

Chapter 32: Pregnancy and Lactation

INTRODUCTION

- Resources on the use of *drugs in pregnancy and lactation* include the Food and Drug Administration (FDA) product labeling, the primary literature, tertiary compendia, textbooks, and computerized databases (eg, www.motherisk.org and www.toxnet.nlm.nih.gov).

PREGNANCY PHYSIOLOGY

- The duration of pregnancy is approximately 280 days (measured from the first day of the last menstrual period to birth). Pregnancy is divided into three periods of three calendar months (ie, trimesters).
- Drug absorption during pregnancy may be altered by delayed gastric emptying and vomiting. An increased gastric pH may affect absorption of weak acids and bases. Hepatic perfusion increases. Higher estrogen and **progesterone** levels may alter liver enzyme activity and increase elimination of some drugs but cause accumulation of others.
- Maternal plasma volume, cardiac output, and glomerular filtration increase by 30%–50% or higher during pregnancy, possibly lowering the plasma concentration of renally cleared drugs. Body fat increases; thus, volume of distribution of fat-soluble drugs may increase. Plasma **albumin** concentrations decrease; thus volume of distribution of highly protein-bound drugs may increase. However, there may be little change in serum concentration, as these unbound drugs are more rapidly cleared by the liver and kidneys.
- The placenta is the organ of exchange between the mother and fetus for drugs. Drugs with molecular weights less than 500 Dalton (Da) transfer readily, drugs with molecular weights from 600 to 1000 Da cross more slowly, and drugs with molecular weights greater than 1000 Da (eg, **insulin** and **heparin**) do not cross in significant amounts.
- Lipophilic drugs (eg, opiates and antibiotics) cross more easily than do water-soluble drugs. Certain protein-bound drugs may achieve higher plasma concentrations in the fetus than in the mother.

DRUG SELECTION DURING PREGNANCY

- The incidence of congenital malformation is approximately 3%–6%, with less than 1% of all birth defects caused by medication exposure.
- Principles for drug use during pregnancy include: (1) selecting drugs that have been used safely for a long time; (2) prescribing doses at the lower end of the dosing range; (3) eliminating nonessential medication and discouraging self-medication; and (4) avoiding medications known to be harmful.
- Adverse effects on the fetus depend on drug dosage, route of administration, and stage of pregnancy when the exposure occurred.
- Fetal exposure to a teratogen in the first 2 weeks after conception may have an “all or nothing” effect (ie, could destroy the embryo or have no ill effect). Exposure during organogenesis (18–60 days postconception) may cause structural anomalies (eg, **methotrexate**, **cyclophosphamide**, **diethylstilbestrol**, **lithium**, **retinoids**, **thalidomide**, some **antiepileptic drugs [AEDs]**, and **coumarin derivatives**).
- Exposure after this point may result in growth retardation, central nervous system (CNS) or other abnormalities, or death. **Nonsteroidal anti-inflammatory drugs (NSAIDs)** and **tetracycline derivatives** are more likely to exhibit effects in the second or third trimester.

PRECONCEPTION PLANNING

- **Folic acid** supplementation between 0.4 and 0.9 mg daily is recommended throughout the reproductive years to reduce the risk for neural tube defects (NTDs) in offspring. Women of childbearing potential who take AED medications should take prenatal **vitamins with folic acid** 0.4–5 mg/day. Higher folate doses should be used in women who have previously delivered a child with an NTD and those taking valproic acid.
- Reduction in the use of **alcohol**, tobacco, and other substances prior to pregnancy improves outcomes. For smoking cessation, behavioral interventions are preferred. Use of **nicotine replacement therapy** during pregnancy is controversial.

PREGNANCY-INFLUENCED ISSUES

Gastrointestinal Tract

- Constipation commonly occurs during pregnancy. Institute education, physical exercise, and increased intake of dietary fiber and fluid. If additional therapy is warranted, give **supplemental fiber** and/or a stool softener. **Polyethylene glycol**, **lactulose**, and **sorbitol**, can be used intermittently. **Senna** and **bisacodyl** can also be used occasionally. Magnesium and sodium salts can cause electrolyte imbalance. Avoid **castor oil** and **mineral oil**.
- Therapy for gastroesophageal reflux disease includes lifestyle and dietary modifications, for example, small, frequent meals; **alcohol**, tobacco, and **caffeine** avoidance; food avoidance before bedtime; and elevation of the head of the bed. If necessary, initiate **aluminum**, **calcium**, or **magnesium antacids**; **sucralfate**; **cimetidine** or **ranitidine**. Proton pump inhibitors are options if response to histamine 2 (H₂)-receptor blockers is inadequate. Avoid **sodium bicarbonate** and **magnesium trisilicate**.
- Therapy for hemorrhoids includes high intake of dietary fiber, adequate oral fluid intake, and use of sitz baths. If response is inadequate, laxatives and stool softeners can be used. Topical anesthetics, skin protectants, and astringents may help irritation and pain. Topical **hydrocortisone** may reduce inflammation and pruritus.
- Nonpharmacologic treatments for nausea and vomiting include eating small, frequent meals; avoiding fatty and spicy foods; and acupressure. Pharmacotherapy may include ginger, antihistamines (eg, **doxylamine**), and **pyridoxine**. The American College of Obstetricians and Gynecologists (ACOG) considers **pyridoxine** alone or in combination with **doxylamine** to be first-line treatment. **Metoclopramide** and phenothiazines are considered safe, but may cause sedation and extrapyramidal effects. **Ondansetron** may cause oral clefts.
- **Corticosteroids** have been effective for hyperemesis gravidarum (ie, severe nausea and vomiting causing weight loss >5% of prepregnancy weight, dehydration, and ketonuria), but the risk of oral clefts is increased. They should not be used during the first trimester.

