CHAPTER 180

Drug Therapy in Pregnancy

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PRINCIPLES

Background

More than 90% of women take at least one prescription or over-the-counter medication during pregnancy, and overall medication use during pregnancy has increased in the last 3 decades.[1-3] One study revealed that only 22% of reproductive-aged women have pregnancy testing done when administered or prescribed US Food and Drug Administration (FDA) category D or X medications in the emergency department (ED).[4] Unfortunately, research in the use of medications in pregnancy is currently insufficient to determine reliable and accurate risks to the mother and fetus. Only a few medications have been tested specifically for safety and efficacy during pregnancy and current methods to assess teratogenicity are limited in determining drug safety especially for newer agents. Prescribing medications during pregnancy is challenging and must account for the physiologic changes associated with pregnancy as well as the benefits and risks to the mother and to the developing fetus using all available data.

The fetal age at exposure is crucial in determining its impact on the pregnancy. The fetus is most vulnerable to toxic insults during the time of organogenesis (days 21–56 of fetal life). Exposure during this period may result in major anatomic defects. Exposure after the period of organogenesis may affect the growth and development of the fetus. Functional development of the central nervous system (CNS) is affected when it is exposed to a CNS teratogen during the 10th to 17th weeks of pregnancy.[5]

Major birth defects affect 3% to 5% of all live births. Most are of unknown cause, but 1% to 3% of these are thought to be due to pharmaceutical or environmental agents. A teratogen is any chemical, pharmacologic, environmental, or mechanical agent that can cause disruptive development of the conceptus. Included in this definition are functional impairment, growth restriction, and congenital malformations. These may range from subtle neurobehavioral effects to devastating physiologic effects and physical deformities, including fetal death.[5]

The process of establishing teratogenicity is tedious and often flawed. Animal research, although valuable in determining risk initially, is not always applicable to humans, and controlled prospective human studies are generally not performed for ethical reasons. As a result, much of our current knowledge on teratogenicity has been derived from less rigorous studies, which are inherently weak in establishing a causal relationship between a specific exposure and malformations. The genetic background of the fetus, timing and duration of the exposure, environmental factors, multiple exposures, nutritional deficits, maternal illness, and illicit drug use all contribute to the outcome of pregnancy. Large population studies are needed to understand the connection between the outcome of a pregnancy and in utero exposures. Finally, as in the case of diethylstilbestrol, teratogenicity may not be apparent for years after birth.

Classification of Teratogenic Risk

To aid physicians in determining the teratogenic potential of a particular medication, the US Food and Drug Administration (FDA) had assigned one of five letters—A, B, C, D and X—to the drug, depending on the strength of evidence for its safety or teratogenicity (Box 180.1). This classification system has been criticized as overly simplistic and perhaps inaccurate.[6] Many believed that the classification system conveyed the incorrect impression that there is a gradation of reproductive risk from exposure across categories (ie, that risk increases from A to B to C to D to X) and that the drugs within a given category present similar reproductive risks.[7] Efforts have been made to address these concerns and other significant gaps in knowledge.[8-11] More than 90% of newly introduced drugs in the United States are assigned to class C, an undetermined teratogenic risk. The FDA issued a final rule for drug labeling during pregnancy, called the Pregnancy and Lactation Labeling Rule (PLLR), effective June 2015, to address these concerns. The PLLR changes the content and format for prescription drug labeling to help health care providers assess the benefits and risks in counseling pregnant and nursing women who are taking medications. The rule requires the removal of letter categories and mandates labeling that includes a summary of risks of drug use during pregnancy and lactation, a discussion of the data supporting that summary, and any relevant information to help health care providers make informed decisions and counsel patients. Drugs already approved before this rule will be phased in gradually.[12] Currently, a number of clinical teratology resources that assign risk are available online, such as Clinical Pharmacology, TERIS, and Micromedex REPRORISK (Shepard's *Catalog of Teratogenic Agents*).

Drug Transfer Across the Placenta

Drug transfer across the placenta usually occurs by simple passive diffusion or protein transport. A thin layer of trophoblastic cells is all that separates maternal from fetal circulation. The degree to which a drug gains access to fetal circulation depends on molecular size, ionic state, lipid solubility, and extent of protein binding. Drugs with a molecular mass of less than 5 kDa readily diffuse. Anionic substances diffuse through the lipid layer more readily than ionized forms. Free drug diffuses more readily than a protein-bound drug. Because fetal pH is slightly more alkalotic than maternal pH, weak organic acids may become ion-trapped in the fetal circulation, increasing fetal exposure.

Drug Transfer During Lactation

Generally, drugs that are ingested or injected by the mother diffuse passively into milk and then back into the maternal circulation for excretion.[13,14] The amount of drug diffusing into milk depends on many factors. Lipid-soluble and nonionic substances diffuse more readily, and highly protein-bound substances diffuse less

BOX 180.1

US Food and Drug Administration Classification for Teratogenic Risk of Drugs

Class A: Controlled studies have shown no risk. Adequate well-controlled studies in pregnant women have failed to show risk to fetus.
Class B: No evidence exists of risk for humans. Animal studies show risk or are negative, but no human studies have been done.
Class C: Use may engender risk for fetus. Human studies are lacking, and animal studies may be positive or lacking. Potential for benefit may outweigh potential for harm.
Class D: Positive evidence of risk is based on studies or postmarketing data. Potential for benefit may outweigh potential for harm.
Class X: Drugs are contraindicated in pregnancy on the basis of human or animal studies or postmarketing reports that indicate benefit is clearly outweighed by risk.

readily. Whether a substance is concentrated in maternal milk or not, the neonate generally is able to detoxify it with no adverse effects, and only a few drugs pose a serious danger to a breast-feeding infant.[15] The interruption of breast-feeding should not be advocated except in rare situations of known drug toxicity to the infant and in all cases of maternal critical illness.

Drug Therapy During Pregnancy

In general, the health of the fetus is directly related to the health of the mother. Physicians should not withhold lifesaving medications from pregnant patients because of a reported risk to the fetus and should resuscitate pregnant patients according to advanced life support guidelines. Physicians may also prescribe any agent when the maternal benefits outweigh the risks to the fetus. Included in this category are therapeutic medications for asthma, arrhythmias, status epilepticus, life-threatening overdoses, and human immunodeficiency virus (HIV) infection. When prescribing drugs to pregnant and lactating women, one must weigh the benefits of treatment against the inherent risks of treatment or disease, consider the pharmacokinetics of the drug during pregnancy and lactation, choose the drug with the lowest known toxicity, and use the lowest effective dose.

PHARMACOLOGIC THERAPY

Analgesic Agents

Over-the-counter analgesics are used commonly during pregnancy, with acetaminophen being used by at least two-thirds of pregnant women.[1,2,16] New evidence has been emerging that calls for a reassessment of the safety of these medications in pregnancy.[15] Several studies have reported increasing use and adverse pregnancy outcomes with opioid use, such as neonatal abstinence syndrome and birth defects (Table 180.1).[17-23]

Acetaminophen

Acetaminophen (paracetamol) is widely used during pregnancy and has not been associated with congenital malformations.[15,24-26] In a population-based, case-control study, acetaminophen was associated with a decreased risk of certain craniofacial malformations when it was used for febrile illnesses in the first trimester. Maternal acetaminophen use has recently been associated with a higher risk for hyperkinetic disorders and attention-deficit hyperactivity disorder–like behaviors in children, possible increased risk of cryptorchidism with early gestational exposure, and increased risk of childhood asthma with exposure in the first trimester.[27-42] Acetaminophen is safe during lactation.[15]

Nonsteroidal Antiinflammatory Drugs

Prostaglandin synthesis inhibitors, such as nonsteroidal antiinflammatory drugs (NSAIDs), taken in the first trimester, have been linked to an increased risk of spontaneous abortions and a slight increase in cardiac septal defects, oral clefts, and gastroschisis (an abdominal wall defect).[15,24,26,43,44] When used in the third trimester, NSAIDs inhibit labor and have been used as tocolytic agents for premature labor. When used in the latter part of pregnancy, NSAIDs have been linked to a number of negative effects on the neonate, most notably premature closure of the ductus arteriosus, leading to neonatal pulmonary hypertension, and death. Recent studies have shown a potential association of exposure during pregnancy with an increased risk of asthma.[35,45,46] An increased incidence of fetal periventricular hemorrhages, fetal nephrotoxicity, oligohydramnios, and neonatal gastrointestinal (GI) hemorrhage has also been reported.[15,24,47] Use in the latter part of pregnancy is therefore discouraged. NSAIDs in general appear to be safe during lactation.

Aspirin

Chronic or high doses of aspirin during pregnancy should be avoided and may affect maternal and newborn hemostasis, leading to increased perinatal morbidity and mortality.[15,44] Aspirin use may increase the risk of gastroschisis in the first trimester, intrauterine growth retardation (IUGR), and fetal and maternal hemorrhage in the third trimester. Aspirin use has been associated with postmaturity, prolonged labor, neonatal hypoglycemia, neonatal metabolic acidosis, premature closure of the ductus arteriosus causing primary pulmonary hypertension in the newborn, and neonatal death.[15,24] Low doses of aspirin may be beneficial in pregnancies complicated by systemic lupus erythematosus with antiphospholipid antibodies and those at risk for gestational hypertension and preeclampsia, as well as fetuses with IUGR. Aspirin is excreted into breast milk and its use is discouraged during breast-feeding.[15]

Opiate Analgesics

In general, short-term, episodic use of opiates such as oxycodone, hydrocodone, morphine, and fentanyl appears to be safe in pregnancy. Their use near term, however, may result in severe respiratory depression of the neonate. In addition, prescribing of narcotics for long periods can lead to fetal addiction, low birth weight, and neonatal abstinence syndrome.[21,24,44,48,49] Neonatal abstinence syndrome is characterized by CNS hyperirritability, autonomic nervous system dysfunction, and higher infant mortality.[7,4,50,51]

The short-term use of opiates during lactation appears to be safe, but nursing infants should be closely monitored for respiratory depression.[15]

Rapid Sequence Intubation Agents

Data regarding the use of these agents during pregnancy is limited and has primarily been obtained from animal studies and retrospective human data. None of the agents has been consistently associated with congenital malformations.[7,15] The effects of nondepolarizing neuromuscular blocking agents on organogenesis in humans are not known, but are not thought to pose a significant teratogenic risk because very little of the maternal dose crosses the placenta (Table 180.2).[15,24]

TABLE 180.1

Analgesic Medications

DRUG	PREVIOUS FDA CLASSIFICATION	BREAST-FEEDING	CLINICAL RISK SUMMARY
Acetaminophen	B most formulations C in parental (IV) route	Compatible, excreted in breast milk	CP, NHT; increased risk of attention-deficit/hyperactivity-hyperkinetic disorder, cryptorchidism with first- and second-trimester use, childhood asthma with first-trimester use
Ibuprofen	C in first and second trimesters D in third trimester	Compatible, excreted in breast milk	CP, association with structural cardiac and other defects; risk in third trimester of premature closure of ductus arteriosus and subsequent primary pulmonary hypertension; potential increased risk of asthma with use in pregnancy
Aspirin	C in first and second trimesters D in third trimester	Potential toxicity	CP; avoid chronic or high doses in pregnancy; high doses may increase perinatal mortality, teratogenic effects; increased risk of gastroschisis in first trimester; increased risk of IUGR and fetal and maternal hemorrhage in third trimester; risk in third trimester of premature closure of ductus arteriosus and subsequent primary pulmonary hypertension; near-term use may prolong gestation, labor
Codeine	C	Potential toxicity Use with caution Excreted in breast milk, metabolized to morphine	LHS; first-trimester exposure and congenital defects have been described; some association with preterm and poor fetal outcomes; avoid prolonged use or high doses near term; may develop respiratory depression and/or withdrawal symptoms, neonatal abstinence syndrome
Oxycodone	B	Potential toxicity Use with caution Potential for SAR	LHS; use during organogenesis associated with low absolute risk of congenital birth defects; may result in preterm birth, poor fetal outcomes, NOWS
Morphine	C	Potential toxicity Usually compatible for short-term use Use with caution	CP; use during organogenesis associated with low risk of CBD; may result in preterm birth and poor fetal outcomes; prolonged maternal use during pregnancy may result in NOWS

CBD, Congenital birth defects; *CP,* crosses placenta; *FDA,* US Food and Drug Administration; *IUGR,* intrauterine growth restriction; *LHS,* limited human studies; *NHT,* no human teratogenicity; *NOWS,* neonatal opioid withdrawal syndrome; *SAR,* serious adverse reactions.

