screening and Diagnosis of Gestational Diabetes Mellitus

One-Step Method	
Complete a 75-g oral glucose tolerance test. Plasma glucose is assessed at fasting, and after 1 and 2 hours. The test should be performed in the morning following an overnight fast of at least 8 hours.	GDM diagnosis is confirmed when one or more of the plasma glucose levels are met or exceeded: Fasting: 92 mg/dL (5.1 mmol/L) 1 hour: 180 mg/dL (10.0 mmol/L) 2 hours: 153 mg/dL (8.5 mmol/L)
Two-Step Method	
Step 1: Complete a 50-g oral glucose loading test. This is typically done in a nonfasting state. Plasma glucose is assessed after 1 hour.	If the plasma glucose level is greater than or equal to 140 mg/dL[a] (7.8 mmol/L), the patient moves to step 2.
Step 2: Complete a 100-g oral glucose tolerance test. Plasma glucose is assessed at fasting, after 1, 2, and 3 hours.	GDM diagnosis is confirmed when at least two of the following plasma glucose levels are met or exceeded: Fasting: 95 mg/dL (5.3 mmol/L) 1 hour: 180 mg/dL (10 mmol/L) 2 hours: 155 mg/dL (8.6 mmol/L) 3 hours: 140 mg/dL (7.8 mmol/L)

[a]A lower threshold of 130 or 135 mg/dL (7.2 or 7.5 mmol/L) may be utilized by some providers; ADA recommends 140 mg/dL (7.8 mmol/L).

Glucose Monitoring

Daily self-monitoring of blood glucose is recommended for all persons with diabetes during pregnancy, including those with GDM. Evidence supporting the optimal frequency of glucose monitoring is lacking; however, in general, patients are recommended to test at least four times daily, with some testing up to seven times a day. Common testing times include fasting glucose, one or two hours after each meal, and before bedtime, with postprandial glucose levels being the best indicator of risk of macrosomia and other complications during pregnancy. Additional testing times are commonly recommended for the following scenarios: premeal glucose monitoring in patients using an insulin pump or if insulin doses are based on premeal values, and between 2 and 3 am if nocturnal hypoglycemia is suspected. Continuous glucose monitoring (CGM) is increasingly being used during pregnancy, especially in patients with type 1 diabetes mellitus. CGM use has been associated with lower incidence of cesarean birth, shorter antenatal and birth maternal hospital stays, fewer large for gestational age infants, less neonatal hypoglycemia, fewer and shorter neonatal ICU admissions, and lower neonatal ICU costs. Regular A1c monitoring is considered a secondary measure of glycemic control during pregnancy and is not routinely utilized for guiding glucose management; however, it may still be assessed once a trimester. Of note, A1c levels decrease by as much as 0.5% (0.006; 0.6 mmol/mol) during normal pregnancy due to an increase in red blood cell turnover. An A1c target of less than 6% (0.06; 42 mmol/mol) is optimal during pregnancy as it is associated with the lowest risk of large for gestational age infants, preterm delivery, and preeclampsia.

Glycemic control can change dramatically during pregnancy and frequent adjustments to management are often needed. Medical nutrition therapy, exercise, and blood glucose monitoring are considered first-line therapies for all with GDM, and as many as 70% to 85% of patients can achieve control with these interventions. Dietary and exercise interventions should be recommended for all patients, but plans are individualized. Refer to the guidelines for specific recommendations.

Glucose Management

Pharmacotherapy should be initiated when medical nutrition therapy and exercise fail to achieve glucose goals within 1 to 2 weeks after initiation. The general threshold that triggers the need for pharmacologic therapy has not been well established; however, many providers will start therapy if most of the glucose concentrations within the most recent week are elevated above goal. The current ACOG guidelines recommend starting insulin under the following parameters: fasting glucose concentrations consistently greater than 95 mg/dL (5.3 mmol/L), 1-hour postprandial concentrations consistently greater than 140 mg/dL (7.8 mmol/L), or 2-hour postprandial concentrations consistently greater than 120 mg/dL (6.7 mmol/L). Insulin is the recommended first line when medication therapy is needed. If patient refuses insulin or has financial limitations, language barriers, or the provider has significant concerns for routine patient follow-up, oral therapy with metformin or glyburide may be considered.

Insulin

Both ADA and ACOG recommend insulin as first-line therapy for glucose management during pregnancy. Human insulin does not cross the placenta, whereas animal insulins can cross in insignificant amounts. A preferred insulin regimen during pregnancy has not been established. Basal insulin options include insulin NPH, and insulin glargine. The initial studies of glucose management in GDM used insulin NPH; thus it is the standard to which all other insulins are compared. Data regarding insulin degludec during pregnancy are limited, although pregnancy outcomes appear to be similar to outcomes with other insulin regimens.

Bolus insulin options include insulin lispro and insulin aspart and both do not cross the placenta and are commonly used during pregnancy. Either insulin lispro or insulin aspart should be used primarily over regular insulin because they are associated with a quicker onset of action which helps prevent hypoglycemia and insulin dosing errors. Data regarding insulin glulisine during pregnancy are limited; however, information available has not shown an increased risk for adverse pregnancy outcomes.

Several daily injections of insulin are often needed during pregnancy to achieve optimal control. The ADA and ACOG do not specify a preferred insulin dosing approach for initiating therapy during pregnancy, nor do they prefer specific insulin. A general weight-based approach suggests starting 0.7 to 1 unit/kg/day of insulin in divided doses. Due to patient variability in dietary intake and increases in insulin resistance that increases throughout pregnancy, insulin doses will likely be titrated often based on the patient's home glucose monitoring.

Metformin

Both ADA and ACOG recommend metformin as an alternative agent for lowering blood glucose during pregnancy. Metformin readily crosses the placenta with umbilical cord blood levels equaling or exceeding maternal levels. Previously, it was used frequently during pregnancy. Metformin is associated with a lower risk of neonatal hypoglycemia and lower weight gain in pregnant individuals compared to insulin, which made it a viable oral option for glucose management during pregnancy. Data evaluating metformin in combination with insulin during pregnancy found individuals on the combination required less insulin, gained less weight, had lower incidence of macrosomia, and had fewer cesarean deliveries compared to insulin alone. In addition, more than 40% of those on metformin monotherapy during pregnancy ultimately require insulin to achieve glycemic control. There are concerns for long-term metabolic changes in offspring exposed to metformin during pregnancy. The long-term metabolic impact of metformin use during pregnancy is not well established; however, there are concerns with exposure during pregnancy and additional data are needed to fully assess the long-term safety and efficacy outcomes. Individuals started on metformin during pregnancy should be educated that metformin crosses the placenta and fetal exposure could result in long-term metabolic effects into childhood.

Glyburide

Both ADA and ACOG recommend glyburide as an alternative to metformin for lowering blood glucose during pregnancy. As a class, sulfonylureas cross the placenta; however, glyburide is the only agent used in pregnancy due to minimal crossing through the placenta. Compared to both insulin and metformin, glyburide is associated with an increased risk of infant macrosomia, neonatal hypoglycemia, and increased neonatal abdominal circumference, even when controlling for similar levels of glycemic control. Observational studies have also reported a higher incidence of preeclampsia, hyperbilirubinemia, and stillbirth in patients taking glyburide compared to insulin. In addition, more than 20% of those on glyburide monotherapy during pregnancy ultimately require insulin to achieve glycemic control.

Postpartum Management and Screening

Insulin resistance begins to decline rapidly postpartum immediately once the placenta is delivered, requiring close glucose monitoring and often

aggressive insulin adjustments. During the first one to two weeks postpartum, insulin sensitivity begins to return to prepregnancy levels. Patients with GDM can often discontinue insulin during this time, and patients with type 1 or 2 diabetes often require significant insulin adjustments. Patients should be educated about the increased risk of hypoglycemia, including how to treat hypoglycemia, especially during this time of decreased sleep and when eating schedules can be erratic. Breastfeeding should be encouraged and supported for patients with diabetes during pregnancy.

Although many individuals with GDM return to normal glycemic control shortly after delivery, patients with GDM have a 50% to 60% lifetime risk for developing diabetes, and a 10-fold increased risk of developing type 2 diabetes compared to patients without GDM. Due to this increased risk, both the ADA and ACOG recommend patients diagnosed with GDM during pregnancy be screened for persistent diabetes during the postpartum period. The ADA recommends screening occur between 4 and 12 weeks postpartum most commonly with a one-step 75-g oral glucose tolerance test. Diagnostic criteria for diagnosing diabetes follow the nonpregnant criteria. If type 2 diabetes is not diagnosed during the postpartum period, periodic screening is recommended every 1 to 3 years with any recommended glycemic test. Lifestyle interventions with a healthier diet and lower weight, and metformin can help prevent or delay the progression to diabetes by 35% to 40%, respectively, over 10 years.

Recently, ACOG updated its recommendation to include the option to screen for type 2 diabetes during the immediate postpartum period while the patient is still hospitalized using the one-step 75-g oral glucose tolerance test. This update was included based on the acknowledgment that fewer than half of patients diagnosed with GDM complete screening during the postpartum period.

Hypertensive Disorders of Pregnancy

6 Hypertensive disorders of pregnancy (HDP) are one of the most common causes of mortality in pregnancy, as well as perinatally. Four categories of HDP are established: (1) chronic hypertension (HTN) (preexisting HTN or developing before 20 weeks gestation); (2) gestational HTN (HTN without proteinuria developing after 20 weeks of gestation); and (3) preeclampsia (HTN with proteinuria) with gestational HTN, may present as the first symptoms of HTN disorder during pregnancy; and (4) chronic HTN with superimposed preeclampsia. Hypertension in pregnancy is defined as either systolic blood pressure (sBP) above 140 mm Hg or diastolic blood pressure (dBP) above 90 mm Hg based upon two or more measurements at least 4 hours apart. Severe hypertension is diagnosed after two measurements of sBP > 160 mm Hg and/or dBP > 110 mm Hg. The two measurements can be confirmed within a short interval (minutes) in order to start antihypertensive therapy quickly.

Risk factors for development of gestational HTN include nulliparity, individuals with first-degree relative with history of gestational HTN (eg, sibling or parent), nonsingleton pregnancies, age less than 20 years or older than 40 years, and a history of HTN or kidney disease in a previous pregnancy.

Preeclampsia is a more complex, multisystem syndrome that complicates up to 8% of pregnancies. Risk factors for the development of preeclampsia are detailed in Table 105-3. Preeclampsia can be divided into early onset (prior to 34 weeks or requiring delivery prior to 37 weeks), late onset, or present up to 6 weeks postpartum. Early onset preeclampsia is typically severe in nature and associated with higher morbidity for pregnant individuals. Diagnosis of preeclampsia includes elevated blood pressure as with HDP and proteinuria (>300 mg/24 hours or a protein/creatinine ratio of >300 mg/g [34 mg/mmol] are preferred, or urine dipstick of 2+). If proteinuria is not present, new onset of any of the following findings with new onset HTN is indicative of preeclampsia: thrombocytopenia (count less than 100×10^3/L [100×10^9/L]), serum creatinine above 1.1 mg/dL (97 µmol/L) or a doubling of serum creatinine, elevated liver transaminases at least twice the upper limit of normal, pulmonary edema, or new onset headache nonresponsive to analgesics or with visual symptoms. Individuals may also experience chest pain or dyspnea, vomiting, and epigastric pain. Other signs and symptoms of preeclampsia that would warrant delivery include: severe uncontrolled HTN, eclampsia, persistent severe headache, pulmonary edema, placental abruption, disseminated intravascular coagulation, and HELLP syndrome (Hemolysis, Elevated Liver enzymes, Low Platelets) or evidence of adverse fetal effects, such as growth restriction.