Gestational Diabetes Mellitus (GDM)

- All high-risk women should be screened for overt diabetes at their first prenatal visit.
- **Table 32-1** summarizes the screening and diagnosis of GDM which should occur during weeks 24–28.
- First-line therapy for GDM includes exercise, dietary modification, and caloric restrictions for obese women. Daily self-monitoring of blood glucose is required. If lifestyle interventions fail to achieve glycemic control, drug therapy is indicated. Glycemic control is preprandial capillary glucose concentrations at or below 95 mg/dL (5.3 mmol/L) along with one of the following: a 1-hour postprandial glucose at or below 140 mg/dL (7.8 mmol/L), or a 2-hour postprandial glucose of 120 mg/dL (6.7 mmol/L) or below. **Human insulin** is the drug of choice for diabetes management during pregnancy, because it does not cross the placenta. **Glyburide** and **metformin** are alternatives, but long-term safety data are limited and they may not be as effective as **insulin**.
- Screening with a 2-hour OGTT at 6 weeks postpartum is recommended for those diagnosed with GDM to diagnose type 2 diabetes not recognized prior to pregnancy.

TABLE 32-1

Screening and Diagnosis of Gestational Diabetes Mellitus

One-Step Method		Two-Step Method	
Give	75-g OGTT ^a		Step 1 Give 50-g OGTT ^b
	<i>If any plasma glucose levels are met or exceeded, GDM is diagnosed</i>		
Fasting	≥92 mg/dL (5.1 mmol/L)	1-hour	≥130 mg/dL (7.2 mol/L), ≥135 mg/dL (7.5 mmol/L), or ≥140 mg/dL (7.8 mmol/L) ^c
			<i>If plasma glucose level is met or exceeded, proceed to Step 2^d</i>
1-hour	≥180 mg/dL (10 mmol/L)	Step 2	Give 100-g OGTT ^a
			<i>If two or more plasma glucose levels are met or exceeded, GDM is diagnosed</i>
2-hour	≥153 mg/dL (8.5 mmol/L)		Carpenter–Coustan Method ^e
		Fasting	95 mg/dL (5.3 mmol/L) ^d
		1-hour	180 mg/dL (10 mmol/L)
		2-hour	155 mg/dL (8.6 mmol/L)
		3-hour	140 mg/dL (7.8 mmol/L)

^aPerform with plasma glucose measurement in a fasting state. Should be performed in the morning after fasting at least 8 hours.

^bPerform with plasma glucose measurement in a fasting or nonfasting state.

^cThreshold set by individual practices; lower thresholds equate to higher false-positive results.

^dIf >200 mg/dL (11.1 mmol/L), diagnosis of GDM is made; do not proceed to step 2.

^eCarpenter and Coustan developed diagnostic criteria for gestational diabetes that lowered diagnostic plasma glucose levels compared to the National Diabetes Data Group.

OGTT, oral glucose tolerance test.

Hypertension (HTN)

- Hypertensive disorders of pregnancy (HDP) include: (1) preeclampsia–eclampsia, (2) chronic hypertension (HTN; preexisting HTN or developing before 20 weeks’ gestation), (3) chronic HTN with superimposed preeclampsia, and (4) gestational HTN (ie, HTN without proteinuria developing after 20 weeks’ gestation).

- Eclampsia, a medical emergency, is preeclampsia with seizures. HTN in pregnancy is either systolic blood pressure above 140 mm Hg or diastolic blood pressure above 90 mm Hg based on two or more measurements at least 4 hours apart. Severe HTN is two measurements of systolic blood pressure >160 mm Hg and/or diastolic blood pressure >110 mm Hg at least 15 minutes apart.
- Nondrug management of HDP includes stress reduction and light exercise or activity restriction. Exercise >50 minutes 3 days a week can reduce the incidence of HTN threefold over women who are more sedentary.
- For women at risk for preeclampsia, low-dose **aspirin** (60–81 mg/day) beginning weeks 12–28 of gestation reduces the risk for preeclampsia. **Aspirin** also reduces the risk of preterm birth by 14% and intrauterine growth restriction by 20%. Calcium and/or vitamin D supplementation may decrease the relative risk of HTN and preeclampsia. ACOG states that these recommendations do not apply to populations with adequate calcium intake, such as the United States.
- Antihypertensive drug therapy is discussed later under Chronic Illnesses in Pregnancy below.
- **Magnesium sulfate** (4–6 g IV over 15–20 minutes followed by a 2 g/hr continuous infusion) decreases the risk of progression of preeclampsia to eclampsia by almost 60%, and it also treats eclamptic seizures. Avoid **diazepam** and **phenytoin**.