Anticoagulants

Low-molecular-weight-heparin (LMWH) is preferred over unfractionated heparin and warfarin when indicated in pregnancy for therapeutic and prophylactic anticoagulation. Warfarin has the highest teratogenicity of the anticoagulants. The heparins, as a class, do not cross the placenta. All three anticoagulants are considered compatible with breast-feeding. Early reports on the use of heparin for the prevention or treatment of venous thromboembolism during pregnancy have noted an increased risk of prematurity, stillbirth, and fetal hemorrhage. However, these risks were recently attributed to the underlying maternal condition, rather than to heparin (Table 180.3).[24,25,27,28,52-54]

Thrombolytic Agents

Alteplase, reteplase, urokinase, and streptokinase have been used successfully in pregnant women in cases of life-threatening pulmonary embolus, myocardial infarction, ischemic stroke, thrombosis of cardiac valve prosthesis, and deep venous thrombosis.[52-61] Complication rates when used for these indications were similar compared to nonpregnant patients, and none of the live-born children had permanent defects. Experience with these agents during pregnancy, however, remains limited. To date, no teratogenic effects have been reported in humans, but intrapartum maternal hemorrhage has been reported with alteplase and urokinase.[24,25] Most thrombolytics are thought to be compatible with breast-feeding (Table 180.4).[15,24]

Antidotes

There are limited human data on the risks of antidote use during pregnancy. Generally, antidotes should be used when there is a clear maternal indication to reduce the morbidity and mortality from the poisoning (Table 180.5).

N-Acetylcysteine

N-Acetylcysteine has been used successfully and without untoward effects in pregnant women who have overdosed on acetaminophen. No teratogenic effects have been reported, and pregnant patients who overdose on acetaminophen should be treated the same as nonpregnant patients.[15,24,25] It is most likely safe during lactation because it has been used in neonates without untoward effects.

Deferoxamine

Deferoxamine has been associated with developmental effects on ossification in some animal species. Experience in humans is

TABLE 180.2

Rapid Sequence Intubation Medications

DRUG	PREVIOUS FDA CLASSIFICATION	BREAST-FEEDING	CLINICAL RISK SUMMARY
Fentanyl	C	Compatible; may cause sedation or respiratory depression	CP; associated with congenital birth defects; may cause neonatal respiratory depression, transient neonatal muscular rigidity, NOWS
Etomidate	C	Probably compatible	CP; animal studies suggest risk of embryonic, fetal death but no teratogenicity; transient decrease in newborn cortisol levels of unknown clinical significance; LHS not harmful when used as induction agent
Propofol		Probably compatible, but not recommended	CP; animal studies show no malformations, LHS with no data on use in first and second trimesters; use at term appears to be safe, but high doses may be associated with neonatal CNS, respiratory depression
Thiopental	C	Probably compatible; use with caution	CP; LHS; animal studies show no congenital defects, even with high doses; may cause respiratory depression
Ketamine	Not classified; LHS; low risk	Probably compatible; plasma levels undetectable after 12 hr	CP; used frequently in obstetrics, not associated with fetal developmental malformations; dose-dependent oxytocic effect; in high doses (>2 mg/kg), associated with uterine tetany; may increase maternal blood pressure and heart rate; may increase neonatal muscle tone or cause apnea and depression of the newborn, SAR usually dose-related
Midazolam	D	Use with caution Avoid with other CNS depressants	CP; animal studies show no congenital effects, even with high doses; LHS, human observational studies show no malformations, no data on use in first and second trimesters; use near term has resulted in adverse neonatal neurobehavior, respiratory depression
Succinylcholine	C	Probably compatible because of rapid hydrolysis	Not embryotoxic or teratogenic in animals; may result in neonatal apnea and partial or complete newborn paralysis in neonates with pseudocholinesterase deficiency
Rocuronium	C	Probably compatible; LHS	CP; LHS; animal data suggest low risk; newborn neuromuscular blockade is potential complication but probably rare, may have prolonged blockade when used with magnesium
Vecuronium	C	Probably compatible	CP; LHS; use late in gestation appear to carry little if any risk to the newborn; use lower doses if administering magnesium sulfate

CNS, Central nervous system; CP, crosses placenta; *FDA,* US Food and Drug Administration; *LHS,* limited human studies; *NHT,* no human teratogenicity; *NOWS,* neonatal opioid withdrawal syndrome; *SAR,* serious adverse reactions.
Additional data adapted from ref. 103.

limited, but it does not appear to affect the fetus. The effects of deferoxamine on the nursing infant are not known, but are probably compatible.[15,24]

Digoxin Immune Fragment

There are very few case reports of the use of digoxin immune fragment (Fab) during pregnancy, so effects on the fetus are inconclusive. In cases of life-threatening digitalis overdose with arrhythmias, the benefits of treatment of the mother outweigh the risk to the fetus. Fab is probably safe for use during lactation.[15,24]

Dimercaprol

Dimercaprol, or British antilewisite, is teratogenic in mice and has been associated with increased mortality, growth restriction, cleft facial features, cerebral herniation, and abnormal digits, but experience in humans is limited. In general, with heavy metal poisonings, the maternal benefits of treatment will outweigh the potential risks to the fetus. Breast-feeding is contraindicated in patients poisoned by heavy metals.[15,24]

Flumazenil

No teratogenic effects have been reported with flumazenil in animals, and there is limited human data. Its use in pregnancy and lactation depends on the potential maternal benefit compared with possible risks to the fetus and nursing infant. Because it has a short half-life, breast-feeding may resume after a few hours.[15,24]

Fomepizole

Fomepizole use during pregnancy has not been studied in animals or humans. Its safety during pregnancy is not known. In cases of

TABLE 180.3

Anticoagulant Medications

DRUG	PREVIOUS FDA CLASSIFICATION	BREAST-FEEDING	CLINICAL RISK SUMMARY
Warfarin	X	Compatible; however, caution advised when breast-feeding premature infants due to increased risk for intraventricular hemorrhage	CP; known dose-dependent teratogen affecting 4%–5% of exposed fetuses; greatest risk at gestational wk 6–9; fetal warfarin syndrome associated with corpus callosum agenesis, hypoplasia of nasal bones, midline dysplasia, optic atrophy and blindness; also associated with fetal osteogenesis, CNS malformations, fetal intraventricular hemorrhage, stillbirths, spontaneous abortions, abnormal development of bones, stippled epiphyses; school-age children exposed in utero had increased incidence of mild neurologic dysfunction
Heparin (UFH)	C	Compatible	DNCP; associated with maternal osteopenia, immune-mediated thrombocytopenia, maternal hemorrhage at delivery, requiring careful monitoring; has reduced bioavailability, shorter half-life, lower peak plasma concentrations during pregnancy; risk of antepartum bleeding ~1%
Low-molecular-weight heparin	B	Compatible	DNCP; lower risk of osteoporosis than UFH has reduced bioavailability, shorter half-life, lower peak plasma concentrations during pregnancy; lower rate of bleeding, HIT, lower allergic response versus heparin; recommended over UFH for VTE

CP, Crosses placenta; *DNCP,* does not cross placenta; *HIT,* heparin-induced thrombocytopenia; *UFH,* unfractionated heparin; *VTE,* venous thromboembolism.
Additional data adapted from refs. 104–107.

TABLE 180.4

Thrombolytic Medications

DRUG	PREVIOUS FDA CLASSIFICATION	BREAST-FEEDING	CLINICAL RISK SUMMARY
Alteplase	C	Compatible Unknown if excreted in breast milk	Embryocidal, not teratogenic, in animal studies; LHS; use if benefits to mother outweigh risks; risk of hemorrhage at any time in gestation
Anistreplase, streptokinase	C	Use with caution; unknown safety	Use with caution; streptokinase (component of anistreplase) CP in minimal amounts; no fetal abnormalities reported; antistreptokinase antibodies cross the placenta
Reteplase	C	Probably compatible Use with caution Unknown if crosses into breast milk	Unknown if CP; risk for bleeding during labor and delivery; abortifacient, but no teratogenicity in animals; LHS; one report of use at 30 wk without sequelae
Tenecteplase	C	Hold breast-feeding Unknown safety	Unknown if CP; use with caution, safety unknown; risk of bleeding during labor and delivery; toxicity to mother in animal studies; LHS
Urokinase	B	Probably compatible Unknown if excreted in breast milk	Probably acceptable in pregnancy; not fetotoxic or teratogenic in animal studies; unknown if CP; placental hemorrhage and separation may occur; increased risk of bleeding during pregnancy; LHS

CP, Crosses placenta; *FDA,* US Food and Drug Administration; *LHS,* limited human studies.

toxic alcohol poisoning, the benefits of treatment of the mother outweigh the possible risks to the fetus or nursing infant. Use of ethyl alcohol in these situations may be considered.[15,24] Breast-feeding is not expected to continue during acute toxic alcohol poisoning.