TABLE 105-3

Risk Factors for Preeclampsia

High-Risk Factors	Moderate-Risk Factors
Preeclampsia in a prior pregnancy	Nulliparity
Nonsingleton pregnancy	Prepregnancy BMI greater than 30 kg/m^2
Chronic hypertension	Family history of preeclampsia (1st degree relative—parent or sibling)
Pregestational diabetes	Sociodemographic characteristics (eg, African American race, low socioeconomic status)
Renal disease	Age greater than 35 years
Autoimmune disease (eg, systemic lupus erythematosus, antiphospholipid syndrome)	Medical history factors (eg, low birth weight or small for gestational age, previous adverse pregnancy outcome, more than 10-year pregnancy interval)
Combinations of multiple moderate-risk factors	

Preeclampsia may progress rapidly to eclampsia, which is defined by new-onset tonic-clonic, focal, or multifocal seizures superimposed on preeclampsia. Eclampsia is a medical emergency that can occur antepartum, intrapartum, or postpartum. It is often preceded by a headache, visual changes such as blurred vision or photophobia, or altered mental status; however, it may present with no warning signs or symptoms.

Complications of Hypertension

All types of HDP are associated with risks to the fetus and pregnant individuals, with these risks increasing with uncontrolled HTN. Complications for the pregnant individual associated with HDP include preeclampsia, eclampsia, stroke, labor induction, and placental abruption. Fetal complications include intrauterine growth restriction, preterm delivery, low birth weight, and stillbirth. Additionally, chronic HTN is associated with increased risk for additional pregnancy and fetal complications including death, pulmonary edema, renal insufficiency and failure, myocardial infarction, cesarean delivery, postpartum hemorrhage, gestational diabetes, and congenital anomalies (eg, heart defects, hypospadias, esophageal atresia).

Management of Hypertension

There is no consensus on treatment thresholds in individuals with mild hypertension. The ACOG recommends pharmacotherapy be initiated quickly in individuals with acute-onset severe HTN that is confirmed as persistent (lasting more than 15 minutes). The ACOG and the Society for Maternal-Fetal Medicine both recommend patients with chronic hypertension maintain a blood pressure threshold of less than sBP 140 mm Hg and dBP 90 mm Hg. However, in gestational hypertension, ACOG recommends that antihypertensive therapy is initiated in patients with persistent blood pressures greater or equal to sBP 160 mm Hg and/or dBP 110 mm Hg. There is a lack of evidence supporting the use of antihypertensive medications in patients with lower blood pressures, but ACOG recommends providers consider using lower blood pressure thresholds in individuals with comorbidities or underlying impaired renal function, but does not provide a specific threshold. When antihypertensive medications are used, it is recommended to maintain blood pressure levels between sBP 120 mm Hg and 160 mm Hg, and dBP between 80 mm Hg and 110 mm Hg. Lowering of blood pressure should occur over a period of hours and aggressive blood pressure lowering should be avoided due to concerns for decreased uteroplacental blood flow.

Treatment of Hypertension

Labetalol and nifedipine are the preferred treatment options for management of HTN during pregnancy. Labetalol is commonly used in practice; however, use may be limited in patients with asthma due to potential for bronchoconstrictive effects. It is also important to monitor the patient for bradycardia. Nifedipine extended-release is also commonly used in practice with twice daily dosing due to increased elimination. Immediate-release

formulations are usually reserved for severe or acutely elevated blood pressure levels in hospitalized patients. Methyldopa is rarely used in practice due to lack of efficacy and increased adverse effects (eg, sedation, dizziness). Hydrochlorothiazide is generally considered a second- or third-line agent for HTN during pregnancy due to theoretical concern for fetal growth restriction and oligohydramnios. Clonidine and prazosin have also been used during pregnancy, but use is generally reserved for patients being closely followed by maternal-fetal medicine or cardiology specialist. Atenolol is associated with fetal growth restriction and generally not utilized during pregnancy. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, renin inhibitors, and mineralocorticoid receptor antagonists are not recommended.

The urgent need for blood pressure control in the setting of severe HTN is typically managed with intravenous labetalol, intravenous or intramuscular hydralazine, or immediate release oral nifedipine. Second-line treatment options include nicardipine or esmolol infusions. Once the patient's blood pressure is controlled, it is important to initiate oral maintenance therapy to maintain control.

Intravenous magnesium sulfate is recommended in patients with severe HTN with preeclampsia to prevent the progression to eclampsia, and to treat eclamptic seizures. Although the duration of magnesium use varies, it is usually administered throughout active labor and continued for 12 to 24 hours postpartum. Benzodiazepines and phenytoin may be considered as treatment for eclampsia in patients with contraindications to magnesium (eg, myasthenia gravis, moderate-to-severe renal failure) or in settings where magnesium is unavailable.

Low-dose aspirin (81 mg/day) prophylaxis is recommended for patients with one high-risk factor or two or more moderate-risk factors for preeclampsia (Table 105-3) to reduce the risk of preeclampsia. Newer data suggests aspirin doses up to 150 mg may provide more protection; however, because this dose is not available in the United States, providers will often recommend 162 mg daily. The exact mechanism of aspirin in the prevention of preeclampsia is not fully understood. Aspirin should be started between 12 and 28 weeks gestation, ideally before 16 weeks, and continued daily until delivery. In high-risk groups, adding low-dose aspirin in 50 pregnant individuals corresponds to preventing one case of preeclampsia. Aspirin prophylaxis is also associated with a risk reduction for preterm birth, small for gestational age, intrauterine growth restriction, and perinatal mortality.

Thyroid Disorders

6 Universal screening for thyroid disorders during pregnancy is not recommended. During pregnancy, stimulation of the thyroid gland may occur because of hCG's structural similarity to thyroid-stimulating hormone (TSH; thyrotropin). This can occur in the first 12 weeks of gestation. In some individuals, gestational transient thyrotoxicosis may result but treatment with antithyroid medication is usually not needed. Occurrence of gestational transient thyrotoxicosis is often associated with hyperemesis gravidarum and the nausea and vomiting symptoms can be treated the same as for patients without this pseudo-hyperthyroid state.

Hypothyroidism is present in 2 to 10 per 1,000 pregnancies. Untreated hypothyroidism increases the risk of low birth weight, preeclampsia, premature birth, miscarriage, fetal death, and placental abruption; impaired neurological development in the fetus may also occur. Causes of hypothyroidism include autoimmune diseases (eg, Hashimoto's thyroiditis), iodine deficiency (uncommon in the United States), and thyroid dysfunction following surgery or ablative therapy for previous hyperthyroidism. If hypothyroidism is present, thyroid replacement should occur with levothyroxine. A reasonable levothyroxine starting dose is 1 to 2 mcg/kg/day or 0.1 mg/day. Individuals receiving thyroid replacement therapy before pregnancy are recommended to receive a 25% dose increase in levothyroxine once the pregnancy is confirmed. Laboratory follow-up of TSH should occur every 4 and 6 weeks during pregnancy to allow for dose titration according to TSH levels of the lower limit of the reference range up to 2.5 mIU/L.

Hyperthyroidism affects 0.2% to 0.7% of pregnancies and is associated with spontaneous abortion, fetal death, low birth weight, and medically indicated preterm delivery. Overall, 95% of hyperthyroidism in pregnancy is due to Graves' disease. Therapy includes the thioamides (eg, methimazole and propylthiouracil). Propylthiouracil is the preferred therapy during the first trimester because methimazole is associated with a higher risk for malformations. Although either thioamide can be used for the remainder of the pregnancy, many providers switch to methimazole because propylthiouracil has been associated with clinically significant hepatotoxicity. The risks of uncontrolled hyperthyroidism outweigh the risks of the thioamides. The goal of therapy is to attain free thyroxine concentrations near the upper limit of normal to allow for dose minimization and to limit fetal or neonatal hypothyroidism. Radioiodine is not recommended because of the risk of thyroid damage in the fetus. If adjunctive therapy is needed to treat symptomatic palpitations, propranolol is the preferred agent.

Although not all pregnant individuals experience postpartum thyroiditis similarly, the typical presentation is characterized by transient hyperthyroidism during the first several months postpartum followed by a period of transient hypothyroidism between 4 and 8 months postpartum. Many cases spontaneously return to euthyroidism. The initial hyperthyroid state usually does not require treatment; however, β-blockers can provide

symptomatic relief of adrenergic symptoms. Because postpartum thyroiditis is from a destructive inflammation process and not overproduction of thyroid hormone, antithyroid medications are ineffective. Up to one-third of individuals affected by postpartum thyroiditis develop permanent hypothyroidism.

Thromboembolic Disorders

Thromboembolism is one of the most common causes of pregnancy-related death in the United States. The risk of developing a venous thromboembolism (VTE) in pregnant or postpartum individuals is increased by fourfold to fivefold over nonpregnant individuals. Low-molecular-weight heparin (LMWH) is recommended over unfractionated heparin and other anticoagulants for both treatment and prophylaxis. Warfarin is reserved as a treatment option in patients with a mechanical valve. Warfarin is not universally used because of the risk for multiple malformations, fetal bleeding, and fetal demise. The direct oral anticoagulants (eg, dabigatran, rivaroxaban, apixaban, and edoxaban) are not recommended due to limited data. If a patient is not a candidate for heparin products (eg, heparin-induced thrombocytopenia, severe allergic reaction), fondaparinux should be considered. Specific recommendations for using prophylaxis, intermediate, or dose-adjusted therapy can be found in the ACOG Practice Bulletin addressing thromboembolism in pregnancy. For acute thromboembolism, anticoagulation therapy should be continued throughout pregnancy and for at least 6 weeks after delivery; the minimum total duration should not be less than 3 months.

Recurrent VTE is divided into three categories: low risk, intermediate risk, and high risk of recurrence. Antepartum monitoring is recommended for individuals with a single episode of VTE who have a low risk of recurrence such as those with one transient risk factor (ie, surgery, injury, lengthy travel, or immobility). For intermediate risk (ie, hormone-related, pregnancy-related, or unprovoked VTE) and high risk (ie, more than one unprovoked VTE or continuous risk factors), antepartum therapy with LMWH or heparin plus 6-week postpartum therapy with either LMWH or warfarin is recommended. Specific recommendations for thrombophilias (eg, antiphospholipid antibodies, Factor V Leiden, prothrombin G20201A, protein C and S deficiencies) can be found in the ACOG Practice Bulletin addressing inherited thrombophilias in pregnancy.

Anticoagulation management of individuals with mechanical heart valves during pregnancy is complex and requires a thorough discussion of the risks and benefits to allow for shared decision making. Management options include continuing warfarin throughout the pregnancy if the patient uses less than 5 mg/day, using dose-adjusted LMWH during the first trimester then warfarin during the second and third trimesters, or using dose-adjusted LMWH throughout the pregnancy. Although warfarin is the most effective therapy for patients with mechanical valves, it crosses the placenta and has fetal risks; however, doses less than 5 mg daily have less risk for malformations than doses greater than 5 mg daily. Additionally, it has been associated with spontaneous abortion, fetal intracranial hemorrhage, neonatal death, and central nervous system defects. Both LMWH and heparin therapies do not cross the placenta but may have a higher risk for thromboembolic events. When heparin products are utilized, dose adjustment should be made to achieve a peak anti-Xa at 4 to 6 hours post-dose of 0.8 to 1.2 U/mL (kU/L) or a prothrombin time (aPTT) at least twice the control value, respectively. Additionally, individuals with mechanical heart valves may also receive low-dose aspirin (75-100 mg/daily). Delivery planning is important to optimize therapy to decrease risks for both the patient and fetus, and patients are switched to unfractionated heparin prior to delivery. See the current American College of Cardiology/American Heart Association guidelines for specific recommendations. Individuals with bioprosthetic valves have a lower risk of thromboembolism than those with mechanical valves; however, management of anticoagulation during pregnancy is similar.