Thyroid Abnormalities

- Gestational transient thyrotoxicosis usually resolves by 20 weeks' gestation. Antithyroid medication is usually not needed.
- Pregnant women with overt hyperthyroidism should be treated with **methimazole** or **propylthiouracil** (PTU), and those with overt hypothyroidism should receive thyroid replacement therapy (ie, **levothyroxine**).

Venous Thromboembolism (VTE)

- For treatment of acute thromboembolism during pregnancy, **low-molecular-weight heparin (LMWH)** is preferred over **unfractionated heparin** or **warfarin**. Continue treatment throughout pregnancy and for 6 weeks after delivery. Duration of therapy should not be less than 3 months. Avoid **fondaparinux**, **lepirudin**, and **bivalirudin** unless a severe allergy to **heparin** exists. **Dabigatran**, **rivaroxaban**, and **apixaban** are not recommended. Avoid **warfarin** because it may cause fetal bleeding, nasal hypoplasia, stippled epiphyses, or CNS anomalies.
- For women at intermediate or high risk for recurrent VTE, provide antepartum prophylaxis with LMWH plus 6-week postpartum prophylaxis with LMWH or **warfarin**. For women with prosthetic heart valves, thrombophilias, and those at very high risk for VTE, consult current guidelines.

ACUTE CARE ISSUES IN PREGNANCY

Headache

- For tension and migraine headaches during pregnancy, first-line therapies are nonpharmacologic, including relaxation, stress management, and biofeedback.
- For tension headache, **acetaminophen** or **ibuprofen** can be used if necessary. All NSAIDs and **aspirin** are contraindicated in the third trimester because of the potential for closure of the ductus arteriosus. **Aspirin** may also cause maternal and fetal bleeding, and decreased uterine contractility. **Opioids** are rarely used.
- For migraine headache, **acetaminophen** and **ibuprofen** can be used. Opioids have been used, but they can contribute to nausea, and long-term use can cause neonatal withdrawal. For nonresponsive migraines, **sumatriptan** can be used. **Ergotamine** and **dihydroergotamine** are contraindicated. For migraine-associated nausea, **promethazine**, **prochlorperazine**, and **metoclopramide** can be used.
- For pregnant women with severe headaches (usually migraine) not responsive to other treatments, **propranolol**, at the lowest effective dose, can be used as preventive treatment. Alternatives include **amitriptyline** or **nortriptyline**, 10–25 mg daily by mouth.

Urinary Tract Infection

- The principal infecting organism is *Escherichia coli*, but *Proteus mirabilis*, *Klebsiella pneumoniae*, and group B *Streptococcus* cause some infections. Untreated bacteriuria may result in pyelonephritis, preterm labor, HTN, anemia, transient renal failure, and low birth weight.
- Treatment of asymptomatic bacteriuria is necessary to reduce the risk of pyelonephritis and premature delivery. Treatment of asymptomatic bacteriuria and cystitis for 7–14 days is common.
- The most commonly used antibiotics for asymptomatic bacteriuria and cystitis are the β -lactams (penicillins and cephalosporins) and **nitrofurantoin**. *E. coli* resistance to **ampicillin** and **amoxicillin** is problematic. **Nitrofurantoin** is not active against *Proteus* and should not be used after week 37 in patients with glucose-6-phosphate dehydrogenase deficiency due to concern for hemolytic anemia in the newborn. **Sulfa-containing drugs** may increase the risk for kernicterus in the newborn and should be avoided during the last weeks of gestation. **Folate antagonists**, such as **trimethoprim**, are relatively contraindicated during the first trimester because of their association with cardiovascular malformations. Regionally, increased rates of *E. coli* resistance to trimethoprim-sulfa limit its use. **Fluoroquinolones** and **tetracyclines** are contraindicated.
- Inpatient therapy for pyelonephritis has included parenteral administration of second- or third-generation cephalosporins, **ampicillin** plus **gentamicin**, or ampicillin-sulbactam. Switching to oral antibiotics can occur after the woman is afebrile for 48 hours, but avoid **nitrofurantoin**. The total duration of antibiotic therapy for pyelonephritis is 10–14 days.