Hydroxycobalamin

The effects of hydroxycobalamin on human pregnancy have not been studied, but benefits of its use in cyanide poisoning outweigh any risk to the fetus. Studies in animals do not reveal an association with any developmental abnormality. Breast-feeding is not expected to continue during cyanide poisoning but hydroxycobalamin, like its related compounds, is considered compatible with breast-feeding.[15,24]

Methylene Blue

Historically, methylene blue was injected into the amniotic sac to identify twins and detect rupture of the membranes, but these practices were associated with hemolytic disease in the newborn, hyperbilirubinemia, and deep blue staining of the newborn. Methylene blue in pregnancy has also been associated with an increased incidence of intestinal obstruction and atresia in the newborn. The effects of methylene blue on the nursing infant are expected to be minimal.[15,24]

TABLE 180.5

Antidotes

DRUG	PREVIOUS FDA CLASSIFICATION	BREAST-FEEDING	CLINICAL RISK SUMMARY
N-Acetylcysteine	B	Probably compatible unknown if excreted in milk so consider waiting 30 hr for elimination	CP; not teratogenic or embryotoxic in animal studies; LHS; no adverse fetal outcome when administered IV as antidote in acetaminophen overdose
Deferoxamine	C	Probably compatible Unknown if excreted in breast milk	LHS; no adverse toxic or teratogenic effects seen; animal studies show toxicity and teratogenicity (delayed ossification, skeletal anomalies)
Digoxin immune fragment	C	Probably compatible Unknown if excreted in breast milk	Unknown if CP; LHS; no adverse outcomes in fetus or newborn
Dimercaprol	C	Contraindicated Unknown if excreted in breast milk	Animal studies show teratogenicity; safety in pregnancy unknown; LHS
Flumazenil	C	Probably compatible Unknown if excreted in breast milk	Unknown if CP, but may occur; animal studies show no teratogenicity or impaired fertility; LHS
Fomepizole	C	Hold breast-feeding	No animal or human studies; safety unknown
Hydroxocobalamin	C	Probably compatible, but monitoring of infant recommended	Limited animal and human studies; safety unknown
Methylene blue	X	Probably compatible Unknown if excreted in breast milk	Epidemiologic evidence of teratogenicity; diagnostic intraamniotic injection resulted in hemolytic anemia, hyperbilirubinemia, methemoglobinemia, jejunal-ileal atresias
Naloxone	B	Probably compatible Unknown if excreted in breast milk LHS	CP; animal studies show no teratogenicity, no adverse fetal outcomes in human studies
Physostigmine	C	Probably compatible but safety unknown	Rarely used in pregnancy; no reports linking it with teratogenicity; safety unknown
Pralidoxime	C	Hold breast-feeding for 6 to 7 hr after dose	Rarely used in pregnancy; safety unknown; limited human case reports, with no adverse outcomes
Pyridoxine	A	Compatible	High doses appear to pose little risk to the fetus; no increased risk of malformations in first trimester in human trials
Succimer	C	Contraindicated Heavy metals may be excreted in breast milk, cause harm to newborn	Teratogenic and fetotoxic in animals; avoidance in first trimester recommended for pregnant women unless severe symptoms; LHS

CP, Crosses placenta; *FDA,* US Food and Drug Administration; *LHS,* limited human studies.
Additional data adapted from refs. 108–110.

Naloxone

Naloxone readily crosses the placenta. Although it has not been associated with reproductive abnormalities, its use during pregnancy results in increased fetal wakefulness, increased fetal movement, and increased heart rate, effects attributable to the antagonism of fetal endorphins. In addition, its use in opiate-addicted mothers may precipitate withdrawal in mother and term fetus. It is compatible with breast-feeding.[15,24]

Physostigmine

Experience during pregnancy is limited, and its effects on the developing fetus are unknown. Use of physostigmine at term has been associated with only mild decreases in Apgar scores at 1 and 5 minutes.[15,24,62] Physostigmine is thought to be probably compatible with breast-feeding.

Pralidoxime

Experience with pralidoxime in pregnancy is limited, and its effects on fetal development are not known.[15,62-64] In cases of organophosphate poisoning, the benefits to the mother generally outweigh the possible risk to the fetus. Breast-feeding can be resumed after 6 to 7 hours after the last dose.[24]

Pyridoxine

Pyridoxine has not been associated with any adverse developmental effects when given in high doses, and it is safe in lactation.[15,24]

Succimer

Succimer has been linked to congenital defects in animal models, possibly because of its negative effects on zinc and copper metabolism. Experience with the use of succimer in human pregnancy is limited to case reports, and adverse effects are unknown. Breast-feeding is contraindicated in heavy metal poisoning.[15,24]

Antiinfective Agents

Infections during pregnancy have the potential to affect outcomes as well as fetal development adversely. In the first trimester,

infections are a common cause of spontaneous abortion and, in the second or third trimester, they are the most common cause of preterm labor and delivery. Antimicrobial agents may also adversely affect the pregnancy. Aminoglycosides, for example, may be nephrotoxic and ototoxic to the mother and newborn, tetracyclines may result in dental staining of the developing fetus, and lincosamides may be skeletotoxic.[15,24] The penicillins, cephalosporins, and macrolide antibiotics remain the drugs of choice for infections during pregnancy. Alternative classes of antibiotics are prescribed only if these have failed to control the infection or in cases of severe maternal intolerance to these drugs. The choice of antimicrobial therapy will depend on the gestational age of the pregnancy, severity of infection, and maternal tolerance for the drug used. Many drugs are secreted into breast milk. Potential problems for the neonate include direct effects on the neonate, changes in bowel flora, diarrhea, and potential interference with culture results (Table 180.6).

Antibiotics

Aminoglycosides

The association of aminoglycosides such as gentamicin, streptomycin, tobramycin, and neomycin with nephrotoxicity and ototoxicity is well known in the literature and in practice.[15,24] Aminoglycosides, however, do not appear to have any structural teratogenic effect in humans, but kanamycin and streptomycin have been reported to cause ototoxicity in the mother and her offspring. There are no reports definitively linking in utero exposure to gentamicin, streptomycin, tobramycin, and neomycin with ototoxicity or nephrotoxicity.[1,27] Aminoglycosides are probably compatible with breast-feeding.

Cephalosporins

The first- to fourth-generation cephalosporins appear to be safe during pregnancy, although there have been no controlled studies examining their safety.[15,24] Some cephalosporins are excreted into breast milk and may interfere with culture results in the evaluation of neonatal sepsis.

Chloramphenicol. Chloramphenicol has been associated with bone marrow suppression and aplastic anemia, which may be fatal. Apart from these complications, its use during pregnancy appears to have no effects on the developing fetus. However, it is contraindicated at birth because chloramphenicol has been associated with cardiovascular collapse in the neonate, the so-called gray baby syndrome.[15,24] The safety of chloramphenicol during breast-feeding is unknown. It is secreted into the breast milk, however and, because of its potential for bone marrow suppression and its association with gray baby syndrome, it is not recommended for use during lactation.

Clindamycin. Clindamycin has not been associated with birth defects in humans or in animal studies. The American Academy of Pediatrics (AAP) considers clindamycin to be compatible with breast-feeding, although there is a rare association with bloody diarrhea in nursing infants.[15,24]

Fluoroquinolones. Fluoroquinolones have been linked to numerous toxic effects on bone and cartilage growth in animal models and are discouraged from use during pregnancy, particularly during the first trimester. A number of observational studies, however, have failed to demonstrate such a toxic effect on the human fetus. Furthermore, a meta-analysis did not reveal any increase in the rates of spontaneous abortions, birth defects, prematurity, or low birth weight in women exposed to fluoroquinolones in the first trimester. The AAP considers ciprofloxacin to be compatible with breast-feeding.[15,24] Data are inconsistent for other quinolones, and they are best avoided in lactation.

Linezolid. Linezolid has been linked to embryonic death, decreased weight, and abnormalities in cartilage and ossification in animal studies, but human data are lacking. Its use in pregnant women should be limited to cases in which the maternal benefits outweigh possible risks to the fetus.[15,24] Linezolid is likely compatible with breast-feeding.[27]

Macrolides. Erythromycin, azithromycin, and clarithromycin are considered safe for use in pregnancy and compatible with breast-feeding, although there are no well-controlled studies examining their effects on the fetus. Some reports have linked erythromycin to pyloric stenosis, but the studies were not controlled.[15,24] The estolate salt of erythromycin has also been associated with the development of hepatotoxicity in pregnant women and should be avoided. Clarithromycin has been associated with an increased risk of fetal and embryonic death, as well as with congenital malformations in animal species. This has not been shown in humans. In a prospective, controlled, multicenter observational study comparing the outcomes of pregnancies exposed to new macrolides (including clarithromycin) with matched controls, no difference in the types or patterns of malformations between the groups was found. Azithromycin is poorly concentrated in breast milk and may be the preferred agent in lactating mothers.

Metronidazole. Metronidazole is mutagenic and carcinogenic in mice and rats. In humans, a number of studies have failed to demonstrate a clear association between metronidazole and congenital malformations when used in the first trimester of pregnancy. Metronidazole has been used during the second and third trimesters to treat bacterial vaginosis, with no untoward effects. However, because of its effects in mice, many physicians avoid prescribing it at all during pregnancy. The use of metronidazole during lactation is discouraged because of its potential mutagenic and carcinogenic effects in rats and its slow elimination from infants.[15,24]

Nitrofurantoin. Nitrofurantoin has traditionally been considered safe for use throughout pregnancy, except near term. However, a population-based, multicenter, retrospective case-control study associated its use in the first trimester to a number of congenital abnormalities. This association with congenital abnormalities has been refuted, however, and there are no confirmatory studies that show teratogenicity. Its use near term has been associated with hemolytic anemia in the newborn.[15,24]

Penicillins. The first- to fourth-generation penicillins and their derivatives (including procaine, benzathine, clavulanate, sulbactam, and tazobactam) are considered safe for use in pregnancy, as is oral probenecid.[15,24,] Penicillins are considered safe during breast-feeding, but their use may interfere with culture results if evaluation is required for a neonatal fever.

Sulfonamides. Sulfamethoxazole is commonly combined with trimethoprim and has traditionally been contraindicated in pregnancy because of an increased risk of neural tube defects and other congenital abnormalities, such as cleft palate. A number of observational studies have demonstrated an increased risk of cardiovascular and urinary tract malformations in the offspring of women treated with trimethoprim-sulfamethoxazole in the first trimester. Sulfonamides are contraindicated near term because of their association with kernicterus; they are excreted in

TABLE 180.6

Antiinfective Medications

DRUG	PREVIOUS FDA CLASSIFICATION	BREAST-FEEDING	CLINICAL RISK SUMMARY
Aminoglycosides	D; human data suggest risk	Probably compatible Excreted in breast milk Oral absorption poor	No definable structural risk of any aminoglycoside when exposed in utero; streptomycin—low incidence of ototoxicity with careful dosing
CEPHALOSPORINS			
• First generation	B	Compatible	CP; NHT (most studies); conflicting studies on risk of congenital defects in first trimester
• Second generation	B	Compatible	CP; immune hemolytic reactions observed, especially with cefotetan
• Third generation	B	Compatible	CP; immune hemolytic reactions observed
• Fourth generation	B	Compatible	CP; LHS
Chloramphenicol	Use with caution Unknown risk Likely compatible	Potential toxicity (LHS) Excreted in breast milk	CP; may cause grey baby syndrome; idiosyncratic bone marrow suppression
Clindamycin	B	Compatible Excreted in breast milk	CP; no reports of fetal toxicity or malformations
Fluoroquinolones	C	Compatible Excreted in breast milk	Ciprofloxacin, ofloxacin, and levofloxacin CP; few reports of arthrotoxicity; risk of major malformations low; caution use during first trimester, risk of cardiac defects
Linezolid	C	Potential toxicity (LHS) Excreted in breast milk	No studies in pregnancy Use with caution
Macrolides	B	Compatible Excreted in low concentrations in breast milk	Estolate salt—may induce hepatotoxicity in pregnant patients; no risk of congenital heart malformations or pyloric stenosis, but use of erythromycin in infancy associated with pyloric stenosis
Metronidazole	B	Compatible Excreted in breast milk—but AAP recommends cessation of breast-feeding during use	CP; in vitro mutagen; NHT
Nitrofurantoin	B	Compatible	Caution advised with G6PD deficiency—may cause hemolytic anemia; limit use in later pregnancy
Penicillins	B	Compatible Small amount excreted in breast milk	CP; long-standing safety data
Sulfonamides	D	Compatible Excreted in breast milk Caution in newborns, infants with known G6PD deficiency	CP; adverse effects rare; most reports fail to demonstrate congenital malformations; concern for jaundice, hemolytic anemia, kernicterus; trimethoprim is folate antagonist—use with caution
Tetracyclines	D	Compatible Excreted in breast milk	CP; doxycycline poses little teratogenic risk; adverse effects on fetal bone development; discoloration of adult teeth; oxytetracycline shows neural tube defects, cleft palate, cardiac defects
Vancomycin	B (oral) C in parenteral (IV) route	Compatible IV form found in breast milk, but, no oral absorption	No toxicity or teratogenicity found
ANTIFUNGAL AGENTS			
Clotrimazole	B (Vaginal and topical) C (oral lozenge)	Compatible	Systemic absorption from skin minimal; NHT; avoid vaginal use during first trimester; some reports suggest increased risk of spontaneous abortions
Fluconazole	C (vaginal) D (other indications)	Compatible	High dose in first trimester associated with malformations
Ketoconazole	C	Compatible Excreted in breast milk	NHT, but teratogenicity seen in animal studies