Urinary Tract Infection

Urinary tract infections (UTIs) are common during pregnancy. Typically, UTIs are characterized as asymptomatic (eg, asymptomatic bacteriuria) or symptomatic (eg, lower [cystitis] or upper [pyelonephritis]). Similar to the nonpregnant population, *Escherichia coli* (*E. coli*) is the most common pathogen found in both asymptomatic bacteriuria and UTIs during pregnancy. Asymptomatic bacteriuria occurs in 2% to 15% of all pregnancies, with most cases occurring during early pregnancy. When asymptomatic bacteriuria is left untreated, it progresses to a symptomatic UTI, including acute pyelonephritis, in 20% to 35% of pregnancies. In addition, it has been associated with increased risk for preterm birth and low birth weight; however, evidence is conflicting.

Multiple organizations based in the United States recommend screening pregnant individuals for asymptomatic bacteriuria, although the timing is not universally agreed upon. The Infectious Diseases Society of America recommends pregnant persons be screened for asymptomatic bacteriuria at least once in early pregnancy (prior to 16 weeks gestation) with a urine culture. Guidelines for rescreening patients with an initial negative culture are unclear and generally not recommended. The use of rapid screening tests, such as dipsticks, should be avoided because of the potential for false-negative results.

Acute cystitis occurs in about 1% to 2% of pregnancies, whereas acute pyelonephritis occurs in up to 2%, with most cases occurring in the second or third trimesters. Acute cystitis has not been associated with an increased risk for preterm delivery, low birth weight, or pyelonephritis, most likely because most pregnant individuals receive treatment for symptomatic UTIs. Pyelonephritis during pregnancy has been associated with preterm birth (primarily between 33 and 36 weeks gestation), septic shock and respiratory distress. Treatment of asymptomatic bacteriuria and acute cystitis is necessary during pregnancy to help prevent progression to pyelonephritis and preterm delivery. The optimal therapy and treatment duration are not well defined. Local antibiograms should be used to direct empiric treatment while also considering medication exposure and safety to the fetus. A short-course therapy for asymptomatic bacteriuria is routinely accepted in practice, with a 3- to 7-day course commonly recommended.

Beta-lactams (including penicillins and cephalosporins) have been widely used to treat asymptomatic bacteriuria and cystitis. Beta-lactams are not known teratogens; however, increasing resistance to ampicillin and amoxicillin limits their use as single agents. Nitrofurantoin is not active against Proteus species and should not be used after week 37 in patients with glucose-6-phosphate dehydrogenase deficiency because of a theoretical risk for hemolytic anemia in the neonate. Sulfa-containing medications can contribute to the development of newborn kernicterus; use should be avoided during the last weeks of gestation. Trimethoprim is a folate antagonist and is relatively contraindicated during the first trimester because of associations with congenital malformations. Regionally, increased rates of resistance to trimethoprim-sulfa may limit its use. Single-dose fosfomycin may be considered, as it successfully treats bacteriuria and acute cystitis. Fluoroquinolones and tetracyclines are contraindicated because of potential associations with impaired cartilage development and deciduous teeth discoloration (if given after 5 months of gestation), respectively.

Hospital admission for parenteral antibiotics is the standard of care for pregnant individuals with pyelonephritis. Intravenous antibiotics are utilized until the patient is afebrile for 24 hours and symptomatically improving; at that point antibiotic therapy can be converted to an oral regimen to complete a 14 day therapy. Broad spectrum beta-lactam antibiotics (eg, cefepime, ceftriaxone, ampicillin plus gentamicin in patients with a beta-lactam allergy) are preferred for the initial empiric treatment. Choice between specific agents should be guided by local antibiograms and patient tolerance. Nitrofurantoin and fosfomycin should be avoided because both fail to achieve therapeutic levels outside of the urine.

Recurrent UTIs occur in 4% to 5% of pregnancies. Due to the risks associated with infections during pregnancy, prophylactic or suppressive antibiotics may be considered in patients with recurrent cystitis. Suppressive therapy with postcoital or continuous prophylaxis throughout the remainder of pregnancy may be considered. Common regimens utilized for suppressive therapy include nitrofurantoin 100 mg daily or cephalexin 250 to 500 mg daily.

Recurrent pyelonephritis is also common during pregnancy, occurring in up to 25% of patients. Data supporting the use of suppressive antibiotics to reduce the recurrence of pyelonephritis is limited. When initiated, nitrofurantoin 100 mg or cephalexin 250 to 500 mg orally every day during the pregnancy and through postpartum week 4 to 6 is recommended. Continued monitoring with monthly urine culture is recommended through the duration of pregnancy.

Sexually Transmitted Infections

Sexually transmitted infections (STIs) in pregnant individuals range from infections that may be transmitted across the placenta and infect the infant prenatally (eg, syphilis) to organisms that may be transmitted during birth and cause neonatal infection (eg, *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, or herpes simplex virus) to infections that pose a threat for preterm labor (eg, bacterial vaginosis). Screening recommendations for STI during pregnancies as well as tests of cure and repeat testing that may be needed for various infections during pregnancy are provided in Table 105-4. Treatment for select STIs is summarized in Table 105-5.

TABLE 105-4

STI Recommendations During Pregnancy

STI	When to Screen in Pregnancy	When to Check Test of Cure After Treatment	When to Repeat Screening
Chlamydia	1st prenatal visit less than 25 years old: all greater than 25 years old: only if increased risk[a] 3rd trimester: if at increased risk[a]	4 weeks after treatment	3 months after treatment
Gonorrhea	1st prenatal visit less than 25 years old: all greater than 25 years old: only if increased risk[a] 3rd trimester: if at increased risk[a]		3 months after treatment
Hepatitis B[b]	All: 1st prenatal visit		
Hepatitis C	All (unless the infection rate is less than 0.01%)		
HIV	All: 1st prenatal visit High risk[c]: 3rd trimester (before 36 weeks)		
Syphilis	All: 1st prenatal visit High risk[d]: 28 weeks and delivery	See guidelines for specific recommendations	

STI, sexually transmitted infection.

[a] Increased risk defined as not monogamous, multiple sexual partners, new sexual partner, or partner with an STI. Additionally, patients should have gonorrhea testing if they are diagnosed with other STIs during pregnancy.

[b] Individuals should be screened with the hepatitis B surface antigen. Additionally, the anti-HBs and total anti-HBc should also be checked if the patient does not have a documented triple negative result after age 18, has not completed the hepatitis B vaccine series, or has ongoing known risks for hepatitis B infection regardless of previous vaccination or negative testing. If the patient has not previously received the hepatitis B vaccine series, all should be vaccinated.

[c] High risk defined as injection substance users, STI diagnosed in pregnancy, not monogamous, new sexual partner during pregnancy, partner with HIV, receive healthcare in a facility with HIV incidence > 1 per 1,000 individuals per year, incarcerated, live in an area with high HIV rates, signs or symptoms of acute HIV (fever, lymphadenopathy, skin rash, myalgia, arthralgia, headache, oral ulcers, leukopenia, thrombocytopenia, or transaminase elevation).

[d] High risk defined as live in a community with high syphilis rate or at risk for syphilis infection during pregnancy (STI diagnosed in pregnancy, multiple partners, sex in conjunction with substance use or transactional sex, late or absent prenatal care, methamphetamine or heroin use, incarceration of the patient or her partner, unstable housing or homelessness).

TABLE 105-5

Management of Sexually Transmitted Infections in Pregnancy

STI	Recommended Therapy	Alternative Therapy
Bacterial vaginosis	Metronidazole 500 mg by mouth twice daily for 7 days Metronidazole 0.75% gel 5 g intravaginally once daily for 5 days Clindamycin 2% cream 5 g intravaginally at bedtime for 7 days	Clindamycin 300 mg by mouth twice daily for 7 days Clindamycin ovules 100 mg intravaginally at bedtime for 3 days
Chlamydia	Azithromycin 1 g by mouth for 1 dose	Amoxicillin 500 mg by mouth three times a day for 7 days
Genital herpes	Suppression (starting at 36 weeks) Acyclovir 400 mg by mouth three times a day Valacyclovir 500 mg by mouth twice daily	
Gonorrhea	Ceftriaxone 500 mg IM for 1 dose. If chlamydia has not been excluded, treat for chlamydia as well	Consult with infectious disease specialists or STI clinical expert if patient has a cephalosporin allergy or other reasons to not use the preferred treatment
Syphilis[a]		
Primary, secondary, early latent	Benzathine penicillin G 2.4 million units IM for 1 dose; a second dose can be given 1 week after initial dose to help reduce the risk for congenital syphilis	
Tertiary[b], late latent[c]	Benzathine penicillin G 2.4 million units IM for 3 doses at 1-week intervals	
Trichomoniasis	Metronidazole 500 mg by mouth twice daily for 7 days	

CSF, cerebrospinal fluid; g, grams; IM, intramuscular; IV, intravenous; mg, milligrams; STI, sexually transmitted infection.

[a] Pregnant individuals with history of penicillin allergy should undergo penicillin desensitization as no proven alternatives exist.

[b] With normal cerebrospinal fluid examination.

[c] If a patient misses a dose (ie, greater than 9 days between doses), series needs to be restarted.

Syphilis

Syphilis is caused by *Treponema pallidum* and can cause many complications in pregnancy (eg, mucocutaneous lesions, altered mental status, visual and auditory abnormalities, gumma, cranial nerve palsies). Syphilis in a pregnant individual increases the risk for congenital syphilis, and all exposed neonates should be evaluated after birth. Ultrasound monitoring of the fetus to evaluate for congenital syphilis (eg, hepatomegaly, ascites, hydrops, fetal anemia, thickened placenta) should be performed if syphilis is diagnosed in the second half of pregnancy. If these signs are detected, a second dose of penicillin G may be administered for fetal treatment. Penicillin effectively prevents transmission to the fetus and treats the fetus, if already infected. Treatment during the second half of pregnancy may increase the risk for preterm labor and fetal distress because a Jarisch–Herxheimer reaction may occur; however, treatment should not be withheld or delayed.

Chlamydia and Gonorrhea

Infections with both chlamydia and gonorrhea in pregnant individuals are capable of vertical transmission (passing of the infection from the pregnant individual to the neonate) through exposure to the infected cervix during delivery. Perinatal infections of *C. trachomatis* most commonly cause conjunctivitis that develops 5 to 12 days postpartum. A subacute, afebrile pneumonia with an onset at ages 1 to 3 months may occur.

With *N. gonorrhoeae* infections, neonatal symptoms usually manifest within 2 to 5 days after delivery. Milder manifestations include rhinitis, vaginitis, urethritis, and scalp infections at sites where fetal monitoring electrodes were placed. More severe presentations include ophthalmia neonatorum and sepsis. Because untreated ocular infections can lead to perforation of the globe of the eye and blindness, the United States Preventative Services Task Force recommends all neonates receive ocular erythromycin ointment as prophylaxis within 24 hours after delivery.

Bacterial Vaginosis and Trichomoniasis

Bacterial vaginosis and trichomoniasis infections are characterized by vaginal discharge. Bacterial vaginosis is not an STI but is more common in sexually active individuals and may increase the risk for other STIs. Bacterial vaginosis results from the lack of normal vaginal flora (ie, *Lactobacillus* species) and replacement with anaerobic bacteria, mycoplasmas, and *Gardnerella vaginalis*. Untreated bacterial vaginosis increases the risk for premature rupture of membranes, preterm labor, preterm birth, intraamniotic infection, and postpartum endometritis.

Trichomoniasis is caused by the protozoa, *Trichomonas vaginalis*, and infection is associated with an increased risk of premature rupture of the membranes, preterm delivery, and low birth weight. Treating the pregnant individual during pregnancy can help prevent neonatal respiratory and genital infections.

Hepatitis Infections

Hepatitis infections may be identified during pregnancy with routine laboratory screening. According to ACOG and the Centers for Disease Control and Prevention (CDC), patients who have not been previously vaccinated nor have immunity for hepatitis B should receive the hepatitis B vaccine during pregnancy. Hepatitis A vaccination is recommended for patients who are at an increased risk for hepatitis A infection, which includes international travelers, patients with occupational risks for exposure, those who are experiencing homelessness, those who use illegal drugs, and patients at risk for severe disease from a hepatitis A virus infection. Although several newer medications are available for treating hepatitis C infections, no recommendations are available now. If a provider decides to treat during pregnancy, ribavirin-based regimens should be avoided.