Sexually Transmitted Infections (STIs)

- Pharmacotherapy for selected STIs is shown in **Table 32-2**.
- Complications of *Chlamydia trachomatis* include pelvic inflammatory disease, ectopic pregnancy, and infertility. *Chlamydia* infection can be transmitted at birth to the neonate and cause conjunctivitis and a subacute, afebrile pneumonia.
- **Benzathine penicillin G** is the drug of choice for all stages of syphilis except neurosyphilis, which is treated with **aqueous penicillin G**. Penicillin is effective for preventing transmission to the fetus and treating the already infected fetus.
- *Neisseria gonorrhoeae* is a risk factor for pelvic inflammatory disease and preterm delivery. Symptoms in the neonate (eg, rhinitis, vaginitis, urethritis, ophthalmia neonatorum, and sepsis) usually start within 2–5 days of birth. Blindness can occur. Oral cephalosporins have been removed as a preferred treatment option for gonorrhea because of antimicrobial resistance. Coinfection with *Chlamydia* is common, so usually treatment of gonorrhea includes treatment for *Chlamydia*.
- The overriding concern with genital herpes is transmission of the virus to the neonate during birth. Maternal use of **acyclovir** during the first trimester is not associated with an increased risk of birth defects. **Valacyclovir** is an alternative.
- Bacterial vaginosis is caused by anaerobic bacteria, mycoplasmas, and *Gardnerella vaginalis*. It is a risk factor for premature rupture of membranes, preterm labor, preterm birth, intra-amniotic infection, and postpartum endometritis.
- Trichomoniasis is associated with an increased risk of premature rupture of membranes, premature delivery, and low birth weight. Treatment may prevent respiratory or genital infection in the neonate.

TABLE 32-2

Management of Sexually Transmitted Infections in Pregnancy

STI	Drug Name (Brand Name)	Usual Dose	Monitoring	Comments
Bacterial vaginosis	<i>Recommended:</i> Metronidazole (Flagyl) OR	500 mg by mouth two times daily \times 7 days 5 g intravaginally once daily \times 5 days	Follow-up testing not required if symptoms resolve	No link between intravaginal clindamycin and newborn complications Oral or vaginal preparations can be used

	<p>Metronidazole 0.75% gel</p> <p>Alternatives^a: Clindamycin (Cleocin)</p>			
Chlamydia	<p>Recommended: Azithromycin (Zithromax)</p> <p>Alternatives^a: Amoxicillin (Amoxil) Erythromycin base Erythromycin ethylsuccinate</p>	1 g by mouth × 1 dose	Test-of-cure at 3–4 weeks after therapy completion; retest all after 3 months	<p>Gonorrheal coinfection common; both are treated concurrently</p> <p>Chlamydia is asymptomatic in men and women</p> <p>Women below age 25 years and those at high risk should be retested in the third trimester</p>
Genital herpes	<p>Recommended: Acyclovir (Zovirax)</p> <p>OR Valacyclovir</p>	<p>400 mg by mouth three times a day</p> <p>500 mg by mouth twice a day</p>	Routine serologic testing for HSV-2 is not recommended	Start treatment at 36 weeks of gestation
Gonorrhea	<p>Recommended: Ceftriaxone (Rocephin)</p> <p>PLUS Azithromycin (Zithromax)</p>	<p>250 mg IM × 1 dose</p> <p>1 g by mouth × 1 dose</p>	Because of high reinfection rate, repeat testing for gonorrhea 3 months after treatment	<p>Chlamydial coinfection common; both are treated concurrently</p> <p>Consult with infectious disease specialist in case of cephalosporin allergy</p>
Syphilis^a				
Primary, secondary, early latent	<p>Recommended: Benzathine penicillin G (Bicillin L-A)</p>	2.4 million units IM × 1 dose; a second dose can be given 1 week after initial dose	Nontreponemal serologic evaluation ^b at 6 and 12 months	For treatment failure or reinfection, use same drug and dose but increase to 3 weekly doses unless neurosyphilis is present
Tertiary, late latent	<p>Recommended: Benzathine penicillin G (Bicillin L-A)</p>	2.4 million units IM × 3 doses at 1-week intervals	Nontreponemal serologic evaluation ^b at 6, 12, and 24 months. CSF examination may be required	Use this regimen for late latent or latent syphilis of unknown duration
Neurosyphilis	<p>Recommended: Aqueous penicillin G (Pfizerpen)</p> <p>Alternative^c: Procaine penicillin</p>	<p>3–4 million units IV every 4 hours or 18–24 million units IV continuously × 10–14 days</p> <p>2.4 million units IM daily × 10–14 days</p> <p>500 mg by mouth four times daily × 10–14 days</p>	If initial elevation of leukocytes in CSF, repeat CSF examination every 6 months until normalization	<p>Consider repeat treatment if CSF leukocytes or protein do not normalize after 2 years</p> <p>Use alternative regimen only if compliance can be ensured</p>

	(Wycillin, Pfizerpen-AS) <i>PLUS</i> Probenecid			
Trichomoniasis	<i>Recommended:</i> Metronidazole	2 g by mouth × 1 dose	Rescreen HIV patients at 3 months after treatment	While tinidazole is an alternative for nonpregnant women, avoid during pregnancy

^aPregnant women with history of penicillin allergy should undergo penicillin desensitization as no proven alternatives exist.