TABLE 180.6

Antiinfective Medications—cont'd

DRUG	PREVIOUS FDA CLASSIFICATION	BREAST-FEEDING	CLINICAL RISK SUMMARY
Nystatin	A (vaginal) C (other preparations)	Compatible Not excreted in breast milk	Poorly absorbed systemically; often first-line therapy in pregnancy
Terbinafine	B	Potential toxicity Excreted in breast milk	LHS
ANTITUBERCULOUS AGENTS			
Isoniazid	C; maternal benefit outweighs fetal risk	Compatible Excreted in breast milk	CP; benefits of treatment outweigh risks; NHT
Ethambutol	B	Compatible Excreted in breast milk	CP; benefits of treatment outweigh risks; no adverse effects seen
Rifampin	C	Compatible Excreted in breast milk	CP; benefits of treatment outweigh risk; hemorrhagic disease of newborn
ANTIHERPETIC AGENTS			
Acyclovir	B	Compatible Excreted in breast milk	CP—found in higher concentrations than in maternal blood; systemic use should be avoided unless benefits outweigh the risks; NHT
Valacyclovir	B	Compatible Excreted in breast milk	CP; LHS
Famciclovir	B; LHS suggest caution	Potential toxicity	Unknown if crosses placenta or enters breast milk; LHS
ANTIINFLUENZA AGENTS			
Amantadine	C	Potential toxicity (LHS) Excreted in breast milk	CP; teratogenicity in animals; associated with cardiac malformations.
Oseltamivir	C	Compatible Excreted in breast milk but in low concentration	Benefits of treatment during gestation likely greatly outweigh risks; no congenital malformations identified

AAP, American Academy of Pediatrics; *CP,* crosses placenta; *FDA,* US Food and Drug Administration; *G6PD,* Glucose-6-phosphate dehydrogenase; *LHS,* limited human studies; *LS,* limited studies; *NHT,* no human teratogenicity,
Additional data adapted from refs. 111 and 112.

breast milk and generally tolerated by a healthy neonate.[11,12,15,24] They should be avoided, however, in ill or premature infants and in infants with hyperbilirubinemia or glucose-6-phosphate dehydrogenase deficiency.

Tetracyclines. Tetracycline and doxycycline readily cross the placenta. Tetracycline has been associated with the development of fatal fatty liver in pregnant women. It chelates calcium, causing abnormalities in bone growth and staining of decidual teeth. It has been associated with fetal genitourinary anomalies, inguinal hernias, and limb abnormalities. Tetracycline should therefore be avoided during pregnancy. Doxycycline, conversely, does not bind to calcium and is associated less with stained teeth than tetracycline. In addition, it does not appear to cause an increase in any type of congenital malformation. Despite these findings, doxycycline is not recommended in pregnancy.[15,24]

Because tetracycline binds to breast milk calcium, only a small amount reaches the nursing infant, and it may be used for short periods (<10 days) during breast-feeding. Doxycycline does not bind to breast milk calcium and is present in greater quantities in breast milk. This could theoretically increase its side effects in the newborn. Its use in nursing infants is best avoided.[15,24]

Vancomycin. Vancomycin has not been linked to birth defects in animals or in humans. Reports of auditory abnormalities and renal insufficiency in neonates of mothers treated with vancomycin are believed to be false-positives because these abnormalities were resolved on retesting. Vancomycin is excreted into milk but not well absorbed by the GI tract. Its effects on the nursing infant have not been studied.[15,24]

Antifungals

Nystatin has a long safety profile during pregnancy and lactation. It is poorly absorbed from skin, mucous membranes, and the GI tract and is considered the antifungal agent of first choice for the treatment of mucocutaneous fungal infections. Clotrimazole, miconazole, and ketoconazole appear to be safe during pregnancy and lactation because they have not been associated with major birth defects. However, a minor increase in the incidence of hypoplastic left ventricle was reported in one case-control study. In addition, ketoconazole is teratogenic in rats. For these reasons, clotrimazole, miconazole, and ketoconazole are considered second-line treatment of fungal infections in pregnancy. Fluconazole is teratogenic in high doses (>400 mg/day) and has been associated with an increased incidence of craniofacial and cardiovascular defects in offspring and multiple abnormalities of the skeleton and cartilage. However, these anomalies were not noted when lower doses were used or with single-dose therapy (150 mg) for vaginal candidiasis.[15,24]

Ketoconazole, fluconazole, and itraconazole are excreted into breast milk. Because of the safe use of ketoconazole in neonates and the lack of negative reports, it is considered compatible with breast-feeding (see Table 180.6).[15,24,65]

Antituberculous Agents

Untreated tuberculosis places the mother and fetus at greater risk than the use of antituberculous medications. Isoniazid, ethambutol, and rifampin cross the placenta and, in a review of antituberculous treatment during pregnancy, no association was found between these medications and major congenital malformations. Rifampin has been associated with hemorrhagic disease of the newborn.[3] Despite this adverse effect, it is considered first-line therapy for the treatment of tuberculosis. All three antituberculous medications are considered compatible with breast-feeding (see Table 180.6).[15,24,65]

Antiviral Agents

Antiherpetic Drugs

Acyclovir readily crosses the placenta and reaches higher concentrations in fetal circulation than in maternal circulation. Neither acyclovir nor valacyclovir has been associated with congenital malformations or adverse effects on the offspring.[66] Intravenous (IV) acyclovir is the drug of choice for life-threatening maternal herpes simplex virus infections, such as disseminated disease, herpes encephalitis, and varicella pneumonia, which carries a maternal mortality of 44% if untreated.[67] For non–life-threatening genital herpes infection in pregnant women, acyclovir or valacyclovir may be used. Experience with famciclovir is limited and therefore is not recommended for use in pregnancy. Because there are no reported adverse outcomes in infants of mothers taking acyclovir or in infants treated with acyclovir for disseminated herpes, it is considered safe during breast-feeding (see Table 180.6).[15,24]

Antiinfluenza Drugs

Influenza in pregnancy carries a high risk of morbidity and mortality. During the 2009–2010 H1N1 pandemic, 6% of confirmed H1N1 deaths in the United States occurred in pregnant women.[68] Antiviral therapy with M2 ion channel inhibitors, such as amantadine and rimantadine, or neuraminidase inhibitors, such as oseltamivir and zanamivir, is associated with improved maternal and pregnancy outcomes.[69] Whereas amantadine had been linked to various malformations, including cardiac defects in humans, and is considered teratogenic and embryotoxic in rats, a cohort study found that neither class of antiinfluenza drugs was associated with an increase in malformations or stillbirths.[15] There was, however, an increase in the incidence of necrotizing colitis in premature newborns exposed to either of these classes of drugs. Oseltamivir appears safe in lactation. In addition to antiviral therapy, the Centers for Disease Control and Prevention (CDC) has also recommended that pregnant women receive the inactivated influenza vaccine at any point during pregnancy (see Table 180.6).[70]

Anti-HIV Drugs

No specific pattern of birth defects has been described with the use of anti-HIV drugs, but the drugs' mutagenesis and carcinogenesis and their long-term effects on the liver, heart, and reproductive system are yet to be determined.[15,24]

Animal and human data suggest that didanosine, lamivudine, stavudine, zidovudine, and zalcitabine present a small risk of structural malformations and mitochondrial dysfunction in the developing fetus, but no specific pattern of birth defects has been described with protease inhibitors, such as ritonavir and nelfinavir. Despite potential risks, it is thought that the benefit from HIV treatment far outweighs the risk of these drugs and should not be withheld. In addition, zidovudine has been shown to reduce vertical and perinatal transmission of HIV from the mother to the fetus significantly.[15,24,67] Because of the risk of postnatal HIV transmission through milk, the CDC advises against breast-feeding by HIV-positive mothers.

Cardiovascular Agents

Antidysrhythmics

Atrial and ventricular arrhythmias are common during pregnancy. Most are benign; however, malignant degeneration occasionally occurs. All unstable tachycardias should be treated with electrical cardioversion and advanced cardiac life support guidelines. Stable patients may be treated medically, but the choice of drugs needs to be modified to protect the patient as well as the fetus from the drug's harmful effects[71-73] (Table 180.7).

Adenosine. Adenosine has been used safely throughout pregnancy and is the drug of choice for termination of maternal supraventricular tachycardia. Adenosine has also been used safely for termination of incessant tachycardia in the fetus.[15,24,71-73] Adenosine is safe in lactation.

Amiodarone. Amiodarone is a class D agent containing large amounts of iodine and has been associated with congenital goiter and transient neonatal hyperthyroidism and hypothyroidism.[71-75] Amiodarone has been linked to many congenital abnormalities, including growth restriction, structural cardiac abnormalities, corneal deposits, and developmental delay. It should be used only in refractory cases of supraventricular or ventricular tachycardias in the mother and incessant tachycardias in the fetus.[6] Because of its high iodine content, excretion into milk, and long elimination half-life, amiodarone should not be used in nursing mothers.[15,24]

Digoxin and Quinidine. Digoxin and quinidine are considered safe for use during pregnancy and lactation. Neither has been linked to congenital defects in humans or animals, and they are first-line agents for the treatment of significant maternal dysrhythmias. They have also been successfully used in fetal tachycardia.[71,73] During lactation, digoxin appears compatible with breast-feeding; there is very little information about quinidine's use in breast-feeding.[15,24]

Lidocaine. Lidocaine rapidly crosses the placenta and becomes ion-trapped in the fetus. There is no evidence of a link between the use of lidocaine in the first trimester and any fetal developmental malformations. However, high doses used near term are associated with neonatal CNS depression, apnea, hypotonia, seizures, and bradycardia.[15,24,71,72] Lidocaine is considered compatible with breast-feeding.