Genital Herpes

Neonatal herpes often occurs in infants born to individuals lacking histories of genital herpes. The risk of neonatal transmission is under 1% for those with a history of recurrent herpes at term or those who acquire herpes in the first half of pregnancy, but is 30% to 50% for individuals who initially acquire genital herpes near term. However, because recurrent herpes occurs more commonly than new acquisition during pregnancy, it remains the cause of most cases of neonatal transmission. Prevention strategies include counseling uninfected individuals to avoid intercourse during the third trimester with partners having known or suspected genital herpes infection. Individuals with no history of orolabial herpes should avoid receptive oral sex during the third trimester with partners who have orolabial herpes. Prevention of genital herpes transmission to pregnant individuals using antiviral agents has not been studied.

All patients should be asked about symptoms of genital herpes at the time of delivery and should be examined for lesions. For those who have no symptoms (including prodromal symptoms) or lesions, proceed with vaginal childbirth; however, in those with evidence of an outbreak it is recommended that a cesarean section be performed to decrease the risk of neonatal transmission. Suppression therapy with either acyclovir or valacyclovir starting at 36 weeks decreases the recurrence of genital herpes at term, which decreases the need for cesarean delivery.

The CDC and ACOG recommend both medications. Due to increased renal elimination, acyclovir needs to be administered three times a day whereas valacyclovir is given twice daily. Both cost and adherence should be considered for patients. For initial or recurrent episodes, most patients receive oral therapy; IV acyclovir is reserved for severe infections. In those seropositive for herpes simplex virus but who have not experienced an outbreak, no data suggest a treatment benefit.

Human Immunodeficiency Virus Infection

The rate of perinatal HIV transmission is 1% or less in the United States and Europe as a result of national recommendations for universal prenatal HIV counseling and testing, antiretroviral (ARV) therapy use, cesarean delivery if the HIV RNA is greater than 1,000 copies/mL (1×10^6/L) near delivery, infant ARV therapy, and breastfeeding avoidance. The primary goal for HIV-infected individuals is to achieve sustained viral load suppression below the limits of detection before conception as well as throughout pregnancy and the remainder of their life. ARV therapy should be started preconception for patients with known HIV, regardless of viral load or CD4 count, for the patient's health and to decrease the risk for perinatal and partner transmission. In patients newly diagnosed with HIV or who have not previously received ARV therapy, pharmacotherapy should be initiated as soon as pregnancy is determined since the risk of perinatal transmission is lower with earlier viral suppression, and the regimen can be adjusted if needed after resistance results are available. Recommendations regarding combination ARV therapy change frequently as new data becomes available, and providers should check the most up to date guidelines (https://aidsinfo.nih.gov).

For pregnant individuals with HIV RNA levels above 1,000 copies/mL (1×10^6/L) or unknown who are approaching delivery, a scheduled cesarean section at 38 weeks of gestation is recommended to reduce the risk of perinatal HIV transmission. Scheduled cesarean section is not recommended if HIV RNA levels are 1,000 copies/mL (1×10^6/L) or below because of the low rate of perinatal transmission. If the viral load is greater than 1,000 copies/mL (1×10^6/L) or not known, IV zidovudine should be initiated with a 1-hour loading dose (2 mg/kg) followed by a continuous infusion (1 mg/kg) for 2 hours with a minimum of 3 hours total. Intravenous zidovudine should still be administered in the presence of resistance to zidovudine. Consider administration of IV zidovudine to individuals with a viral load between 50 and 1,000 copies/mL (0.05×10^6 and 1×10^6/L) near delivery. Although there is inadequate information that zidovudine provides additional protection, there may be benefit as there is a slightly higher rate of transmission with a viral load in this range. Patients with a viral load below 50 copies/mL (0.05×10^6/L) near delivery do not require IV zidovudine, but they should continue their ARV therapy. Specific recommendations for different clinical scenarios during antepartum, intrapartum, and postpartum are provided in the clinical guidelines.

Headache

6 Primary headaches (eg, tension and migraine) in pregnant and nonpregnant individuals are the most common types of headaches. Hormonal fluctuations, particularly changes in estrogen, can be a trigger for headaches throughout pregnancy. Secondary headaches can also occur, indicating a more serious underlying condition, and include those caused by preeclampsia, stroke, postdural puncture, cerebral angiopathy, and cerebral venous thrombosis. Warning signs for a secondary headache include severe pain or "thunderclap" headache, rapid onset or change from baseline, elevated blood pressure, visual changes, altered mental status or confusion, fever, vomiting, abnormal findings on neurologic examination, and laboratory changes (presence of thrombocytopenia, thrombocytosis, elevated liver enzymes, elevated creatinine).

Pregnant individuals with a history of migraine headaches have an increased risk of developing hypertension, including preeclampsia. In early pregnancy, migraine frequency typically decreases, with improvement seen in roughly 60% to 80% of patients by the second trimester. By the third trimester, 87% of individuals have improved migraine symptoms and frequency. In 3% to 7% of cases, patients will experience new onset migraine headaches during pregnancy, typically developing during the first trimester.

Relaxation therapy, avoidance of triggers, stress management, and cognitive-behavioral therapy are all effective nonpharmacologic treatment methods that can be utilized during pregnancy. Sleep hygiene should be encouraged as a poor sleep pattern can increase headache frequency. In addition, maintaining adequate hydration, reducing caffeine intake, and exercise may all benefit as well.

Pharmacologic treatment for migraines typically involves acetaminophen 1,000 mg orally initially, and antiemetics (eg, metoclopramide). Over-the-counter acetaminophen plus caffeine product (no aspirin) may be considered, but patients should be cautioned to limit caffeine intake below 200 mg/day. Opioids have been used but may contribute to migraine-associated nausea and routine use can increase migraine frequency and severity. Long-term use of opioids near the end of pregnancy can cause neonatal opioid withdrawal syndrome. For migraines that are not responsive to other treatments, triptans may be used. Of note, the package insert for sumatriptan indicates pregnancy as a contraindication for use; however, no human data have suggested teratogenicity for any medication in the triptan class. Sumatriptan is the triptan of choice because medication transport across the placenta is small and it has a short elimination half-life of 2 hours. Migraine prophylaxis may be indicated for patients with frequent, disabling headaches to help decrease headache frequency and severity. A few dietary supplements have shown benefits for prophylaxis, and include daily riboflavin, or magnesium supplementation. Ergotamine and dihydroergotamine are contraindicated because of the risk of uterine contractions. Other typical migraine prophylactic therapy is often evaluated on an individual basis for medication safety and necessity.

Tension headaches are less studied; however, most patients report no change in the frequency or intensity of tension headaches, although remission is possible. Tension headaches are treated similarly, with acetaminophen being the treatment of choice for pain management. The NSAIDs are generally not recommended for use during pregnancy, particularly in late pregnancy (after 20 weeks gestation) or during labor and delivery, because they inhibit prostaglandin synthesis, which may cause harm including oligohydramnios, prolonged labor, or premature closure or constriction of the ductus arteriosus. Antiemetics may be added in patients experiencing nausea and vomiting. Products containing butalbital or opioids should be avoided.

Allergic Rhinitis and Asthma

Asthma and rhinitis are common chronic illnesses in pregnancy, and asthma affects approximately 4% to 8% of pregnancies. During pregnancy, a third of patients have symptoms that worsen, a third will have symptoms improve, and a third will have symptoms remain unchanged. Diagnosis, goals, and staging of asthma during pregnancy are the same as in nonpregnant individuals, although more frequent follow-up is necessary because of changes in disease severity. Bronchoprovocation should be avoided. Health consequences of poorly controlled asthma include morbidity and mortality, preterm labor, preeclampsia, cesarean delivery, intrauterine growth restriction, premature birth, and low birth weight for infants; therefore, the treatment goal is to achieve and maintain control of asthma symptoms to prevent hypoxic episodes in both the pregnant patient and fetus.

Risks of medication use to the fetus are lower than the risks of untreated asthma; therefore, the use of medications to achieve and maintain control is warranted. Routine pulmonary function evaluation, peak flow testing, and symptom monitoring are recommended during pregnancy because asthma severity can change during pregnancy. Treatment recommendations are divided into multiple steps based on symptom control and follow a stepwise approach. Because inhaled corticosteroid therapy decreases the risk for exacerbations and discontinuation of these medications can significantly increase the risk for an exacerbation, the Global Initiative for Asthma (GINA) guidelines recommend continuing inhaled corticosteroids for individuals who are planning to become or are currently pregnant. Oral corticosteroids may be considered when needed. Currently, the ACOG, 2020 focused update to the asthma management guidelines (EPR3 update), and GINA guidelines vary in recommendations for rescue therapy, which is likely due to available literature at the times of publication, FDA approved indications for rescue therapies, and available data specifically in the obstetric population. In general, patients should have rescue therapy during pregnancy to help with symptom management. Additionally, the GINA guidelines recommend that step-down therapy should be a low priority until the patient is postpartum.

Preexisting or newly developed allergic rhinitis occurs during pregnancy and nasal congestion can be caused by pregnancy because of vascular engorgement in the nasal passages and hormonal effects on mucus secretion. Treatment strategies for allergic rhinitis during pregnancy are similar to those used in nonpregnant individuals and include avoidance of allergens, immunotherapy, and pharmacotherapy. Oral antihistamines and leukotriene receptor antagonists as well as intranasal antihistamines, decongestants (limit duration because of the risk for medication-induced rhinitis), cromones, and corticosteroids can be used. Immunotherapy is not contraindicated in pregnancy; however, it should not be initiated for the first time during pregnancy due to the risk of anaphylaxis.

Epilepsy

Seizure frequency does not change for most pregnant individuals with epilepsy. Of those who have been seizure free for at least 9 months prior to pregnancy, 84% to 92% will remain seizure free during pregnancy. Studies have demonstrated no change in seizure frequency in 54% to 80% of pregnant individuals with epilepsy, while decreased seizure frequency occurs in 3% to 24% and increases approximately 14% to 32%. Seizures may become more frequent because of changes in hormones, sleep deprivation, and medication adherence problems due to perceived teratogenic risk. Another potential cause is changes in free serum concentrations of antiseizure medications resulting from changes in absorption, increased volume of distribution in the pregnant individual, decreased protein binding from hypoalbuminemia, increased hepatic metabolism, and increased renal clearance. A patient's clinical condition and serum concentrations, either total or free depending on the medication, should be the basis for dose adjustments, and some experts recommend checking levels preconception and monthly during the pregnancy. The 2019 International League Against Epilepsy guidelines recommend monitoring levels for phenobarbital, phenytoin free concentrations, oxcarbazepine monohydroxy-derivative, lamotrigine, gabapentin, topiramate, levetiracetam, and zonisamide as well as optional level monitoring for carbamazepine and valproic acid free concentrations.

The risks of uncontrolled seizures to the fetus, particularly tonic-clonic seizures, are considered to be greater than those associated with antiseizure medications. Pregnant individuals with epilepsy are at an increased risk for spontaneous abortion, preeclampsia, pregnancy-induced hypertension, preterm labor and delivery, bleeding complications, death, and cesarean delivery compared to those without epilepsy. Additionally, focal seizures with

loss of consciousness are associated with uterine contractions and fetal heart rate changes whereas frequent tonic-clonic seizures have been associated with decreased neurodevelopment in the child. Teratogenic effects with some antiseizure medications such as valproic acid and potentially also carbamazepine, lamotrigine, and phenobarbital are related to the dose, often with a threshold above which risks increase. Use of valproic acid should be avoided during pregnancy due to high risk of neural tube defects and facial clefts with first trimester exposure, and cognitive teratogenicity with exposure throughout pregnancy. Although many antiseizure medications are associated with potential risks during pregnancy, including malformations, it is important to consider the benefits of preventing seizures for both the pregnant individual and the fetus. Because some organs form early in gestation, the ideal time to switch to a preferred therapy is prior to pregnancy. Recent literature has found that medications such as levetiracetam and lamotrigine were not associated with malformations whereas conflicting results or limited exposures for others makes it difficult to fully evaluate the potential risks. It is important for healthcare professionals to utilize pregnancy specific references and epilepsy in pregnancy guidelines to find the most up to date information for each agent.