^bNontreponemal evaluation consists of VDRL (Venereal Disease Research Laboratory) and RPR (rapid plasma regain).

^cRefer to Reference 50 for specific dosing recommendations.

CSF, cerebrospinal fluid; IM, intramuscular; STI, sexually transmitted infection.

CHRONIC ILLNESSES IN PREGNANCY

- **Table 32-3** shows treatment of some chronic illnesses in pregnancy.

TABLE 32-3

Treatment of Chronic Illnesses in Pregnancy

Chronic Illness	Treatment	Comments
Allergic rhinitis	<ul style="list-style-type: none"> • Intranasal corticosteroids • Intranasal cromolyn • Antihistamines (chlorpheniramine, diphenhydramine, hydroxyzine) 	<p>Budesonide and beclomethasone most widely studied intranasal corticosteroids</p> <p>Second-generation antihistamines do not appear to increase fetal risk, but are less extensively studied than first-generation products</p> <p>Use of external nasal dilator, short-term topical oxymetazoline, or ICS is preferable to oral decongestants</p>
Asthma Step 1 (intermittent) Step 2 and above (persistent)	<ul style="list-style-type: none"> • SABA (albuterol) • SABA (albuterol) • Step-appropriate ICS • LABA 	<p>Budesonide is the preferred ICS, but any may be used</p> <p>Alternatives are cromolyn (less effective), leukotriene receptor antagonists (less experience in pregnancy), and theophylline (more potential toxicity)</p> <p>Systemic corticosteroids recommended to gain control in patients with most severe disease</p>
Epilepsy	<p>Probably safest AEDs</p> <ul style="list-style-type: none"> • Carbamazepine • Lamotrigine • Levetiracetam • Phenytoin <p>Lower risk than VPA</p> <ul style="list-style-type: none"> • Gabapentin • Oxcarbazepine 	<p>Polytherapy carries higher risk of major malformations than monotherapy</p> <p>Rates of major malformation with AEDs range between 0.7 and 10 per 100 exposures</p> <p>Phenytoin, phenobarbital, and topiramate may cause cleft palate</p> <p>Phenobarbital is associated with cardiac malformations</p> <p>Risk for most AED-associated malformations is dose-dependent</p>

	<ul style="list-style-type: none"> Zonisamide <p>Significant risk greater than other AEDs</p> <ul style="list-style-type: none"> Phenobarbital Topiramate VPA 	
HIV	<p>Currently receiving ART:</p> <ul style="list-style-type: none"> Continue current regimen if viral load is suppressed ART-naïve, no evidence of resistance, preferred regimen: <ul style="list-style-type: none"> Dual NRTI backbone PLUS Ritonavir-boosted PI Integrase inhibitor 	<p>ARV drug resistance testing should be performed to guide ART if HIV RNA is >500 copies/mL (0.5×10^6/L) for ART-naïve women</p> <p>For women already receiving ART with virologic failure and HIV RNA >1000 copies/mL (1.0×10^6/L), ARV drug-resistance testing should be performed to inform change in ARV therapy</p>
Hypertension, chronic	<p>Initial treatment:</p> <ul style="list-style-type: none"> Labetalol Nifedipine Methyldopa 	<p>ACE inhibitors, ARBs, renin inhibitors, mineralocorticoid receptor antagonists are not recommended</p> <p>Atenolol has been associated with fetal growth restriction</p> <p>Thiazide diuretics theoretically lower the increase in plasma volume during pregnancy, but are considered second-line</p>
Thyroid disorders	<p>Hypothyroid</p> <ul style="list-style-type: none"> Levothyroxine 	<p>For hypothyroidism, attain a TSH of 0.1–2.5, 0.2–3, and 0.3–3 milli-international units/L (mIU/L) in the first, second, and third trimester, respectively</p>
	<p>Hyperthyroid</p> <ul style="list-style-type: none"> PTU Methimazole 	<p>Use PTU in first trimester followed by switch to methimazole in second and third trimester to balance the risk of PTU-induced hepatotoxicity and methimazole embryopathy</p>

ACE, angiotensin converting enzyme; AED, antiepileptic drug; ARB, angiotensin receptor blocker; ART, antiretroviral therapy; ARV, antiretroviral; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NTDs, neural tube defects; PI, protease inhibitor; PTU, propylthiouracil; SABA, short-acting beta agonist; TSH, thyroid-stimulating hormone; VPA, valproic acid.