Procainamide. Procainamide has been safely used in the treatment of stable, wide-complex tachydysrhythmias during pregnancy. It has not been associated with fetal developmental abnormalities and appears well tolerated when used for a short duration.[71-73] It has been associated with a high incidence of maternal antinuclear antibodies and the occurrence of a lupus-like reaction in humans. During lactation, procainamide and its metabolite, *N*-acetylprocainamide, have been found in breast milk and, although the AAP considers its short-term

TABLE 180.7

Antidysrhythmic Medications

DRUG	PREVIOUS FDA CLASSIFICATION	BREAST-FEEDING	CLINICAL RISK SUMMARY
Adenosine	C	Compatible	Many reports show compatibility during pregnancy; LHS; effects on fetus unknown, but teratogenicity or malformations not expected
Amiodarone	D	Contraindicated excreted in breast milk Concern for hypothyroidism	CP; linked to many congenital abnormalities; thyroid abnormalities, congenital goiter have been observed; contains high concentration of iodine; use only in refractory tachydysrhythmias
Digoxin	C	Compatible excreted in breast milk	CP; NHT; one of the safest antiarrhythmics during pregnancy
Quinidine	C	Probably compatible (LHS) Excreted in breast milk	CP; no teratogenic effects in humans reported; LHS
Lidocaine	B	Compatible excreted in breast milk	CP; animal studies—no harm; high doses near term associated with neonatal CNS depression, hypotonia, seizures, bradycardia
Procainamide	C	Probably compatible (LHS) Excreted in breast milk	LHS
Flecainide	C	Compatible Concentrated in breast milk	LHS; animal data suggest possible teratogenicity
Ibutilide	C	Probably compatible (LHS)	Unknown if CP; animal studies show teratogenicity, embryocidal events
Sotalol	B	Potential toxicity (LHS) Concentrated in breast milk. Conflicting reports	CP; may cause fetal bradycardia and/or IUGR

CP, Crosses placenta; *FDA,* US Food and Drug Administration; *IUGR,* intrauterine growth restriction; *LHS,* limited human studies; *NHT,* no human teratogenicity.

use compatible with breast-feeding, other authorities do not recommend it.[15,24]

Flecainide. Flecainide has been used safely to terminate maternal and fetal tachycardia,[5] but it has been associated with fetal hyperbilirubinemia, hepatotoxicity, and loss of fetal heart rate variability. Flecainide has also been found to be teratogenic in some animal species, resulting in cardiac and musculoskeletal abnormalities.[15,24,71-73] The AAP considers flecainide compatible with breast-feeding, despite limited experience.

Ibutilide. There are only a few case reports of the successful and safe use of ibutilide during the latter part of pregnancy in humans.[71-73] In animals, however, ibutilide was found to be teratogenic and caused cardiac septal defects as well as skeletal dysgenesis in rats, especially when high doses were given. Ibutilide should be reserved for refractory cases in which the benefits of therapy outweigh any fetal risk.[15,24]

Sotalol. Sotalol has been used in pregnant women to treat atrial arrhythmias successfully and safely, as well as hypertension. It has also been successfully used to terminate fetal atrial tachycardias.[71-73] It does not appear to have teratogenic effects in animals. Some of the negative effects of sotalol include bradycardia in the newborn, persisting for 24 hours. Sotalol is concentrated in milk but does not appear to result in bradycardia or hypotension in the nursing infant and, according to the AAP, it is compatible with breast-feeding.[15,24]

Antihypertensives

Labetalol is the agent of choice for hypertensive emergencies in pregnancy (Table 180.8).

Angiotensin-Converting Enzyme Inhibitors. Angiotensin-converting enzyme (ACE) inhibitors, classified as category D drugs, are contraindicated for use during pregnancy.[74] Furthermore, ACE inhibitors are embryocidal in animals and increase the rate of stillbirths in some animal species. In humans, the most significant adverse fetal effects occur when used in the second and third trimesters.[75,76] These include oligohydramnios, anuria, renal agenesis resulting in death, increased risk of stillbirth, intrauterine growth restriction, fetal skull abnormalities, pulmonary hypoplasia, respiratory distress syndrome, and fetal and neonatal hypotension.[77] Captopril and enalapril are considered compatible with breast-feeding.[15,24]

Angiotensin II Receptor Antagonists. Angiotensin II receptor antagonists should be avoided during pregnancy because their use has been reported to result in fetal abnormalities similar to the abnormalities seen with ACE inhibitors, including renal agenesis, neonatal anuria, oligohydramnios, intrauterine growth restriction, persistent patent ductus arteriosus, abnormal ossification, and death.[15,24,75,76] Their safety in lactation is unknown.

Beta Blockers. Beta blockers have become a first-line treatment of hypertension in pregnancy. They have not been associated with fetal malformations and appear to be safe when used for short periods. Adverse fetal effects include intrauterine growth restriction and a low placental weight. Beta blockers lacking intrinsic sympathomimetic activity, such as acebutolol, atenolol, nadolol, and propranolol, are more likely to be associated with these adverse effects. When beta blockers are given near term, they have been associated with persistent beta blockade in the newborn. Nonselective beta blockers, such as propranolol, also have resulted in neonatal hypoglycemia, respiratory depression, and hyperbilirubinemia in the newborn. These adverse effects

TABLE 180.8

Antihypertensive Medications

DRUG(S)	PREVIOUS FDA CLASSIFICATION	BREAST-FEEDING	CLINICAL RISK SUMMARY
Angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists	D	Probably compatible, but variable safety	Use in second and third trimesters may cause teratogenicity, severe fetal/neonatal toxicity; reduce fetal renal function; associated with anuria, PDA, IUGR, prematurity, abnormal bone, lung development, renal failure, death
Esmolol	C	Safety unknown Appears to be low risk	LHS; not thought to cause structural anomalies; may result in persistent beta blockade of fetus or newborn[a]
Labetalol	C	Probably compatible Low excretion in breast milk	LHS; little risk to fetus except possibly in first trimester; most studies found no effect on fetal growth; IUGR and RPW may occur if used near delivery; newborn should be monitored for 24–48 hr for symptoms of beta blockade[a]
Metoprolol	C	Conflicting reports Concern for toxicity Excreted in breast milk	CP; LHS; no animal teratogenicity; may cause IUGR, RPW, and persistent beta blockade in newborns[a]
Propranolol	C	Conflicting reports Concern for toxicity	CP; NHT; fetal and neonatal toxicity may occur; may cause IUGR and RPW if used near delivery; newborn should be monitored for 24–48 hr for symptoms of beta blockade[a]
Amlodipine	C	Probably compatible, but safety unknown Neonatal myocardium sensitive to changes in calcium status Caution during breast-feeding	LHS; animal studies demonstrated fetotoxicity; safety unknown; case reports of IUGR, fetal death, neonatal rash
Diltiazem	C	Probably compatible, but safety unknown Neonatal myocardium sensitive to changes in calcium status Caution during breast feeding	LHS; animal studies demonstrate fetotoxicity, teratogenicity; safety unknown
Nicardipine	C	Probably compatible but safety unknown LHS	Dose-related embryonic toxicity but not teratogenicity in animals; LHS; neonatal hypotension and acidosis reported, but safety unknown; causes hypotension, reflex tachycardia, PPH, tocolysis, headache, nausea, dizziness, flushing in pregnancy
Nifedipine	C	Probably compatible but safety unknown Advised to delay breast-feeding for 3–4 hr	LHS; safety unknown; NHT; has been used as a tocolytic agent; may potentiate neuromuscular blocking action of magnesium
Verapamil	C	Probably compatible	CP; animal studies show adverse effects on fetal growth and fetotoxicity, LHS; appears to be low risk during any stage of pregnancy
Furosemide	C	Probably compatible Caution advised May suppress lactation	CP; LHS; fetotoxic and teratogenic in animals; no significant alteration of amniotic fluid volume; monitor fetal growth because may cause higher birth weight
Hydrochlorothiazide	B (class D in women with reduced uteroplacental perfusion)	Compatible Excreted in breast milk May suppress lactation	CP; NHT; risks to fetus and newborn include hypoglycemia, thrombocytopenia, hyponatremia, hypokalemia, death; may inhibit labor by direct effect on smooth muscle
Nitroglycerin	B to C depending on the product	Probably compatible Monitoring infants recommended	LHS; no adverse effects in animal studies; safety unknown, but appears safe; tocolytic
Nitroprusside	C	Potential toxicity	CP; LHS; adverse effects in animal studies, caution advised; transient fetal bradycardia noted; accumulation of cyanide in fetus may occur
Clonidine	C	Probably compatible May alter prolactin and oxytocin levels, affecting lactation	CP; LHS; safety unknown; no observed adverse fetal effects in humans; may develop sleep disorders later in life with prolonged use during pregnancy

TABLE 180.8

Antihypertensive Medications—cont'd

DRUG(S)	PREVIOUS FDA CLASSIFICATION	BREAST-FEEDING	CLINICAL RISK SUMMARY
Hydralazine	C	Probably compatible LHS Excreted in breast milk	CP; use with caution, no known congenital defects, but fetal toxicity associated with third-trimester use; meta-analysis on use in preeclampsia demonstrated more hypotension, placental abruption, cesarean section, maternal oliguria, adverse fetal heart rates, lower Apgar scores compared with labetalol or nifedipine
Methyldopa	B	Probably compatible	Long history of safety and efficacy in pregnancy

[a]Beta blockade = bradycardia, respiratory depression, and hypoglycemia.
CP, Crosses placenta; *FDA,* US Food and Drug Administration; *IUGR,* intrauterine growth restriction; *LHS,* limited human studies; *NHT,* no human teratogenicity; *PDA,* patent ductus arteriosus; *PPH,* postpartum hemorrhage; *RPW,* reduced placental weight.

are less common when a cardioselective beta blocker, such as atenolol or metoprolol, is used. Esmolol has been associated with fetal bradycardia, neonatal bradycardia and hypotonia, and fetal distress requiring emergent cesarean section.[75,76] Beta blockers have variable effects on the nursing infant, and close monitoring of the infant for adverse effects is recommended.[15,24]

Calcium Channel Blockers. Calcium channel blockers have been used for the treatment of hypertension and the termination of supraventricular rhythm disturbances during pregnancy.[78] IV verapamil has also been used to terminate fetal tachycardia, and IV nicardipine has been used for severe preeclampsia. In addition, some calcium channel blockers, such as nifedipine and diltiazem, have been used as tocolytic agents. In laboratory animals, use of calcium channel blockers in the first trimester was associated with a dose-dependent increase in embryonic mortality and skeletal abnormalities. To date, however, these abnormalities have not been seen in humans, although data remain limited. Some complications of calcium channel blocker use during pregnancy include maternal hypotension, tachycardia, and fetal distress, especially pronounced when sublingual nifedipine or IV nicardipine is used.[15,24] The AAP considers these drugs compatible with breast-feeding.