When possible, antiseizure medication monotherapy is recommended with medication regimen optimization occurring before conception. If gradual medication withdrawal is attempted because of epilepsy remission, it should be fully completed and evaluated before trying to conceive. Medication changes to avoid the use of valproic acid, phenytoin, carbamazepine, phenobarbital, and polytherapy are suggested ideally during preconception; however, if these are used during pregnancy because of treatment failure with other medications, the lowest effective dose should be used. All pregnant individuals taking antiseizure medications should receive folic acid supplementation starting before pregnancy and continuing through at least the first trimester. Many experts continue to recommend 4 mg daily dose, but this recommendation is not universal. Because evidence has not definitively shown the efficacy of high dose folic acid supplementation with antiseizure medications, the American Academy of Neurology recommends at least 0.4 mg daily.

Mental Health Conditions

6 Approximately 20% of women will experience a mental health incident during pregnancy or postpartum. Psychotherapy and medications can be utilized during pregnancy for management of mental health disorders. Pregnancy and lactation status alone should not be a reason to withhold medications for the treatment of mental health conditions. ACOG recommends some general principles regarding medication use during pregnancy and lactation. Practitioners should use the lowest effective dose but recognize that medication dosages may need to be increased during pregnancy due to increased metabolism and/or elimination during pregnancy. During pregnancy and postpartum, all patients should have mental health treatment that is available and accessible. When possible, practitioners should try to use monotherapy and minimize switching therapy during pregnancy to decrease fetal exposure. Finally, untreated and undertreated mental health disorders should be considered a pregnancy exposure as well since uncontrolled mental health conditions also pose a risk to the mother-child dyad (Table 105-6). Additionally, patients using various medications for mental health conditions during pregnancy should be encouraged to enroll in registries to help add to the understanding of these conditions and medications during pregnancy.

TABLE 105-6

Risks of Uncontrolled Mental Health Conditions and Medications During Pregnancy

Risks of Uncontrolled Mental Health Conditions		
Depression	**Anxiety Disorders**	**Bipolar Disorder**
Limited participation in medical and self-care Substance use Preterm delivery Low birth weight Preeclampsia Postpartum depression Impaired infant attachment (impacts long-term development) Impaired partner relationship Suicide	Preterm delivery Low birth weight Behavioral changes in children Suicide risk Postpartum depression Maternal functional impairment	25%-50% increased risk for postpartum psychosis Postpartum worsening of mood Intrauterine growth restriction Preterm delivery Adverse neurodevelopmental outcomes
Risks of Selected Mental Health Medications		
SSRI	**SNRI**	**Benzodiazepines**
Persistent pulmonary hypertension Transient poor neonatal adaption syndrome (late pregnancy exposure)	Persistent pulmonary hypertension Transient poor neonatal adaption syndrome with late pregnancy exposure Preeclampsia Spontaneous abortion	Spontaneous abortion (1st trimester) Preterm delivery Low birth weight Low Apgar Score NICU admission (late pregnancy exposure)
Lithium	**Second-Generation Antipsychotics**	**Valproic Acid**
Cardiac malformations (1st trimester)	Generally, not associated with malformations except olanzapine may increase the risk for oral clefts (1st trimester) Transient poor neonatal adaption syndrome (late pregnancy exposure)	Neural tube defects (1st trimester) Cardiac malformations (1st trimester) Orofacial clefts (1st trimester) Limb defects (1st trimester) Neurodevelopmental delays (any exposure)
Registry Information		
National Pregnancy Registry for Antidepressants **866-961-2388** https://womensmentalhealth.org/research/pregnancyregistry/antidepressants/ **North American Antiepileptic Drug (NAAED) Registry** **888-233-2334** https://www.aedpregnancyregistry.org/ **National Pregnancy Registry for Psychiatric Medications** **866-961-2388** https://womensmentalhealth.org/research/pregnancyregistry/		

All patients should be screened for depression and anxiety during the first prenatal visit, later in the peripartum period, and at postpartum visits. Symptoms of depression are often overlooked during pregnancy because they overlap with many symptoms of pregnancy (eg, irritable mood, weight loss or gain, appetite and sleep changes, fatigue/loss of energy). There are several survey tools that can be utilized during pregnancy and during the postpartum period to help evaluate and monitor depression symptoms (eg, the Edinburgh Postnatal Depression Scale, Patients Health Questionnaire-9). Additionally, these tools should be administered every four weeks for those on treatment to monitor for response and remission. Additionally, ACOG recommends screening patients for bipolar disorder before prescribing antidepressants since 22.6% of patients with a positive depression screen actually have bipolar disorder.

Patients and providers often stop medications during pregnancy due to concerns about risks. Patients who stop taking antidepressants are more likely to relapse, which can also have implications for the well-being of the fetus. The risks and benefits of mental health medication use during pregnancy and the risks of untreated depression must be discussed with all patients in order to increase understanding. Because most mental health medications are used to treat more than one condition, the reader should refer to the mental helath section for information about the treatment of specific mental health diagnoses.

The ACOG recommends selective serotonin reuptake inhibitors (SSRIs) as the first-line treatment for depression and anxiety during pregnancy; however, serotonin-norepinephrine reuptake inhibitors (SNRIs) and atypical antidepressants are also utilized (see Chapter 92, “Depressive Disorders”). Selection of therapy should be based on prior response if available. If the patient does not have a history of being on medication therapy, sertraline or escitalopram are considered first-line treatment options. Conflicting studies about the risk of cardiac malformations with paroxetine are published in the literature. One study found the risk was associated with doses greater than 25 mg a day. Despite this association, antidepressants are not considered major teratogens, as no consistent information supports an association with structural malformations. SSRIs have been associated with an increased risk of persistent pulmonary hypertension in the newborn; however, the risk is small (additional 1-2 cases per 1,000 treated). Use of SSRIs in the latter part of pregnancy is associated with poor neonatal adaptation syndrome which encompasses transient neonatal complications of irritability, restlessness, tremors, hyperreflexia, hypoglycemia, hypothermia, sleep disruption, poor feeding, and rarely seizures. Symptom onset is usually within a few days after delivery and resolves within 2 weeks. This impacts approximately 10% to 30% of exposed infants. Nonpharmacologic supportive care such as skin-to-skin contact and increased feedings can be recommended. Second-generation antipsychotics are generally well tolerated and effective in managing symptoms of treatment-resistant depression. Although second generation antipsychotics have metabolic risks, ACOG recommends screening for gestational diabetes at standard times for obstetric patients. Some providers may also use buspirone for anxiety symptoms.

In general, benzodiazepine use is not recommended during pregnancy. If patients are taking benzodiazepines during pregnancy, they should be used sparingly and should not be abruptly discontinued due to risk for withdrawal. Benzodiazepine use in the third trimester can cause infant sedation, decreased muscle tone, respiratory depression, and neonatal intensive care admission. Alternatively, hydroxyzine can be considered for relief of anxiety symptoms.

Mood stabilizers, such as lithium, lamotrigine, valproic acid, and second-generation antipsychotics are often used to treat bipolar disorder. The reader can find information related to the safety of the therapies used for mood stabilization in Chapters 79, “Epilepsy” and 93, “Bipolar Disorder.” In general, ACOG advises against discontinuing mood stabilizers during pregnancy due to the increased risk of exacerbation of mood symptoms, with the exception of valproate.

Abrupt discontinuation of lithium therapy during pregnancy is associated with an increased risk for relapse. Lithium use in early pregnancy has also been associated with cardiovascular anomalies, particularly Ebstein’s anomaly. The risk of cardiac malformation was only found with doses higher than 900 mg daily. In addition, when lithium is used during pregnancy providers need to be aware of potential changes in lithium levels due to pharmacokinetic changes, dehydration in the pregnant individual, and medication interactions. Due to these changes in pregnancy and its narrow therapeutic index, lithium needs monitoring during pregnancy and postpartum. Because lithium use near term is associated with toxicities in the newborn, including respiratory difficulties, tachycardia, tremor, somnolence, and hypoglycemia, it is recommended by some experts that lithium is held starting 24 to 48 hours before or at the onset of labor. Once the patient is medically stable after delivery, therapy can be resumed. Other reported neonatal adverse effects that have been observed with concomitant maternal toxicity include cyanosis, hypotonicity, nephrogenic diabetes insipidus, neuromuscular abnormalities, and hypothyroidism have been reported if maternal toxicity is observed at the time of delivery. The decision to use lithium during pregnancy should be a shared decision making between the patient and provider, and be based on disease severity, history of illness, and timing of exposure. When mothers taking lithium breastfeed, their infant levels of lithium were 10% to 60% of maternal levels. Because of the potential for high infant levels and toxicity, the infant’s lithium levels and hydration status should be monitored.

LABOR AND DELIVERY

Management of pregnant individuals during the perinatal period often requires medication therapy for pain and potential complications associated with labor and delivery.

Preterm Labor

Preterm birth occurs in approximately 12% of all live deliveries in the United States, and is the leading cause of infant mortality and hospitalization. Preterm labor is generally diagnosed when uterine contractions start before 37 weeks gestation in the presence of changes in cervical dilation and/or effacement, or when the initial presentation includes regular contractions and cervical dilation of at least 2 cm. Risk factors for preterm delivery include previous preterm delivery, history of cervical surgery, short cervical length, infections, vaginal bleeding, UTIs, and periodontal disease. In addition, low prepregnancy weight, smoking, substance use disorders, and shortened intervals between pregnancies have all been associated with increased risk factors for preterm delivery.

Historically, nonpharmacologic recommendations have included bed rest, refraining from sexual intercourse and orgasm, and hydration; however, they do not decrease the risk and should not be routinely recommended. Pharmacologic interventions include tocolytic medications to stop uterine contractions, antibiotics to treat potential intrauterine infections, antenatal steroids to help with fetal lung maturation, and magnesium for fetal neuroprotection.

Tocolytic Therapy

The purposes of tocolytic therapy are (a) postpone delivery long enough to allow for the maximum effect of antenatal corticosteroid and magnesium administration; (b) allow for transportation of the pregnant patient to a facility equipped to deal with high-risk deliveries; and (c) prolongation of pregnancy when there are underlying, self-limited conditions that can cause labor, such as pyelonephritis or abdominal surgery, that are unlikely to cause recurrent preterm labor. Tocolytics are generally not utilized before neonatal viability or beyond 34 weeks of gestation.

Four classes of tocolytics are available in the United States: β-adrenergic receptor agonists, magnesium, calcium channel blockers, and NSAIDs. All four therapies prolong pregnancy between 48 hours to 1 week; however, this prolongation is not associated with a significant neonatal benefit. The β-adrenergic receptor agonist, terbutaline, has been used off-label for tocolytic therapy; however, it has been associated with a higher incidence of adverse effects in the pregnant individual, including hyperkalemia, arrhythmias, hyperglycemia, hypotension, and pulmonary edema. In addition, terbutaline has a boxed warning against oral dosing or prolonged parenteral use (eg, beyond 48-72 hours) because of the risk of cardiotoxicity and death in the pregnant patients.

Intravenous magnesium sulfate has been used for tocolysis; however, it is primarily utilized for fetal neuroprotection and reducing the incidence of cerebral palsy. Adverse effects associated with magnesium therapy in the pregnant individual are common and include a general feeling of warmth, flushing, diaphoresis, nausea, loss of deep tendon reflexes, and respiratory depression. If magnesium sulfate is used during preterm labor for fetal neuroprotection and the patient is still experiencing preterm labor, an additional agent should be added for short-term tocolysis.