Allergic Rhinitis and Asthma

- Diagnosis and staging of asthma during pregnancy is the same as in nonpregnant women, but more frequent follow-up is necessary. The risks of medication use to the fetus are lower than the risks of untreated asthma.
- Treatment of asthma follows a stepwise approach. As step 1, all pregnant patients with asthma should have access to a short-acting inhaled β_2 -agonist (albuterol is the preferred agent). For persistent asthma (step 2 or higher), low, medium, or high doses of controller corticosteroids are foundational. Budesonide is preferred, but corticosteroids used before pregnancy can be continued. Long-acting β_2 -agonists are safe. Cromolyn, leukotriene receptor antagonists, and theophylline are considered alternative agents, but they are not preferred. For patients with the most severe disease, systemic corticosteroids are recommended.
- First-line medications for allergic rhinitis during pregnancy include intranasal corticosteroids, nasal cromolyn, and first-generation antihistamines (eg, chlorpheniramine, diphenhydramine, and hydroxyzine). Intranasal corticosteroids are the most effective treatment

and have a low risk for systemic effect. **Beclomethasone** and **budesonide** have been used most. **Loratadine** and **cetirizine** do not appear to increase fetal risk, but they have not been extensively studied.

- Use of an external nasal dilator, short-term **topical oxymetazoline**, or **inhaled corticosteroids** may be preferred over oral decongestants, especially during early pregnancy.

Diabetes Mellitus

- Glycemic control can change dramatically during pregnancy, and frequent adjustments may be needed. Self-monitored blood glucose should occur before and after meals, and sometimes between 2 and 4 AM. Patients with type 1 or 2 diabetes may continue human **insulin**. Data have not shown that the use of **insulin** analogs (eg, **insulin aspart**, **insulin detemir**, **insulin glargine**, **insulin lispro**) to cause major safety concerns in pregnancy. **Metformin** (and to lesser extent **glyburide**) can be considered, however, safety data are limited.

Epilepsy

- Major malformations are two to three times more likely in children born to women taking AEDs than to those who do not, but the risks of untreated epilepsy to the fetus are considered to be greater than those associated with the AEDs.
- When possible, avoid valproic acid during pregnancy to minimize the risk of NTDs, facial clefts, and cognitive teratogenicity. **Phenobarbital** and topiramate should also be avoided. If either is used during pregnancy, the lowest effective dose should be used.
- Drug therapy should be optimized prior to conception, and AED monotherapy is recommended when possible.
- If drug withdrawal is planned, it should be fully completed prior to conception.
- All women taking AEDs should take **folic acid**, 4–5 mg daily, starting before pregnancy and continuing through at least the first trimester and preferably through the entire pregnancy.

Human Immunodeficiency Virus (HIV) Infection

- In women newly diagnosed with HIV, or who have not previously received antiretroviral therapy (ART), it should be initiated as soon as pregnancy is determined, since risk of perinatal transmission is lower with earlier viral suppression. ART therapy is selected from those recommended for nonpregnant adults (with consideration given to the teratogenic profiles of each drug). Women already taking ART therapy should continue their regimen provided that viral suppression below the level of detection is documented.
- Recommendations regarding combination ART change frequently and the most recent clinical guidelines can be found at <https://aidsinfo.nih.gov>.
- Pregnant women with HIV RNA levels above 1000 copies/mL ($1000 \times 10^3/L$) approaching delivery should have cesarean section at 38 weeks' gestation to reduce the risk of perinatal HIV transmission. Cesarean section is not recommended if HIV RNA levels are at or below that level. If maternal viral load is greater than that level or unknown, IV **zidovudine** should be initiated with a 1-hour load (2 mg/kg) followed by a continuous infusion (1 mg/kg/hr) for 2 hours (cesarean) or until vaginal delivery. Women with a viral load at or below 1000 copies/mL ($1000 \times 10^3/L$) near delivery do not require **zidovudine** IV, but should continue their ART.

Hypertension

- HTN occurring before 20 weeks of gestation, the use of antihypertensive medications before pregnancy, or the persistence of HTN beyond 12 weeks postpartum defines chronic HTN in pregnancy. It is classified as mild/nonsevere (systolic blood pressure [sBP] 140–159 mm Hg or diastolic blood pressure [dBP] 90–109 mm Hg), or severe (sBP 160 mm Hg or higher or dBP 110 mm Hg or higher). Chronic HTN can cause maternal complications, fetal growth restriction, and hospital admission.
- ACOG recommends drug therapy for pregnant women with persistent chronic HTN with a blood pressure of 160/105 mm Hg and above. When antihypertensive therapy is used, maintenance of sBP between 120 and 160 mm Hg and dBP between 80 and 105 mm Hg is recommended. If there is no evidence of end-organ damage, and sBP is below 160 mm Hg and dBP is below 105 mm Hg, drug therapy is not suggested.

- Severe HTN in pregnancy requires treatment, and lowering of BP should occur over a period of hours to prevent compromise of uteroplacental blood flow. Recommended agents are parenteral **labetalol** and **hydralazine**, but **hydralazine** is associated with more maternal and fetal adverse effects. Oral **nifedipine** may also be used. Limited evidence supports the use of **magnesium sulfate**, except when it is being used concomitantly for preeclampsia. **Nitroprusside**, **diazoxide**, and **nitroglycerin** should be reserved for refractory HTN in an appropriately monitored environment.