Diuretics

Loop diuretics such as furosemide are indicated in the treatment of pulmonary edema due to congestive heart failure. In laboratory animals, furosemide has been linked to renal and skeletal abnormalities when used in pregnancy. These effects have not been seen in humans, but a slightly increased risk of hypospadias has been reported. Furosemide is secreted into breast milk but is considered compatible with breast-feeding.[15,24]

Thiazide diuretics have been associated with hypoglycemia and electrolyte abnormalities in neonates when given near term and with an increase in meconium staining and perinatal mortality. Moreover, thiazide diuretics may have a direct effect on smooth muscle and inhibit labor. In general, these agents are considered safe during breast-feeding.[15,24]

Nitrates. Nitroglycerin has not been shown to cause fetal harm in animal studies. Limited reports in humans have not shown any major effects on the fetus or neonate. Nitroglycerin is rarely used during pregnancy, but it appears to be a safe, effective, rapidly acting, and short-acting agent.[79] Nitroprusside for the treatment of hypertensive emergencies in pregnancy has the same advantages and disadvantages as in nonpregnant patients. During prolonged administration of high doses, nitroprusside may result in cyanide toxicity and severe acidosis. It readily crosses the placenta, and fetal levels of cyanide can increase as high as twice maternal levels. Standard doses do not seem to subject the fetus to a major risk of toxicity but, with the availability of safer alternatives, notably labetalol, nitroprusside is considered a last resort agent.[15,24,79] No data are available on its use during lactation, but breast-feeding is not expected to continue during a critical illness.

Clonidine. Clonidine has been safely used throughout pregnancy, but experience during the first trimester remains limited. It does not appear to be teratogenic in laboratory animals and does not increase fetal mortality. Transient neonatal hypertension has been reported in neonates.[80] Its effects on breast-feeding neonates are unknown, but it is considered compatible with breast-feeding.[15,24]

Hydralazine. Hydralazine use has been associated with higher rates of maternal hypotension, placental abruption, and neonatal distress compared with labetalol. It is therefore no longer recommended as a first-line agent in the treatment of severe acute hypertension in pregnancy. It may still be used as a second-line agent. Hydralazine is considered compatible with breast-feeding.[15,24]

Methyldopa. Methyldopa has been safely used throughout pregnancy, and most reviews have not linked it to any teratogenic effects on the offspring or adverse effects on the pregnancy. Many emergency clinicians continue to prescribe it as first-line therapy for hypertension during pregnancy. Methyldopa is compatible with breast-feeding.[15,24]

Vasopressors

Vasopressors all have the potential to increase uterine vascular resistance, resulting in a proportional decrease in placental blood flow. At this time, on the basis of its safety profile, phenylephrine appears to be the vasopressor of choice in the treatment of vascular collapse during pregnancy (Table 180.9).[79,81]

Endocrine Agents

Diabetes Medications

Diabetes mellitus is associated with a number of congenital malformations involving multiple organ systems, as well as with a significant increase in perinatal morbidity. Glycemic control in

TABLE 180.9

Vasopressors

DRUG	PREVIOUS FDA CLASSIFICATION	BREAST-FEEDING	CLINICAL RISK SUMMARY
Dobutamine	B	Probably compatible (LHS)	CP; LHS; animal data suggest low risk; no adverse effects on human fetuses found
Dopamine	C	Probably compatible (LHS)	LHS; used in maternal shock, including spinal shock due to spinal anesthesia; low-dose dopamine can be used to improve cardiac and urine output in patients with preeclampsia and oliguria, but has not been shown to improve mortality or renal function; animal studies suggest maternal toxicity, but no fetal teratogenicity found; decreases uterine blood flow
Epinephrine	C	Potential toxicity (LHS)	CP; NHT; preferred treatment agent for anaphylaxis, used for status asthmaticus and shock during pregnancy; associated with fetal anoxic injury, intracranial hemorrhage, and increased incidence of inguinal hernias; decreases uterine blood flow, which may lead to fetal anoxia
Norepinephrine	C	Potential toxicity (LHS)	CP; animal studies demonstrate malformation—situs inversus, cataracts, hemorrhages, bone abnormalities; increased incidence of cerebral hemorrhage; decreased placental flow and fetal anoxia, but overall effects unknown
Ephedrine	C	Potential toxicity	CP; NHT; effective in treatment of shock in pregnancy; compared to phenylephrine, ephedrine associated with higher heart rates, gastric upset, increased incidence of fetal acidosis; no major or minor malformations shown
Phenylephrine	C	Probably compatible (LHS)	Preferred agent to treat shock during pregnancy; severe hypertension during delivery when reacting to oxytocics or ergots; malformations when used in first trimester; use during late pregnancy, labor, or cesarean section may cause fetal anoxia, bradycardia due to uterine contractions, decreased uterine blood flow

CP, Crosses placenta; *FDA,* US Food and Drug Administration; *LHS,* limited human studies; *NHT,* no human teratogenicity.
Additional data adapted from ref. 113.

pregnancy is therefore important and should be accomplished in a controlled manner, because hypoglycemia is also associated with adverse pregnancy outcomes. Insulin is considered the drug of choice for diabetes mellitus types 1 and 2 in pregnancy and gestational diabetes, if treatment is needed. Metformin has been associated with serious adverse effects in adults, including life-threatening metabolic acidosis and hepatotoxicity. It has not been associated with fetal malformations in animals and humans (Table 180.10).[15,24,81]

Thyroid Medications

Maternal hyperthyroidism is associated with an increased risk of spontaneous abortion, preterm labor, placental abruption, and maternal congestive heart failure. Effects of the disease on the offspring include intrauterine growth restriction, intrauterine fetal death, and neonatal goiter. Propylthiouracil (PTU) is the drug of choice during pregnancy. There does not appear to be an increase in the risk of congenital defects with PTU. Other drugs used to control hyperthyroidism in pregnancy include methimazole and carbimazole, both of which have been associated with abnormal development of the skin, albeit inconsistently. Hypothyroidism in pregnancy may result in an increased risk for spontaneous abortion, intrauterine growth restriction, placental abruption, and fetal demise and has been associated with severe neurologic impairment of the offspring.[15,24] Levothyroxine is the treatment of choice for hypothyroidism in pregnant women (Table 180.11).

Gastrointestinal Agents

Gastroesophageal reflux disease (GERD) occurs in up to 80%, of pregnancies and peaks in the third trimester. The exact mechanism and pathogenesis of this condition associated with pregnancy is likely multifactorial (Table 180.12).[82]

Antacids

H2 Receptor Antagonists. Antacids are commonly prescribed throughout pregnancy. None of the H2 receptor antagonists has been linked to congenital malformation, and they all appear to be safe for the nursing infant. There are multiple reports in the literature, however, linking in utero gastric suppression to an increased incidence of asthma and allergies during childhood, which require confirmation.[15,24,83]

Proton Pump Inhibitors. Studies on proton pump inhibitor (PPI) use in pregnancy are limited but several studies and a meta-analysis have found no association with an increased risk for major congenital birth defects, spontaneous abortions, or preterm delivery.[82,84,85] Esomeprazole, lansoprazole, pantoprazole, and rabeprazole may be used during pregnancy. There are reports, however, of an increased incidence of GI, hepatic, and thyroid cancers in rats and mice. Several studies have demonstrated a possible link between in utero exposure to gastric acid suppressors and childhood allergic disorders and asthma.[15,24,83,86,87] There are no human data studying the effect of PPIs on nursing infants.

Antiemetic Medications

Nausea and vomiting occur in up to 80% of all pregnant women between 6 and 12 weeks of gestation, but these symptoms are usually self-limiting. One-third of women with nausea and vomiting of pregnancy have clinically significant symptoms, and 1% will progress to hyperemesis gravidarum, which poses health risks

TABLE 180.10

Diabetic Medications

DRUG	PREVIOUS FDA CLASSIFICATION	BREAST-FEEDING	CLINICAL RISK SUMMARY
Insulin	B	Compatible Degraded by infant's GI tract	Maternal hypoglycemia; DNCP; no observable effects found
Sulfonylureas	B	Compatible	Minimal amounts found in fetal circulation; no greater risk of adverse effects compared with insulin therapy; infant 200 g heavier with use of sulfonylureas; stop ≈2 wk before birth to prevent neonatal hypoglycemia
Metformin	B	Compatible Excreted in breast milk Monitoring advised	CP; NHT Less likely to experience maternal and neonatal hypoglycemia

CP, Crosses placenta; *DNCP,* does not cross placenta; *FDA,* US Food and Drug Administration; *GI,* gastrointestinal; *NHT,* no human teratogenicity.
Additional data adapted from refs. 113 and 114.

TABLE 180.11

Thyroid Medications

DRUG	PREVIOUS FDA CLASSIFICATION	BREAST-FEEDING	CLINICAL RISK SUMMARY
Levothyroxine	A	Compatible Excreted in breast milk	Minimal transfer across placenta; treatment of choice for hypothyroidism in pregnancy; minimal side effects; maternal benefits outweigh risks to fetus
Potassium iodide	D	Compatible Excreted in breast milk	CP; reserved for thyrotoxic patients; easily taken up by fetal thyroid, resulting in prolonged fetal hypothyroidism and goiter
Propylthiouracil (PTU)	D	Compatible Excreted in breast milk	CP; causes fetal goiter, hypothyroidism, hepatic injury, death; preferred drug for hyperthyroidism in pregnancy; maternal benefits outweigh risk to fetus
Methimazole	D	Compatible Excreted in breast milk	CP; may cause a methimazole embryopathy—congenital skin defects, umbilical defects

CP, Crosses placenta; *FDA,* US Food and Drug Administration.
Additional data adapted from ref. 115.

to the mother and fetus.[88] Despite these symptoms being common in pregnancy, there is a lack of high-quality evidence to support any particular intervention (Table 180.13).[89]

Pyridoxine (Vitamin B_6), Doxylamine-Pyridoxine Combination. Pyridoxine has been used alone and in combination for the treatment of nausea and vomiting of pregnancy. Combination therapy of doxylamine and pyridoxine was recently approved by the FDA for the treatment of nausea and vomiting of pregnancy after having been taken off the market. Doxylamine is an antihistamine. Positive associations with congenital malformations have been observed but are not thought to be causal in nature.[15,88,90]

Phenothiazines. Phenothiazines, such as metoclopramide, prochlorperazine, and promethazine, are dopamine antagonists commonly used in the treatment of nausea and vomiting during pregnancy. Although there have been reports of increased risk of cardiac defects, these reports did not consider other factors, such as the mother's health, when the drug was reviewed. The bulk of evidence does not support a link to congenital abnormalities.[24,91] The AAP cautions against their use in nursing mothers because they may cause sedation and other untoward effects.[15]

Serotonin 5-HT_3 Receptor Antagonists. Dolasetron, granisetron, and ondansetron have not been linked to any fetal malformations, although experience with the newer agents remains limited.[15,24] Recent studies of ondansetron have suggested a low teratogenic risk; however, an increased risk for a cardiac septum defect is possible, but data are inconsistent,[92] but this has not been confirmed in other studies.[93] The AAP considers these agents compatible with breast-feeding.[15]

Neurologic Agents

Anticonvulsants

Anticonvulsants are known teratogens, and 30% of neonates exposed to commonly used anticonvulsants exhibit congenital anomalies.[15,24] The risks for birth defects increase with the duration of exposure and with the number of agents used. Valproate is associated with the most frequent serious adverse effects on the pregnancy and fetus (20.3% incidence of serious adverse outcomes) compared with phenytoin, carbamazepine, and lamotrigine (10.7%, 8.2%, and 1.0%, respectively). Despite the risks, most practitioners believe that it is important to control seizures during pregnancy. Generalized seizures during pregnancy are associated with an increased risk of spontaneous abortion, hypoxic injury to the fetus, and impaired neuropsychological functioning.