Nifedipine is also often used and associated with fewer adverse effects than magnesium or β-adrenergic receptor agonist therapy. Common adverse medication reactions include dizziness, flushing, and hypotension.

NSAIDs, such as indomethacin, have been used effectively for tocolysis. An increased rate of premature constriction of the ductus arteriosus has been noted in infants with indomethacin use after 32 weeks of gestation and with use exceeding 48 hours. In addition, indomethacin is the preferred tocolytic agent in patients receiving magnesium for neuroprotection prior to 32 weeks gestation, because other agents can cause hypotension when administered concurrently with magnesium.

Other Medication Therapies for Preterm Labor Prevention

Intrauterine bacterial infections are a common cause of preterm labor before 32 weeks gestation. Infection and inflammation are thought to be associated with contractions; however, due to lack of evidence for improved outcomes, antibiotics are not routinely recommended for preterm labor.

If a patient experiences prelabor rupture of membranes (PROM) before 34 weeks of gestation, prophylactic antibiotics should be initiated to prolong pregnancy, reduce infections in the patient and neonate, and reduce major morbidities including death, respiratory distress syndrome, early sepsis, severe intraventricular hemorrhage, and necrotizing enterocolitis. A 7-day course of broad-spectrum antibiotics should be used with the intent to prolong latency, which is the time from ruptured membranes to delivery. Multiple antibiotic regimens have shown benefit with a common regimen including IV ampicillin and erythromycin for 2 days followed by oral amoxicillin and erythromycin for 5 days. Amoxicillin-clavulanate is not recommended due to increased rates of necrotizing enterocolitis. In patients allergic to β-lactam antibiotics, another agent effective against Group B *Streptococcus* (GBS) may be considered to replace the β-lactam.

Progesterone is also often administered in patients with a history of prior preterm birth. Progesterone use is based upon its effects to diminish cervical ripening (softening of the cervix necessary for cervical dilation before birth), reduce uterine wall contractility, and modulate inflammation. Evidence also supports progesterone supplementation in patients with no prior history of preterm birth who have a singleton pregnancy and a short cervix. Progesterone is not indicated for multiple gestation pregnancies. Progesterone supplementation is offered through either vaginal route or intramuscularly.

Antenatal Corticosteroids

The ACOG recommends antenatal corticosteroids for fetal lung maturation to prevent respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, and neonatal mortality in infants delivered prematurely. Patients between 24 and 34 weeks gestation who are at risk of preterm birth within the next 7 days, including those with ruptured membranes, are recommended to receive a single course of corticosteroids. When patients present between 23 and 24 weeks gestation, administration of corticosteroids may be considered. Due to the infant's small size and a low chance of survival if delivered before 24 weeks gestation, the family's wishes regarding resuscitation must be carefully considered. In addition, a single course of steroids should be considered in patients presenting in the late preterm period between 34 and 37 weeks gestation who are at risk of delivery and have not previously received corticosteroids. The most common steroid regimens include betamethasone administered intramuscularly in two doses 24 hours apart and dexamethasone in four doses 12 hours apart for 48 hours. A rescue course is often administered to patients who have received a previous corticosteroid course more than 14 days prior and who are at risk of delivering before 34 weeks gestation.

Group B *Streptococcus* Infection

Between 10% and 30% of pregnant individuals are colonized with GBS, leading to an increased risk for pregnancy loss, premature delivery, and transmission of the bacteria to the infant during delivery. Approximately 50% of patients colonized with GBS will transmit the bacteria to their newborns. The consequences of neonatal infections include death, apnea, and the need for blood pressure support and neonatal intensive care.

Universal screening for GBS colonization is recommended between 36 and 38 weeks gestation. Intrapartum antibiotics are given if the patient has GBS colonization, if they previously gave birth to an infant with invasive GBS disease, or if GBS bacteriuria was identified at any time during the pregnancy. If a patient presents in labor and no screening information is available, antibiotics are given for fever greater than or equal to 100.4°F (38°C), amniotic membrane rupture at least 18 hours prior, gestation under 37 weeks, or known positive GBS colonization in previous pregnancy.

Intravenous penicillin given every 4 hours until delivery is the recommended treatment regimen. Alternatively, ampicillin can be given IV, every 4 hours. For patients with a penicillin allergy but not at risk for anaphylaxis, cefazolin IV every 8 hours is recommended. In patients at high risk for anaphylaxis, clindamycin IV every 8 hours is recommended. For penicillin-allergic patients, GBS cultures should be sent for sensitivities. If resistant to clindamycin or erythromycin, vancomycin IV every 8 hours until delivery is appropriate. A minimum of 4 hours of therapy with a beta-lactam antibiotic is required for adequate prophylaxis.

Cervical Ripening and Labor Induction

Cervical ripening is the process of softening and thinning the cervix to facilitate labor. If a patient needs an induction and the cervix is not ready for labor, agents to induce cervical ripening may be utilized.

Nearly 26% of patients undergo labor induction, either elective or medically indicated. The most common indications for induction are post-term pregnancies (beyond 42 weeks) and pregnancy-induced hypertension. Other reasons for induction include fetal growth restriction or compromise, hypertension, premature rupture of membranes with no active onset of labor, and social factors. A number of nonpharmacologic methods are used

for cervical ripening including membrane stripping, amniotomy, and nipple stimulation; however, available evidence is inconclusive on the efficacy of these methods.

Prostaglandin E_2 analogs (eg, dinoprostone [Prepidil gel, Cervidil vaginal insert]) are commonly used for cervical ripening. Prepidil 500 mcg is administered intracervically and may be repeated after 6 hours to a maximum of three doses in 24 hours. After administration, the patient remains supine for 30 minutes. Cervidil contains 10-mg of dinoprostone with a slower, more constant release of medication compared to the gel formulation. The patient should lie down for 2 hours after placement and the insert should be removed when labor begins or after 12 hours. Fetal heart rate monitoring is recommended with both agents.

Misoprostol, a prostaglandin E1 analog, is an effective and inexpensive medication for cervical ripening and labor induction. Intravaginal administration of misoprostol (oral tablets are split to obtain dose) given every 3 to 6 hours is at least as effective as other prostaglandin agents and results in a shorter time to delivery. Oral misoprostol has been used successfully and results in a quicker onset and shorter duration. Sublingual and buccal routes of misoprostol administration have less information regarding the efficacy compared to other routes. There is little benefit to using misoprostol for longer than 24 hours. The most common adverse effects are uterine hyperstimulation and meconium-stained amniotic fluid. The use of misoprostol is contraindicated in individuals with a previous uterine scar because of its association with uterine rupture, a catastrophic medical event.

Oxytocin is the most commonly used agent for labor induction after cervical ripening. Patients may vary in response and sensitivity to oxytocin, but in theory administration should trigger a response similar to spontaneous labor. Upon administration, a uterine response begins to occur after 3 to 5 minutes. Patients with a lower BMI, a greater cervical dilation at the time of induction, more previous deliveries after 24 weeks gestation, and higher gestational age are more likely to have a successful response to labor induction from oxytocin. Refer to the ACOG practice bulletin for detailed administration information.

Labor Analgesia

7 The first phase of labor occurs from the onset of labor to complete cervical dilation, while the second phase of labor is the period between complete cervical dilation and delivery. During the first phase of labor, patients perceive visceral pain caused by uterine contractions. Pain in the second phase of labor is somatic pain associated with perineal stretching.

Nonpharmacologic Approaches to Analgesia

Greater than 70% of patients use at least one nonpharmacologic measure for pain relief during labor. The most used measures include breathing techniques, position changes, massage, and relaxation techniques. In addition, water immersion during the first stage of labor, acupressure and acupuncture, relaxation techniques including deep breathing and music therapy, using a birthing ball, hypnotherapy, yoga postures, and facilitated partner support have been effective at easing pain during labor.

Pharmacologic Approaches to Labor Pain Management

The two main types of pharmacologic approaches in the United States are parenteral opioids and epidural analgesia. The use of nitrous oxide during labor is an alternative for pain management.

Parenteral opioids (eg, fentanyl, morphine, butorphanol) are commonly used to alleviate labor pain. Up to 42% of individuals receive parenteral medications, although there is no consensus that one agent is more effective or safe than another. Overall, they are less effective than epidural analgesia, have more adverse effects, and possibly have less reliable pain response.

Epidural analgesia is the most common and effective treatment for pain relief during labor in the United States. With epidural analgesia, a catheter is introduced into the epidural space, and an opioid and/or an anesthetic (eg, fentanyl and/or bupivacaine) is administered. Combined spinal-epidural analgesia consists of injecting a single opioid bolus into the subarachnoid space to provide instant pain relief with additional use of a local anesthetic epidural. Compared with traditional epidurals, combined spinal-epidural anesthesia has a slightly shorter mean time to onset of effective analgesia. Patient-controlled epidural analgesia results in a lower total dose of local anesthetics used throughout labor compared with continuous epidural infusions.

Adverse effects of regional anesthesia include hypotension, and pruritus. Epidural analgesia is associated with prolongation of the second stages of labor by a mean difference of less than 8 minutes, but it does not lead to negative effects on the fetus or infant once delivered. A rare complication of epidural anesthesia is a puncture of the subarachnoid space leading to a severe headache, which occurs in approximately 1% of patients. Other complications include hypotension, nausea, vomiting, itching, and urinary retention. Low back pain has not been associated with the use of epidural analgesia.

Nitrous oxide, as a 50% mixture with oxygen, can be employed in patients desiring a nonmedicated labor. It is less effective than epidural anesthesia but is quickly reversible and does not limit the patient's mobility.

Postpartum Hemorrhage

7 Postpartum hemorrhage (PPH) in pregnant patients is defined as blood loss of more than 1,000 mL, regardless of vaginal or cesarean delivery, or blood loss with signs and symptoms of hypovolemia within 24 hours after delivery. There are various risk factors for PPH, some of which include prior PPH, incomplete placenta at delivery, a macrosomic fetus or multiple gestation, preeclampsia, operative vaginal delivery, chorioamnionitis, and prolonged or augmented labor.

Administration of oxytocin should be initiated before placental delivery to institute active management of labor after all uncomplicated vaginal deliveries, as this practice results in reduced blood loss, fewer cases of PPH, and a shorter third stage of labor. Other uterotonic agents should be used if an inadequate response is attained with oxytocin alone. Methylergonovine, carboprost, and rectal, sublingual, or oral misoprostol can all be used as second-line agents. None is more effective than another. Tranexamic acid, an antifibrinolytic agent, reduces deaths from obstetric hemorrhage if given within 3 hours of delivery. A limited amount of evidence has shown a modest decrease in blood loss when tranexamic acid is given prophylactically. If uterotonic medication therapies fail to control the bleeding, a variety of different surgical techniques can be used.

POSTPARTUM

Medication Use During Lactation

8 A wide variety of benefits (eg, health, nutritional, immunologic, psychological, economic, developmental, and social) are imparted by breastfeeding, not only to the infant, but also to the family. The American Academy of Pediatrics recommends that infants be given human milk exclusively for 6 months and that this continue until at least 24 months of age while other foods are introduced, provided this is still desired by both the infant and parent. Recent studies indicate that approximately 72% of patients initiate breastfeeding, and an increasing number of patients are choosing to exclusively feed breast milk to their infants. Unfortunately, many patients who choose to discontinue breastfeeding do so based on advice from their health care providers in order to restart medications. It is important for healthcare providers to understand the health benefits of breast feeding in addition to the impact of medication transfer into breastmilk.