Depression

- Antidepressants should be used at the lowest possible dose for the shortest possible time to minimize adverse fetal and maternal pregnancy outcomes. Monotherapy is preferred over polytherapy even if higher doses are required.
- Pregnant women who stopped taking antidepressants are more likely to relapse than women who completed treatment.
- The **selective serotonin reuptake inhibitors (SSRIs)** are not considered major teratogens with the exception of **paroxetine**. Initiation of **paroxetine**, for women who intend to become pregnant, or are in their first trimester of pregnancy, should be considered only after other treatment options have been evaluated because of the risk for cardiovascular malformations in the fetus. The **serotonin/norepinephrine reuptake inhibitors (SNRIs)** are less well defined. Use of SSRIs and SNRIs in the latter part of pregnancy is associated with persistent pulmonary HTN of the newborn and prenatal antidepressant exposure syndrome (ie, cardiac, respiratory, neurologic, gastrointestinal, and metabolic complications from drug toxicity or withdrawal of drug therapy). Tricyclic antidepressants are not considered major teratogens but have been associated with neonatal withdrawal syndrome when used late in pregnancy.

Thyroid Disorders

- For hypothyroidism in pregnancy, initiate **levothyroxine** 0.1 mg/day. Women receiving thyroid replacement therapy before pregnancy may require increased dosage during pregnancy. Monitor thyroid-stimulating hormone (TSH) levels every 4–6 weeks during pregnancy to allow for dose titration according to TSH levels.
- Hyperthyroidism therapy includes the thioamides (eg, **methimazole**, **PTU**). The goal of therapy is to attain free thyroxine concentrations near the upper limit of normal.

LABOR AND DELIVERY

Preterm Labor

- Preterm labor is labor that occurs between 20 and 37 weeks of gestation when changes in cervical dilations and/or effacement happen along with regular uterine contractions or when the initial presentation includes regular contractions and cervical dilation of at least 2 cm.

Tocolytic Therapy

- Tocolytic therapy is used to postpone delivery long enough to allow for maximum effect of antenatal steroids, for transportation of the mother to a facility equipped to deal with high-risk deliveries, and to prolong pregnancy when there are underlying self-limited conditions that can cause labor. Tocolytics can be started when there are regular uterine contractions with cervical change. They are not generally used beyond 34 weeks of gestation. Do not use them in cases of previability, intrauterine fetal demise, a lethal fetal anomaly, intrauterine infection, fetal distress, severe preeclampsia, vaginal bleeding, or maternal hemodynamic instability.
- There are four classes of tocolytics in the United States: **β-agonists**, **magnesium sulfate**, **prostaglandin inhibitors** (ie, **NSAIDs**), and **calcium channel blockers**. Prolongation of pregnancy with tocolytics is not associated with significant reduction in rates of respiratory distress syndrome, neonatal death, or birth before 37 weeks of gestation. Prostaglandin inhibitors and calcium channel blockers may be preferable, based on delaying delivery and improving neonatal outcomes.
- β-Agonists (**terbutaline** and **ritodrine** [unavailable in the United States]) have a higher risk for maternal side effects. A common dose of **terbutaline** is 250 mcg subcutaneously which may be repeated in 15–30 minutes for inadequate response, with a maximum of 500 mcg given in a 4-

hour period.

- ✓ An FDA black box warning cautions against oral dosing or prolonged parenteral use (beyond 48–72 hours) because of maternal cardiotoxicity and death.
- A Cochrane review does not support the effectiveness of **magnesium sulfate** for tocolysis. However, it can be used IV during preterm labor to decrease the occurrence of moderate-to-severe cerebral palsy.
- **Nifedipine** is associated with fewer side effects than magnesium or β -agonist therapy and decreases risk of delivery within 7 days compared to β -agonist. **Nifedipine** loading doses range between 10 and 40 mg, with subsequent dosing of 10–20 mg every 4–6 hours, with dose adjustment based on patterns of preterm contractions. Five to 10 mg **nifedipine** may be administered sublingually every 15–20 minutes for three doses. Once stabilized, 10–20 mg may be administered orally every 4–6 hours for preterm contractions.
 - ✓ It can cause hypotension and a change in uteroplacental blood flow.
- **Indomethacin**, 50–100 mg orally or rectally, followed by 25–50 mg orally every 6 hours for 48 hours has been used.
 - ✓ Premature constriction of the ductus arteriosus has been reported.