Monotherapy is the most appropriate option and is recommended at the lowest effective anticonvulsant dose. Dividing the

TABLE 180.12

Gastrointestinal Medications

DRUG	PREVIOUS FDA CLASSIFICATION	BREAST-FEEDING	CLINICAL RISK SUMMARY
Famotidine	B	Probably compatible Secreted less than other H2 blockers Considered low risk	CP; no fetal toxicity or teratogenicity in animal studies[a]
Ranitidine	B	Probably compatible Considered low risk	CP; no toxicity or teratogenicity in animal studies; considered H2 blocker of choice due to efficacy and safety data; ranitidine-induced anaphylactoid shock has been reported[a]
Cimetidine	B	Compatible Has antiandrogenic activity, so use with caution	CP; no toxicity in animal studies, has some weak anti-androgenic activity that could result in feminism of male fetuses but no documented cases in humans[a]
Omeprazole	C	Potential toxicity LHS	CP; animal data show dose related embryonic and fetal mortality; low risk of fetal harm or teratogenicity; overall slightly higher rates of congenital malformations and stillborns after exposure in first trimester of pregnancy, but studies limited/unconfirmed[a]
Esomeprazole	B (esomeprazole magnesium) C (esomeprazole strontium)	Potential toxicity LHS Wait 5–7.5 hr after dose for breast-feeding to limit exposure Strontium formulations—should not be used	CP; LHS; some changes in bone morphology observed in animal studies; should be used with caution[a]
Lansoprazole	B	Potential toxicity Should be avoided	Unknown whether CP but likely; carcinogenic in animals; LHS; should be avoided in first trimester[a]
Pantoprazole	B	Probably compatible Potential for tumorigenicity and carcinogenicity in animals Caution advised	Animal and human data—suggest low risk in pregnancy[a]

CP, Crosses placenta; *FDA,* US Food and Drug Administration; *LHS,* limited human studies.
[a]Several studies have shown a possible link between in utero exposure to gastric acid suppressors and childhood allergy and asthma.
Additional data adapted from ref. 116.

daily dose to decrease peak plasma levels may be considered. Adjustment of the dosage upward is often required to maintain adequate seizure control.[15]

Classic Anticonvulsants. The classic anticonvulsants are considered class D agents and are teratogenic. Carbamazepine has been linked to an increased risk of craniofacial defects, neural tube defects, and developmental delay. Phenobarbital has been associated with a slightly increased risk of congenital heart disease and cleft lip or palate. In addition, its chronic use during pregnancy has been associated with neonatal withdrawal. Phenytoin use during pregnancy has been associated with the fetal hydantoin syndrome, which affects 5% to 10% of pregnancies. This syndrome is characterized by varying degrees of ossification abnormalities of the extremities and digits, craniofacial abnormalities, including cleft lip and palate, impaired growth, delayed neurologic development, and multiple cardiovascular anomalies. Valproic acid is associated with multiple facial anomalies, neural tube defects, strabismus, and congenital heart defects.[15,24]

Carbamazepine, phenobarbital, and phenytoin have also been associated with hemorrhagic disease of the newborn, presumably because they competitively inhibit placental transport of vitamin K.[15,24]

Carbamazepine, phenytoin, and valproic acid are considered compatible with breast-feeding. Phenobarbital, on the other hand, has been associated with neonatal sedation and toxicity and is not advised during breast-feeding.[15,24]

Newer Anticonvulsants. Newer anticonvulsants, such as lamotrigine, levetiracetam, and topiramate, have been associated with a slightly increased incidence of major birth defects, such as oral clefts, skeletal abnormalities, and hypospadias. The incidence of these birth defects increases significantly when these substances are combined with other anticonvulsants, such as valproic acid.[15,24] These findings, however, were not seen in two studies comparing the newer anticonvulsants. In the lamotrigine pregnancy registry,[94] a study conducted by the manufacturer of lamotrigine, and in an observational study from Denmark,[95] first-trimester exposure to lamotrigine, oxcarbazepine, topiramate, gabapentin, or levetiracetam was not associated with an increased risk of major birth defects.

These agents also appeared to be well tolerated by the nursing infant, except for topiramate, which caused excess sedation.[15]

Antipsychotics

These agents sometimes cause extrapyramidal side effects of the infants when exposed in utero.[15,24] These effects are seen with use of the first- and second-generation antipsychotics. Haloperidol has been shown to cause some limb defects when the mother is exposed during the first trimester. However, this effect is not seen with other first-generation antipsychotics.[15] Most second-generation antipsychotics do not show teratogenicity. However, there are insufficient data for all antipsychotics (Table 180.14).

Migraine Medications

Ergot Alkaloids

Neither ergotamine nor dihydroergotamine has been associated with teratogenic effects but are contraindicated in pregnancy

TABLE 180.13

Antiemetic Medications

DRUG	PREVIOUS FDA CLASSIFICATION	BREAST-FEEDING	CLINICAL RISK SUMMARY
Pyridoxine	A	Compatible Excreted in breast milk	High doses pose little risk to fetus; vitamin B_6 deficiency common during pregnancy—pyridoxine required for good maternal and fetal health
Doxylamine, pyridoxine	A (FDA-approved for use in nausea, vomiting in pregnancy)	Probably compatible, but sedative and antihistamine actions are potential concern	Safe in pregnancy, including first trimester; several meta-analyses demonstrated no increased risk of malformations, fetal abnormalities
Metoclopramide	B	Potential toxicity Concern for CNS effects but data lacking	CP; no association with adverse fetal and neonatal outcomes while with used during all stages of pregnancy
Prochlorperazine	C	Potential toxicity Use caution—may cause sedation, lethargy in infant	CP; LHS; fetal toxicity, teratogenicity in animals; adverse effects of extrapyramidal effects, agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, feeding disorder reported in infants exposed during third trimester; isolated reports of congenital defects when exposed in utero; considered low risk for mother and fetus if used occasionally in low doses
Promethazine	C	Probably compatible May cause sedation in infant	CP; LHS; reports of embryonic and fetal harm may be considered low risk for embryo, fetus; may cause platelet aggregation in newborn if given within 2 wk of delivery, of unknown clinical significance
Ondansetron	B	Probably compatible Unknown safety	CP; animal, human data suggest low risk of birth defects; studies show increased risk of cardiac anomalies—therapy recommended only after 10 wk of gestation

CP, Crosses placenta; *FDA,* US Food and Drug Administration; *LHS,* limited human studies.
Additional data adapted from refs. 117–120.

TABLE 180.14

Antipsychotic Medications

DRUG	PREVIOUS FDA CLASSIFICATION	BREAST-FEEDING	CLINICAL RISK SUMMARY
FIRST GENERATION			
Haloperidol	C	Potential toxicity (LHS) Excreted in breast milk	CP; antipyramidal symptoms can be seen in infants exposed in utero; limb defects seen with first-trimester exposure
Droperidol	C	Potential toxicity (LHS)	CP; no effect on respiratory drive when given perinatally; no observed fetal or maternal SAR
SECOND GENERATION			
Olanzapine	C (insufficient data)	Potential toxicity (LHS) Concentrated in breast milk	CP; no teratogenicity or mutagenicity in animal studies; extrapyramidal effects noted in infants exposed in third trimester
Risperidone	C (insufficient data)	Potential toxicity (LHS)	CP; extrapyramidal effects noted in infants exposed in third trimester

CP, Crosses placenta; *FDA,* US Food and Drug Administration; *LHS,* limited human studies; *SAR,* serious adverse reactions.

because of their oxytocic effects and effects on uterine blood flow. In a number of animals, these alkaloids have been associated with intrauterine growth restriction, probably because of reductions in uteroplacental blood flow. They are also contraindicated during breast-feeding because of possible ergot poisoning of the nursing infant manifested by convulsions and gastrointestinal symptoms.[15,24]

Triptans

Triptans have been found to be teratogenic in a number of animal species, but recent human studies appear to favor their safety during pregnancy.[15,24] Sumatriptan is considered compatible with breast-feeding, especially if the breast milk is not used for 8 hours after the last dose.

Respiratory Agents

Antihistamines

Approximately 10% to 15% of women reportedly take an antihistamine during pregnancy. Chlorpheniramine, diphenhydramine, doxylamine, hydroxyzine, and meclizine have been safely used for the treatment of allergic reactions during pregnancy and as

TABLE 180.15

Antihistamine Medications

DRUG	PREVIOUS FDA CLASSIFICATION	BREAST-FEEDING	CLINICAL RISK SUMMARY
Chlorpheniramine	C	Probably compatible; use with caution: may cause sedation, irritability, disturbed sleep, hyperexcitability, excessive crying	LHS; no known congenital defects, low risk in pregnancy; recommended antihistamine in pregnancy, especially in first trimester[a]
Diphenhydramine	B	Probably compatible; use with caution, can be sedating; parenteral use contraindicated	LHS; animal and human studies demonstrate safety in pregnancy; association with cleft palate in one study; drug of choice if parenteral antihistamine is indicated[a]
Hydroxyzine	X first trimester only; C in second and third trimesters	Probably compatible, LHS; not recommended with breast-feeding: may interfere with establishment of lactation	Likely CP; teratogenic in animals, with high doses associated with developmental toxicity; low potential risk for fetus in humans; withdrawal or seizures noted in newborn exposed near term; possible increased risk of oral clefts, but limited data[a]
Meclizine	B	Probably compatible Safety unknown Occasional dose should not pose risk	Teratogenic in animals but not in humans; frequently used as antiemetic; considered low risk in pregnancy[a]
Cetirizine	B	Probably compatible Excreted in breast milk Not recommended—safety unknown	Animal studies—no teratogenicity; LHS; no evidence of increased risk of adverse fetal outcomes; may be used as alternative to oral first-generation antihistamine
Fexofenadine	C	Probably compatible excreted in breast milk	Animal studies—embryonic and fetal toxicity; no human studies available
Loratadine	None	Probably compatible considered antihistamine of choice in breast-feeding	Unknown if CP, but expected; no evidence of teratogenicity in animals or humans

CP, Crosses placenta; *FDA,* US Food and Drug Administration; *LHS,* limited human studies.
[a]H1 blockers are not recommended for use in last 2 wk of pregnancy due to association with retrolental fibroplasia in premature neonates.
Additional data adapted from refs. 121 and 122.

antiemetics in the treatment of nausea and vomiting during pregnancy. This has been further confirmed in meta-analyses involving more than 200,000 patients. First-generation antihistamines are not recommended during breast-feeding because they are thought to inhibit lactation.[15,24] In addition, serious adverse CNS effects, including seizures, have been reported to develop in neonates receiving antihistamines, especially when they are premature.