Adequate milk removal from the breast by nursing or pumping is necessary to maintain or increase milk production. Milk supply is considered adequate when the baby is feeding 8 to 12 times per day, steady weight gain is occurring by day 4 to 5 after delivery, and has 6 to 8 wet diapers per day; whereas signs of dehydration and low milk supply include jaundice, insufficient number of dry or soiled diapers, lethargy, inconsolability, stools are not bright yellow by day 5, and lack of steady weight gain by day 4. Relactation is the process of increasing the milk supply for those whose milk has not "come in," who have inadequate milk production despite appropriate nursing frequency or pumping, or who have weaned or never breastfed after delivery. Nonpharmacological measures should be implemented first and include massage, eating snacks and increasing hydration to at least 2 liters of water a day, looking at a picture of baby when pumping, listening to music, massaging downward toward the nipple, applying warmth to the breast, pumping after feeding, feeding/pumping 8 or more times a day, and switching breasts several times while feeding especially if baby is sucking but not drinking, etc. Maintaining adequate caloric intake is also important, as individuals producing breastmilk have an increased caloric need of 340 to 400 kcal/day (1.4×10^3 to 1.7×10^3 kJ/day). Additionally, education, especially with a lactation specialist, may be helpful to review positioning, latching, and duration of feedings as pharmacologic and herbal agents' efficacy is inconclusive. The ACOG and the Academy of Breastfeeding Medicine do not recommend any specific galactagogues as a first-line agent due to the inconclusive evidence and potential for adverse events. Although metoclopramide and domperidone have been used to increase milk production, both carry risks for the parent and infant. Metoclopramide may increase the risk for gastrointestinal symptoms, extrapyramidal symptoms, and methemoglobinemia in the infant. The FDA recommends against the use of domperidone during lactation because of cardiac arrhythmias, arrest, and sudden death. Because of the cardiac risks, it is not approved for any

indication in the United States. In circumstances where a patient has contraindications to breastfeeding, is unable to produce enough milk, or does not desire to breastfeed, formula is an acceptable option to consider for supplemental or full nutrition.

Most medications transfer into breast milk, but breastfeeding may be continued in most circumstances. Healthcare providers should encourage breastfeeding individuals who require medications to continue whenever possible. Passive diffusion is the primary mechanism for medication transfer into breast milk, but other medication-related factors influence medication transfer from the parental circulation into breast milk, including (a) degree of protein binding in parental plasma, (b) molecular weight, (c) lipid solubility (and corresponding fat content of milk), (d) plasma concentration in the parent, (e) medication half-life, and (f) medication pH. The degree of protein binding to parent plasma proteins is one of the most significant factors affecting medication transfer to breast milk; highly bound medications transfer in low amounts. Low-molecular-weight medications passively diffuse into breast milk, but larger molecules are not likely to transfer in large amounts. Higher lipid solubility of medications also increases the likelihood of transfer. Colostrum is secreted in the first couple of days after birth and has high quantities of immunoglobulins, parental lymphocytes, and parental macrophages. While greater amounts of medications are present in colostrum, the amount received by the nursing infant is minimal because of the limited volume of colostrum produced. A greater volume of mature milk is produced, but medication transfer into mature milk is lower because of tight cell-to-cell junctions. The higher the concentration of medication in the parent's serum, the higher the concentration in the breast milk. As the medication is metabolized and excreted by the parent, the parent's serum concentration drops, and the medication in the breast milk may be redistributed back into the parent's bloodstream. The pH of plasma is 7.4, while the pH of breast milk ranges between 6.8 and 7. Weak bases are not ionized in the parental circulation and easily transfer to breast milk. In the lower pH of breast milk, molecules become ionized and are less likely to diffuse back into parental circulation ("ion trapping"). Likewise, medications with longer half-lives are more likely to maintain higher levels in breast milk, resulting in greater exposure to the infant.

Infant-related factors may also influence the amount of medication ingested through breastfeeding as the frequency of feedings and the amount of milk ingested are important considerations. Exclusively breastfed infants are more likely to ingest larger amounts of medications than older infants who receive other foods. Medications that are unstable in gastric acid (aminoglycosides, PPIs, and insulin) are less likely to be absorbed by infants. Finally, infants may vary in their ability to metabolize and excrete ingested medication. For example, premature and full-term infants may not have full renal and liver function.

Strategies for reducing the risk to the infant include the selection of medications that would be considered safe for use in the infant. Medications with shorter half-lives accumulate less, and those that are more protein bound do not cross into breast milk as well as those that are less protein bound. When choosing between different pharmacotherapies, medications with lower oral bioavailability and lower lipid solubility may be better choices to reduce infant exposure. If the parent is using a once-daily medication, administration before the infant's longest sleep period may be advised to increase the interval to the next feeding. For medications taken multiple times per day, administration immediately after breastfeeding provides the longest interval for back diffusion of medication from the breast milk to the parent's serum. During short-term medication therapy, the parent can avoid breastfeeding for 4 to 6 hours after ingestion of the drug to avoid peak levels. This may be accomplished by pumping and discarding milk to preserve their milk-producing capability if the necessary medication is not considered compatible with breastfeeding.

Information regarding medication use during breastfeeding is available from expert committees (eg, American Academy of Pediatrics Committee on Drugs) and evidence-based textbooks or databases (eg, LactMed [http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm]). All may be of assistance in determining safety and appropriate medications to use during breastfeeding.

Mastitis

Mastitis can be infectious or noninfectious and the most common cause is milk stasis. Signs and symptoms include breast tenderness, redness, warmth, flu-like symptoms, chills, and fever (temperature 101.3°F [38.5°C] or greater). Risk factors for developing mastitis include breast engorgement, infrequent or short duration of feedings, poor attachment or uncoordinated suckling leading to inefficient milk removal, parental or infant illness, rapid weaning, pressure on the breast (eg, tight bra), parental stress and fatigue, plugged milk ducts, oversupply of milk, and cracked nipples.

The most common pathogens responsible for mastitis include *Staphylococcus* species *(S. aureus, S. epidermis, S. lugdunenis,* and *S. hominis),* and *Streptococcus* species (*S. mitis, S. salivarius, S. pyogenes,* and *S. agalactiae).* Ice and NSAIDs are recommended to help reduce edema and inflammation and will also provide symptomatic relief. Ice may be applied to the affected breast(s) every hour, or more frequently as tolerated. Ibuprofen may be dosed at 800 mg every 8 hours in the acute setting. Acetaminophen may be considered for pain relief and is dosed at 1,000 mg every 8 hours A 10- to 14-day course of antibiotics is usually given for the treatment of mastitis; penicillinase-resistant penicillins (eg, dicloxacillin, oxacillin)

and alternatively first-generation cephalosporins (eg, cephalexin) are frequently prescribed. Application of heat before to feeding may also be helpful for some; however it may worsen symptoms for others. Direct massage of the affected area toward the nipple during feeding as tolerated may provide some relief. Affected individuals should be educated to continue breastfeeding from both breasts throughout treatment and to pump if breasts are not completely emptied with feedings. Feedings should start on the affected breast and occur more frequently.

Postpartum Depression

Mood disorders in the postpartum period may include postpartum blues, postpartum depression, and postpartum psychosis. Postpartum blues ("baby blues") is common, usually affecting 70% to 80% of new patients within the first 4 to 5 days of delivery, and generally does not require treatment. The baby blues can present with symptoms of anxiety, anger, fatigue, insomnia, tearfulness, or crying for no apparent reason, impatience, irritability, restlessness, mood changes, poor concentration, and sadness. Symptoms typically occur for a few minutes to up to a few hours daily and begin to lessen or disappear within the first two weeks after delivery.

Postpartum depression affects up to 13% of individuals, with almost 5% experiencing major depression. Symptoms may develop during pregnancy or up to 12 months after delivery, although the strict definition for major depressive disorder after delivery specifies symptom occurrence within 4 weeks postpartum. Uncontrolled postpartum depression increases the risk for poor parental health, decreased quality of life, risky behaviors, and relationship difficulties including bonding with and caring for the infant as well as impacts infant physical health, growth, sleep, and development of motor, cognition, language, emotional, social, and behavior skills. Psychotherapy, including interpersonal psychotherapy, cognitive behavioral therapy, and group/family therapy, is effective in the treatment of postpartum depression. In severe circumstances, postpartum psychosis can present with symptoms of mania, depression, or a mixed episode with psychotic features and typically present within the first 4 weeks after delivery. The incidence is rare, affecting less than 1 to 2 postpartum patients per 1,000 pregnancies. When psychosis is present, hospitalization is usually indicated.

The presence of a mental health condition should not discourage one from breastfeeding. In cases where pharmacotherapy is warranted, the selection of medication with low transfer to breast milk is desirable. If a patient is stable on medication during pregnancy, the medication should be continued. Sertraline, paroxetine, fluoxetine, and nortriptyline are the most studied in the postpartum period. Given that the long-term effects of exposure to antidepressants are largely unknown, monitoring growth and neurodevelopment should be considered for children exposed to antidepressants present in breast milk. In addition, the FDA approved brexanolone for the treatment of postpartum depression (see Chapter 92, "Depressive Disorders"). ACOG recommends brexanolone administration be considered in patients with moderate to severe depression presenting in the third trimester or within the first four weeks postpartum. Brexanolone is given as an IV infusion over 60 hours and must be administered inpatient with continuous monitoring. The decision to use brexanolone should be made based on shared decision making, being careful to consider the benefit of rapid onset of action, and the associated challenges including limited access, high cost, requirement of inpatient monitoring during the infusion, and lack of data supporting safety while breastfeeding.

CONCLUSION

Pregnant individuals may experience pregnancy-induced, acute, and chronic conditions during pregnancy, with some requiring pharmacotherapy. Medication exposure during pregnancy can elicit fear and anxiety since many believe that the risk of birth defects with exposure is high.

Very few medications carry an absolute contraindication for use during pregnancy and providers must weigh the risk of medication exposure with the risk of the untreated disease state using the available evidence and considering the timing of exposure. Individuals using medications during pregnancy should be educated using this same approach. In some situations, optimal parental health requires treatment with medications that have been associated with a higher risk of adverse effects on the fetus. The healthcare provider should provide realistic information about the types and likelihood of adverse effects to assist the patient in making the best possible decisions based on the patient's beliefs, concerns, and need for treatment.

Evidence-based resources, databases and reference books related to medication use in pregnancy and lactation, and primary and secondary literature provide healthcare practitioners with access to relevant and current medication information to manage medication therapy needs during pregnancy and lactation. Collaboration among healthcare providers who care for pregnant individuals is essential to seek, evaluate, and present the most up to date and accurate information to their patients.

KEY RESOURCES

KEY RESOURCES

American College of Obstetricians and Gynecologists. Treatment and management of mental health conditions during pregnancy and postpartum. Clinical practice guideline No. 5. Obstet Gynecol 2023;141:1262–88.

This guideline summarizes risks of uncontrolled depression, anxiety, and bipolar disorder during pregnancy as well as postpartum psychosis. In addition, the guideline reviews treatment and monitoring recommendations for each condition during pregnancy and postpartum. Medication safety during pregnancy is also discussed.

American Diabetes Association Professional Practice Committee. 15. Management of diabetes in pregnancy: standards of care in diabetes 2024. Diabetes Care 2024;47(Suppl 1):S282–94.

This guideline provides information on glycemic goals, blood sugar monitoring, nonpharmacologic recommendation, medication management, pregnancy considerations for medications, and postpartum recommendations.

American College of Obstetricians and Gynecologists. Gestational hypertension and preeclampsia. ACOG practice bulletin No. 222. Obstet Gynecol 2020;135:e237–60.

This guideline provides information on gestational hypertension and preeclampsia diagnosis, risk factors, management, severe symptoms, and medication safety in pregnancy.

American College of Obstetricians and Gynecologists. Nausea and vomiting of pregnancy. ACOG practice bulletin No. 189. Obstet Gynecol 2018;131:e15–30.

This guideline overviews management of nausea and vomiting during pregnancy. A treatment algorithm is provided.