Antenatal Glucocorticoids

- A Cochrane review shows the benefit of antenatal **corticosteroids** for fetal lung maturation to prevent respiratory distress syndrome, intraventricular hemorrhage, and death in infants delivered prematurely.
- Current recommendations are **betamethasone**, 12 mg IM every 24 hours for two doses, or **dexamethasone**, 6 mg IM every 12 hours for four doses, to pregnant women between 24 and 34 weeks' gestation who are at risk for preterm delivery within the next 7 days. Benefits from antenatal glucocorticoid administration are believed to begin within 24 hours.

Group B *Streptococcus* Infection

- Prenatal screening (vaginal/rectal cultures) for group B *Streptococcus* colonization of all pregnant women at 35–37 weeks' gestation is recommended. If cultures are positive, or if the woman had a previous infant with invasive group B *Streptococcus* disease, or if the woman had group B *Streptococcus* bacteriuria, antibiotics are given.
- The currently recommended regimen for group B *Streptococcus* disease is **penicillin G**, 5 million units IV, followed by 2.5 million units IV every 4 hours until delivery. Alternatives include **ampicillin**, 2 g IV, followed by 1 g IV every 4 hours; **cefazolin**, 2 g IV, followed by 1 g every 8 hours; **clindamycin**, 900 mg IV every 8 hours; or **erythromycin**, 500 mg IV every 6 hours. In penicillin-allergic women in whom sensitivity testing shows resistance to **clindamycin** and **erythromycin**, **vancomycin**, 1 g IV every 12 hours until delivery, can be used.

Cervical Ripening and Labor Induction

- Prostaglandin E₂ analogues (eg, **dinoprostone** [Prepidil Gel and Cervidil Vaginal Insert]) are commonly used for cervical ripening. Fetal heart rate monitoring is required when Cervidil Vaginal Insert is used and for 15 minutes after its removal. **Misoprostol**, a prostaglandin E₁ analogue, is effective and inexpensive.
 - ✓ It has been associated with uterine rupture.
- **Oxytocin** is the most commonly used agent for labor induction after cervical ripening.

Labor Analgesia

- Nonpharmacologic options for labor analgesia include continuous support from nurses, midwives, childbirth educators, or doulas (lay women trained in labor support) as well as warm water baths and acupuncture.

- The IV or IM administration of narcotics is commonly used for pain associated with labor. Compared with epidural analgesia, parenteral **opioids** are associated with lower rates of **oxytocin** augmentation, shorter stages of labor, and fewer instrumental deliveries.
- Epidural analgesia involves administering an opioid and/or an anesthetic (eg, **fentanyl** and/or **bupivacaine**) through a catheter into the epidural space to provide pain relief. Patient-controlled epidural analgesia results in a lower total dose of local anesthetic.
 - ✓ Epidural analgesia is associated with longer stages of labor, more instrumental deliveries, and maternal fever compared to parenteral narcotic analgesia. Complications of epidural analgesia include hypotension, itching, and urinary retention.
- Other options for labor analgesia include spinal analgesia, combined spinal-epidural analgesia, and nerve blocks.

POSTPARTUM HEMORRHAGE (PPH)

- PPH is an obstetrical emergency and is a major cause of morbidity and mortality worldwide.
- A stepwise approach to the treatment is advised starting with exclusion of retained products of contraception.
- **Oxytocin** administration results in reduced maternal blood loss, fewer cases of PPH, and a shorter third stage of labor. Other agents to use include **methylergonovine**, **carboprost**, and **tranexamic acid**.

DRUG USE DURING LACTATION

- Medications enter breast milk via passive diffusion of nonionized and non-protein-bound medication. Drugs with high molecular weights, lower lipid solubility, and higher protein binding are less likely to cross into breast milk, or they transfer more slowly or in smaller amounts. The higher the maternal serum concentration of drug, the higher the concentration will be in breast milk. Drugs with longer half-lives are more likely to maintain higher levels in breast milk. The timing and frequency of feedings and the amount of milk ingested by the infant are also important.
- Strategies for reducing infant risk from drugs transferred into breast milk include selecting medications for the mother that would be considered safe for use in the infant and choosing medications with shorter half-lives, higher protein binding, lower bioavailability, and lower lipid solubility.
- Penicillin-resistant *Staphylococcus aureus* is the most common bacterial cause of mastitis. Treatment with penicillinase-resistant penicillins or cephalosporins may be indicated. Application of heat and direct massage along with NSAIDs may be used for pain relief.

POSTPARTUM DEPRESSION

- Postpartum depression affects up to 13% of women, with almost 5% experiencing major depression
- Nonpharmacologic treatment may include interpersonal psychotherapy, cognitive behavioral therapy, and group/family therapy.
- **Sertraline**, **paroxetine**, **fluoxetine**, and **nortriptyline** are the most studied in the postpartum period and selection of medication with low transfer to breast milk is desirable.

RELACTATION

- For relactation use **metoclopramide**, 10 mg three times daily for 7–14 days only if nondrug therapy is ineffective.

See Chapter 95, *Pregnancy and Lactation: Therapeutic Considerations*, authored by Kristina E. Ward, for a more detailed discussion of this topic.