The newer generation antihistamines, such as cetirizine and loratadine, also appear safe during pregnancy. They may be acceptable alternatives for severe allergies if the first-generation antihistamines are not tolerated.[24] The AAP has classified these drugs as compatible with breast-feeding (Table 180.15).[15]

Asthma Medications

The prevalence of asthma in pregnancy is estimated at 8.8%,[96] and one-third of pregnant asthmatics experience a worsening of their asthma that may progress to a critical asthma syndrome, including status asthmaticus and near-fatal asthma. Pregnant women with asthma are at risk for neonatal death, preterm birth, low-birth-weight infants, preeclampsia, and small-for-gestational-age infants.[97,98] Asthmatic mothers may also have a higher rate of chorioamnionitis, hypertensive disorders of pregnancy, cesarean section, and prolonged hospital stay compared with control mothers. Better asthma control has been associated with an improved outcome.

Albuterol is the most commonly prescribed and is the treatment of choice in asthma. It appears safe, even when used long term.[99] None of the β-adrenergic medications has been linked to fetal or congenital malformations, but some have been associated with significant cardiovascular and metabolic effects, which are transient and generally well tolerated by the fetus. Transient hyperglycemia followed by insulin secretion may also occur, resulting in neonatal hypoglycemia, especially in diabetic patients. Terbutaline, when used IV or orally in pregnant women, may result in significant maternal and fetal arrhythmias, maternal pulmonary edema, and death. The FDA has recommended a label change to add a warning against its use in preterm labor because safer β_2-agonists and tocolytic agents are available.[100] Long-acting beta agonists also appear to be safe during pregnancy. Albuterol is compatible with breast-feeding.[15,24]

Ipratropium has not been found to be teratogenic in numerous animal models, but there are few data regarding its safety in human pregnancy.[15,24] It is considered compatible with breast-feeding.

Cromolyn sodium has not been associated with any significant risk of birth defects or negative perinatal outcomes.[15,24] It is considered compatible with breast-feeding (Table 180.16).

Corticosteroids

Inhaled corticosteroids are the main therapy for the prevention of asthma exacerbations during pregnancy. Oral corticosteroids are the mainstay of therapy for acute exacerbations of asthma. Although they are not considered human teratogens, there may be a slightly increased incidence of orofacial clefts when oral steroids are used during the first trimester.[101] Furthermore, their use in the third trimester has been linked to an increased incidence of preterm delivery, low birth weight, preeclampsia, and cataracts in the newborn. Other authors have also raised concerns about the development of congenital adrenal hyperplasia in newborns.[15,24] Prednisone is considered safe during breast-feeding.

Data on the use of leukotriene antagonists in pregnancy are limited. One study has found no association with congenital abnormalities, but there was a slight increase in intrauterine

TABLE 180.16

Asthma Medications

DRUG	PREVIOUS FDA CLASSIFICATION	BREAST-FEEDING	CLINICAL RISK SUMMARY
Ipratropium	B	Probably compatible, LHS May appear in breast milk	LHS; NHT; no teratogenicity in animals; recommended for use in severe asthma as additional therapy
Albuterol	C	Probably compatible, LHS Unknown if excreted in breast milk	May act as tocolytic; drug of choice for treatment of asthma; association with functional and neurobehavioral toxicity with prolonged use; may cause maternal and fetal tachycardia, hyperglycemia
Epinephrine	C	Potential toxicity, LHS Not known if excreted in breast milk	CP; teratogenic in animals; avoid during active labor and delivery—can delay labor progression; may lead to decrease in uterine blood flow with placental, uterine vasoconstriction
Terbutaline	C	Probably compatible Excreted in breast milk in small amounts	CP; NHT; may act as tocolytic; association with autism spectrum disorders (if used >2 wk); cardiac defects in first trimester; fetal tachycardia and hypoglycemia after parenteral use; avoid in early gestation, continuous use in second and third trimesters; may cause serious maternal cardiovascular events (eg, increased heart rate, hyperglycemia, hypokalemia, cardiac arrhythmias, pulmonary edema and MI), death; black boxed warnings against use for prevention or prolonged use (beyond 2–3 days) of preterm labor

CP, Crosses placenta; *FDA,* US Food and Drug Administration; *LHS,* limited human studies; *MI,* myocardial ischemia; *NHT,* no human teratogenicity.

growth restriction. However, these results should be interpreted with caution because of the small sample size of the study. Zileuton is mutagenic in animal studies and should be avoided during pregnancy and lactation.[15,24]

Decongestants

Decongestants with strong vasoconstrictive properties, such as phenylpropanolamine, phenylephrine and pseudoephedrine, cause placental vasoconstriction and are not recommended during pregnancy. There are limited data suggesting that their use in the first trimester may result in an increased incidence of abnormalities typically associated with placental vascular disruption, such as gastroschisis and intestinal atresia.[15,24] Recent evidence has supported the association of phenylephrine and endocardial cushion defect, phenylpropanolamine and ear defects, and phenylpropanolamine and pyloric stenosis with oral and intranasal decongestion use in the first trimester.[102] The risk, however, appears to be low. The AAP classifies pseudoephedrine as compatible with breast-feeding.

KEY CONCEPTS

- Chemically induced birth defects are believed to be responsible for approximately 1% to 3% of anomalous births.
- Gestational age is crucial in determination of the impact of any given exposure, especially during organogenesis (days 21–56 of fetal life), when major body organs are formed.
- Human data on teratogenicity and fetal toxicity of medications is often limited, and causal associations are difficult to determine, especially with newer medications.
- In general, the health of the fetus is directly related to the health of the mother, and drugs should be given when the maternal benefits outweigh the risks to the fetus.
- Certain medications should be avoided during pregnancy, if possible, because they are known teratogens or cause potential toxic effects in the newborn; these include anticonvulsants, warfarin derivatives, NSAIDs, sulfonamides, fluoroquinolones, and ACE inhibitors.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 180: QUESTIONS AND ANSWERS

180.1. A 42-year-old woman who is 7 months pregnant presents with severe, pressure-like chest pain that occurred while she was washing her clothes. The pain radiates to both shoulders and is associated with dyspnea and dizziness. Vital signs show heart rate, 92 beats/min, respiratory rate (RR), 22 breaths/min, blood pressure (BP), 134/70 mm Hg, and O_2 saturation, 97% on room air. She appears pale and diaphoretic and has a subdued affect. Lung examination reveals equal breath sounds without rales, rhonchi, wheezes, or friction rubs. Cardiac examination reveals a regular rhythm at 92 beats/min. There were no murmurs, gallops, or rubs appreciated. An electrocardiogram (ECG) shows ST elevations in leads I, aVL, and V_2–V_6, with reciprocal T wave inversions. Of the following, which would be the most appropriate?

A. Administer beta blockers.
B. Administer heparin drip, and admit the patient to the critical care unit.
C. Administer thrombolytic therapy.
D. Schedule the patient for computed tomography (CT) angiography of the chest STAT.

E. Start nonsteroidal antiinflammatory drugs (NSAIDs), and schedule the patient for two-dimensional echocardiography.

Answer: C. The patient has an acute myocardial infarction (MI) and requires immediate reperfusion therapy. This may be accomplished by thrombolytic therapy or by performing a percutaneous coronary intervention (PCI). Of the choices given, only C provides reperfusion therapy. In this case, treatment of the life-threatening MI in the mother outweighs the possible dangers to the embryo or fetus.

180.2. A 23-year-old woman who is 6 months pregnant was well until earlier in the morning, when she experienced sudden onset of shortness of breath and right-sided sharp chest pain. The pain is worse on inspiration and is not related to exertion, although her dyspnea becomes worse with any activity. She is alert and appears in distress. Her pulse is 112 beats/min, RR, 32 breaths/min, and BP, 98/48 mm Hg. Her temperature is 100.8°F (32°C), and O_2 saturation is 92%. Lung examination reveals splinting of the respirations, with rales and wheezing on the right. Cardiac examination reveals tachycardia. No murmurs, gallops, or rubs were noted. Chest radiograph reveals elevated right hemidiaphragm but no infiltrates. ECG reveals generalized T wave inversions. Of the following, which would be most appropriate?

A. Administer a low-molecular-weight heparin subcutaneously, as well as oral warfarin sodium (Coumadin).
B. Administer intravenous ceftriaxone and azithromycin for clinical pneumonia.
C. Administer nebulized bronchodilators, and start prednisone.
D. Administer oxygen, schedule for a diagnostic study, and start heparin.
E. Place a central line, and start early goal-directed therapy for sepsis.

Answer: D. On the basis of the information provided, the patient most likely has a pulmonary embolus. The patient is hypoxic and requires oxygen administration and anticoagulation. This may be accomplished with heparin and Coumadin. Coumadin, however, is teratogenic and is contraindicated in pregnancy. The patient has no symptoms of an infectious process; choices B and E are therefore not appropriate. Bronchodilators and steroids are indicated for asthma but not for thromboembolic disease. Choice C is therefore not appropriate.

180.3. In determining a causal link between a specific drug and congenital malformations, which of the following may be viewed as confounding factors?

A. All of these
B. Genetic background of the fetus
C. Maternal illicit drug use
D. Presence of maternal illness
E. Presence of nutritional deficits

Answer: A. The process of establishing teratogenicity of a substance is often flawed. Much of our current knowledge on teratogenicity has been derived from case reports, case-controlled studies, and cohort studies, which are inherently weak in establishing a causal link. These reports are often complicated by a number of confounding factors, which make a causal link difficult to establish. The presence of any of the listed choices may confound results. In the presence of maternal illness, for example, the outcome of pregnancy may be related to the medical condition and not the medication.

180.4. Which of the following drugs is a known teratogen?

A. Acetaminophen
B. Hydroxycobalamin
C. Levothyroxine
D. Penicillin VK
E. Phenytoin

Answer: E. Phenytoin or diphenylhydantoin is an anticonvulsant that is a class D agent and is highly teratogenic. It is associated with the fetal hydantoin syndrome, which is characterized by abnormal ossification of the digits, craniofacial clefts, multiple cardiovascular abnormalities, and impaired neurologic development. It affects 5% to 10% of pregnancies and should be used only if other, safer anticonvulsants fail to control convulsions. The other drugs listed are safe during pregnancy.

180.5. Which of the following drugs may be associated with complications in the newborn when used at term?

A. All of these
B. Nitrofurantoin
C. Nonsteroidal antiinflammatory drugs
D. Propranolol
E. Sulfonamides

Answer: A. All the choices have been associated with complications in the newborn when used at term. Sulfonamides compete with bilirubin for protein-binding sites, leaving large amounts of free bilirubin to diffuse freely into the brain. This results in bilirubin deposition in the infant's brain, thus causing kernicterus. Nitrofurantoin at term has been associated with hemolytic disease of the newborn. Nonsteroidal antiinflammatory drugs are associated with premature closure of the ductus arteriosus. Propranolol at term has been associated with neonatal hypoglycemia, respiratory depression, and neonatal jaundice.

180.6. Which of the following antiarrhythmic agents is a known teratogen?

A. Adenosine
B. Amiodarone
C. Digoxin
D. Lidocaine
E. Procainamide

Answer: B. All the listed antiarrhythmics are safe for use in pregnancy and have not been associated with structural effects except for amiodarone. Amiodarone is a class D agent. It contains a large amount of iodine and may result in congenital goiter and neonatal thyroid abnormalities. In addition, it has been linked to a number of congenital abnormalities affecting growth, cardiac, ophthalmic, and neurologic development. It should only be used for patients who are refractory to other drugs.