Tomson T, Battino D, Bromley R, et al. Management of epilepsy in pregnancy: a report from the International League Against Epilepsy Task Force on women and pregnancy. Epileptic Disord 2019;21:497–517.

This guideline reviews information on maternal and fetal risks of seizures, medication use, pharmacokinetic changes of medications during pregnancy. Tables are provided that overview medication risks for malformations from several major international epilepsy registries, recommendations for monitoring various medications during pregnancy, and management strategies preconception, during each trimester, and postpartum.

Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. MMWR Recomm Rep 2021;70:1-187.

This guideline discusses risks and treatments during pregnancy for several sexually transmitted infections.

ABBREVIATIONS

ACOG	American College of Obstetricians and Gynecologists
ADA	American Diabetes Association
ARV	antiretroviral
BMI	body mass index
CGM	continuous glucose monitoring

dBP	diastolic blood pressure
FDA	Food and Drug Administration
GBS	Group B *Streptococcus*
GDM	gestational diabetes mellitus
GINA	Global Initiative for Asthma
H_2RA	histamine-2 receptor antagonist
hCG	human chorionic gonadotropin
HDP	hypertensive disorders of pregnancy
HELLP	hemolysis, elevated liver enzymes, low platelets
HIV	human immunodeficiency virus
HTN	hypertension
LMWH	low-molecular-weight heparin
NSAID	nonsteroidal anti-inflammatory drug
NTD	neural tube defect
NVP	nausea and vomiting of pregnancy
PPH	postpartum hemorrhage
PPI	proton pump inhibitor
PROM	prelabor rupture of membranes
sBP	systolic blood pressure
SNRI	serotonin–norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
STIs	sexually transmitted infections
TSH	thyroid-stimulating hormone
UTI	urinary tract infection
VTE	venous thromboembolism

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SELF-ASSESSMENT QUESTIONS

1. Which of the following drug properties limits the ability of a drug to readily transfer across the placenta?

   A. Low protein binding

   B. Molecular weight above 1,000 Da

   C. Lipophilicity

   D. Weak base

2. A 34-year-old patient is attempting pregnancy. Their past medical history is complicated by obesity (current BMI 32 kg/m^2), gastroesophageal reflux disease, type 2 diabetes, and hypothyroidism. They are currently on omeprazole 20 mg and levothyroxine 100 mcg daily. What is the best recommendation for starting folic acid supplementation?

   A. Start folic acid 0.4 mg daily once pregnancy is confirmed

   B. Start folic acid 0.4 mg daily before trying to conceive, and continue through at least the first trimester of pregnancy

   C. Start folic acid 4 mg daily once pregnancy is confirmed

   D. Start folic acid 4 mg daily before trying to conceive, and continue through at least the first trimester of pregnancy

3. The patient in Question 2 also asks what they should do with their diabetes medications. They are currently taking liraglutide and canagliflozin. They tell you that they couldn't tolerate metformin. Their A1c is 7.8% (0.078; 62 mmol/mol). What is the best recommendation?

   A. Continue liraglutide and canagliflozin.

   B. Stop both medications and start insulin.

   C. Continue liraglutide and canagliflozin and add glyburide.

   D. Stop both medications and start metformin.

4. A 29-year-old pregnant individual is at 30 weeks gestation, and reports new onset straining and difficulty to pass bowel movements, despite increasing their dietary fiber and water intake. They report currently having a bowel movement every other day. Prior to pregnancy, the patient reports they had regular bowel movements daily. Which of the following recommendations is the most appropriate?

   A. Psyllium

   B. Docusate

   C. Bisacodyl

D. Senna

5. A 36-year-old individual is currently at 9 weeks gestation and has a history of preeclampsia during their last pregnancy 3 years ago. Which of the following interventions should be recommended for this patient?

   A. Low-dose aspirin today

   B. Low-dose aspirin at 12 weeks gestation

   C. Aspirin 325 mg daily

   D. Aspirin 325 mg daily at 12 weeks gestation

6. An individual at 34 weeks gestation develops a deep vein thrombosis. What is the best treatment to initiate?

   A. Warfarin

   B. Rivaroxaban

   C. Enoxaparin

   D. Fondaparinux

7. A 28-year-old individual at 30 weeks gestation presents to the community pharmacy requesting medication to help with symptoms of GERD. Symptoms are occurring daily, mostly in the evening after dinner. Which of the following is the best choice for treatment?

   A. Calcium carbonate

   B. Famotidine

   C. Omeprazole

   D. Nonpharmacological therapy

8. A 32-year-old individual presents to their physician expressing a desire to conceive. They have a history of complex partial seizures since childhood for which they take divalproex sodium ER 1,000 mg twice daily and their last seizure was 6 months ago. Which of the following management strategies would you recommend to reduce the risk of congenital malformations should pregnancy occur?

   A. Switch drug therapy to phenobarbital.

   B. Use low doses of several antiseizure medications to minimize the dose of each received.

   C. Continue divalproex sodium.

   D. Medication change to levetiracetam before conception is attempted.

9. A 29-year-old individual at 32 weeks gestation presents with an acute migraine headache not responsive to acetaminophen. They report their last migraine was 6 months ago, before conception. Which of the following is an appropriate treatment option?

   A. Sumatriptan

   B. Magnesium supplement

   C. Ibuprofen

   D. Propranolol

10. A 23-year-old individual had intermittent asthma treated with albuterol before pregnancy. Now at 13 weeks gestation they are increasingly having symptoms and meet the definition of mild persistent asthma. The *most* appropriate treatment for this patient is:

    A. Use only albuterol for the duration of the pregnancy.

    B. Continue albuterol and add low-dose fluticasone/salmeterol.

    C. Continue albuterol and add oral prednisone.

    D. Continue albuterol and add low-dose budesonide.

11. At 33 weeks gestation, an individual presents to the local, rural hospital, and is found to be in preterm labor. The team has decided to transfer them to a large medical center that has a neonatal intensive care unit. What is the best recommendation(s) now?

    A. Nifedipine

    B. Nifedipine and betamethasone

    C. Indomethacin

    D. Indomethacin and betamethasone

12. A 23-year-old patient is at their first prenatal visit. They are currently 8 weeks gestation. Laboratory results revealed (+) RPR and syphilis titer of 1:20 and they are diagnosed with late latent syphilis. The patient has an allergy to penicillin with a reaction of hives. What is the best recommendation?

    A. Desensitize with penicillin, and then give penicillin G 2.4 million units intramuscularly for 1 dose.

    B. Desensitize with penicillin, and then give penicillin G 2.4 million units intramuscularly weekly for 3 doses.

    C. Desensitize with penicillin, and then give ceftriaxone 500 mg intramuscularly for 1 dose.

    D. Metronidazole 500 mg by mouth twice a day for 7 days.

13. A patient diagnosed with gestational diabetes has failed first-line treatment with dietary and lifestyle modifications. Which of the following is *most* appropriate to use in an individual who refuses insulin?

    A. Sitagliptin

    B. Pioglitazone

    C. Glyburide

    D. Metformin

14. A 28 weeks gestation patient is diagnosed with gestational hypertension today. Their medical history is significant for allergic rhinitis, eczema, and asthma. What is the best recommendation?

    A. Labetalol

    B. Nifedipine

    C. Amlodipine

    D. Hydrochlorothiazide

15. Strategies to lower infant exposure to medications through breast milk include all of the following *except*:

    A. Recommend a drug with a shorter half-life

B. Recommend a drug with low bioavailability

C. Recommend a highly protein-bound drug

D. Recommend a drug with high lipid solubility

ANSWERS

1. **B.** Drugs with a high molecular weight do not substantially cross the placenta. Drugs with low protein binding, lipophilicity, and those that are weak bases all contribute to the passage of drug to the placenta. See "Transplacental Medication Transfer" section for additional information.

2. **B.** The American College of Obstetricians and Gynecologists (ACOG) recommends that at least 0.4 mg of folic acid should start 1 month prior to conception and continue throughout at least the first trimester to reduce the risks of neural tube defects. See "Preconception Planning" section for additional information.

3. **B.** According to ACOG, the preferred therapy for diabetes management in pregnancy is insulin. Additionally, the patient has uncontrolled A1c, so achieving control prior to the pregnancy and help further reduce the risks in pregnancy. Neither liraglutide nor canagliflozin are recommended therapies in pregnancy and have limited to no data in pregnancy. See "Glucose Management" section for additional information.

4. **B.** Both docusate and psyllium are recommended agents for constipation in pregnancy. Since the patient is also experiencing straining and has adequate dietary fiber intake, adding the stool softener can help improve symptoms. See "Constipation" section for additional information.

5. **B.** ACOG recommends starting low-dose aspirin between 12 and 28 weeks (ideally 12-16 weeks) in patients who have 1 high-risk factor or 2 moderate-risk factors for preeclampsia. This patient has a high-risk factor of history of preeclampsia. See "Complications of Hypertension" section for additional information.

6. **C.** According to ACOG, low-molecular-weight heparin like enoxaparin is the recommended therapy for treatment of acute thromboembolism during pregnancy. Fondaparinux should be avoided unless the patient has a severe heparin allergy. Warfarin is avoided because of its risk of teratogenicity. Due to the limited data with direct oral anticoagulants, these agents are not recommended for use in pregnancy. See "Thromboembolic Disorders" section for additional information.

7. **B.** An H2 receptor antagonist, like famotidine, is the preferred therapy to prevent heartburn/GERD symptoms during pregnancy. See "Gastroesophageal Reflux Disease" section for additional information.

8. **D.** Medication change to avoid the use of valproic acid and phenobarbital is suggested before conception is attempted because of known teratogenic risks and the availability of less teratogenic medications. Antiseizure medication monotherapy is recommended with regimen optimization occurring before conception. See "Epilepsy" section for additional information.

9. **A.** Sumatriptan is the least likely to cross the placenta. Ibuprofen should not be used during pregnancy, especially after 20 weeks gestation. Magnesium and propranolol are both used for prophylaxis of migraines. See "Headache" section for additional information

10. **D.** According to recommended step therapy, step 2 adds a low-dose inhaled corticosteroid as the preferred step therapy. Continuing only albuterol for the duration of the pregnancy is inappropriate as the patient's asthma is uncontrolled. Adding a lowdose steroid plus salmeterol would be indicated for step 3 of asthma treatment. Adding an oral steroid would not be recommended as controller therapy as inhaled therapies are preferred as well as the risks associated with long-term oral steroid use. See "Allergic Rhinitis and Asthma" section for additional information.

11. **B.** One of the purposes of tocolysis is to postpone delivery long enough to allow for the maximal effect of antenatal corticosteroid administration. Tocolysis duration should be limited to 1 week and should not be initiated beyond 34 weeks. So, this patient would require tocolysis with nifedipine and antenatal steroids for lung maturity. Indomethacin use after 32 weeks is not recommended due to the risks to the fetus. See "Preterm Labor" section for additional information.

12. **B.** Since the patient has late latent syphilis, penicillin is the preferred treatment. This patient should undergo desensitization with penicillin to receive three doses of penicillin to treat the infection. See Table 105-5 in "Sexually Transmitted Infections" section for additional information.

13. **D.** Metformin and glyburide have both been used as alternatives in patients who decline insulin therapy. However, glyburide appears inferior to insulin in preventing neonatal morbidity (eg, higher NICU admission, respiratory distress, birth trauma, excessive fetal growth). See "Glucose Management" section for additional information.

14. **B.** Both labetalol and nifedipine are preferred agents to manage hypertension in pregnancy according to ACOG; however, this patient has asthma so nifedipine would be preferred. Labetalol is an alpha-1 and nonselective beta blocker, so it has the potential to constrict the beta receptors in the lungs to worsen asthma control. See "Treatment of Hypertension" section for additional information.

15. **E.** High lipid solubility contributes to a greater likelihood of transfer to breast milk. Drugs with a short half-life, that have low bioavailability, or are highly protein bound are less likely to pass into breast milk. See "Medication Use During Lactation" section for additional information.