CHAPTER 178

Drug Therapy in Pregnancy

Rania Habal

PERSPECTIVE

The placenta was previously believed to act as a barrier, excluding toxins from the fetal circulation and protecting the fetus from environmental and pharmacologic exposures. In 1961, when an epidemic of amelia, a rare malformation characterized by an absence of limbs, was linked to the use of thalidomide during pregnancy, the vulnerability of the fetus to medications came into focus. Thalidomide was a sedative-hypnotic agent introduced in 1956. It immediately became popular in the treatment of nausea and vomiting during the first trimester of pregnancy, but in the years that followed, it was established that thalidomide was the agent responsible for the amelia/phocomelia epidemic. By the time thalidomide was withdrawn from the market, an estimated 5850 children were affected worldwide.[1] Similarly, it took an epidemic of debilitating congenital anomalies and deaths in the children of fishermen in Minamata, Japan, to recognize the teratogenicity of environmental pollutants.[2,3] Minamata disease was due to the ingestion of fish contaminated by methylmercury, an industrial by-product that was dumped into Minimata Harbor in the early 20th century. These two events sparked the development of numerous control agencies to oversee the safety of drugs in pregnancy and numerous environmental protection laws.

Thalidomide's legacy continues to haunt physicians worldwide. Many physicians are reluctant to prescribe medications to pregnant women or to nursing mothers. However, only a few medications have been identified as teratogens, and medication use during pregnancy is extremely common. In a worldwide survey of more than 14,000 patients, the World Health Organization reported that more than 86% of women used at least one prescription drug while pregnant. In a similar survey in the United States, more than 80% of pregnant women reported using medications during pregnancy, with 30% using more than four drugs.[4] The contribution of these substances to the incidence of birth defects is thought to be low, accounting for 1 to 3% of all live birth defects.[5,6]

The emergency physician must understand when the maternal benefit of prescribing a particular agent will outweigh any potential risk of fetal harm, and he or she must be able to discuss those risks and benefits with the patient.

PRINCIPLES OF DISEASE

Major birth defects affect 3 to 5% of all live births.[6] Most are of unknown etiology, but 1 to 3% of these are thought to be due to pharmaceutical agents.[5,6] A *teratogen* is any chemical, pharmacologic, environmental, or mechanical agent that can cause deviant or disruptive development of the conceptus.[5-7] Included in this definition are physical malformations, growth retardation, fetal demise, and functional impairment.[6] Although serious effects on the mother are identified immediately, a drug's teratogenic effect may not be apparent for years. Malformations may range from subtle neurobehavioral effects to devastating physical deformities and physiologic effects, including death.[5-7] Why one pregnancy would be affected and not another remains to be elucidated. Highly teratogenic medications seem to be few in number, estimated at well below 50 agents (Box 178-1).[7,8]

When examining the effects of substances on the outcome of pregnancy, it is important to keep in mind that the process of establishing the risk and safety of drugs in pregnancy is tedious and often flawed. For ethical reasons, few controlled prospective human studies analyzing the risk-benefit relationship for any given exposure are available. As a result, much current knowledge has been derived from case reports, case-controlled studies, or cohort studies, which are inherently weak in establishing a causal relationship,[1,5,6,9] and from animal research. Knowledge extrapolated from animal models, although valuable in determining risk initially, is not always applicable to humans.[1,5,6,9]

In evaluating data on the relationship between an exposure during pregnancy and a particular outcome, a multitude of confounding factors make the determination of a causal link difficult. The genetic background of the fetus, the timing and duration of the exposure, environmental factors, the occurrence of multiple exposures and the presence of nutritional deficits, maternal illness, and illicit drug use all contribute to the outcome of pregnancy.[1,5-9] In the presence of maternal illness, for example, the outcome of pregnancy may be related to the medical condition and not the medication, and separating the risks of an anomaly from the expected background risk may be difficult.

The study of teratogenicity is also hindered by several additional factors. First, the history of drug or environmental exposure is often obtained in retrospect, after 9 months of pregnancy and the delivery of an abnormal infant. By that time, significant recall bias may have been introduced, which may depend on the outcome of the birth.[9] Second, because many pregnancies are spontaneously aborted before maternal knowledge that conception has occurred, the cited prevalence of drug-induced birth defects may not be accurate.[5,6,8,9] Finally, as in the case of diethylstilbestrol, teratogenicity may not be appar-

BOX 178-1 DRUGS AND AGENTS CONSIDERED HUMAN TERATOGENS AND DEVELOPMENTAL TOXINS

Alkylating agents (busulfan, chlorambucil, cyclophosphamide, etc.)
Lead*
Aminopterin and methotrexate*
Lithium*
Amnioglycosides (streptomycin and others)
Methimazole
Amiodrone
Methylmercury*
Androgens*
Methylene blue
Angiotensin enzyme inhibitors*
Misoprostol
Carbamazepine
Nonsteroidal anti-inflammatory agents
Carbon monoxide
Paramethadione, trimethadione*
Chlorobiphenyls*
Phenytoin*
Cocaine*
Polychlorinated biphenyls*
Corticosteroids
Progestins
Coumarin derivatives*
Quinine
Danazole
Diethylstilbestrol*
Tetracycline*
Ergotamine
Ethanol (in large doses)*
Tobacco
Fluconazol (in high doses)
Iodine
Thalidomide *
Ionizing radiation*
Trimethadione*
Isotretinoin (systemic) *
Valproic acid*
Statins

*Teratogen.
Modified from Shepard TH: Catalog of Teratogenic Agents, 12th ed. Baltimore, Johns Hopkins University Press, 2008; and Fine JS: Reproductive and perinatal principles. In Goldfrank LR, et al (eds): Goldfrank's Toxicologic Emergencies, 8th ed. New York, McGraw-Hill, 2006, pp 465–485.

ent for years after birth. Large population studies are needed to understand the connection between the outcome of a pregnancy and an associated in utero exposure.[10]

Classification of Teratogenic Risk

To aid physicians in determining the teratogenic potential of a particular medication, the U.S. Food and Drug Administration (FDA) has published a classification system that assigns risk based on currently available human and animal studies and case reports. Drugs are assigned one of five letters—A, B, C, D, and X—depending on the strength of evidence for their safety or teratogenicity (Box 178-2). The FDA classification system has been criticized as oversimplistic and perhaps inaccurate because it relies on data that are generally of poor quality. In addition, using this classification, more than 90% of drugs approved in the United States between 1980 and 2000 were assigned an undetermined teratogenic risk.[11] Furthermore, some clinicians believe that the classification system conveys the incorrect impression that there is a gradation of reproductive risk from exposure across categories (i.e., 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.[12] The FDA has acknowledged these problems, and in 2008 it proposed new rules regarding drug labeling during pregnancy and the elimination of the current ABCDX pregnancy categories. A number of clinical teratology resources, such as TERIS, REPROTOX, and REPRORISK (Shepard's catalogue of teratogenic agents), are now available online. These databases assign teratogenic risk to drugs based on a consensus of opinion of an expert panel.

BOX 178-2 FOOD AND DRUG ADMINISTRATION CLASSIFICATION: 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 based on human or animal studies or postmarketing reports that indicate benefit is clearly outweighed by risk.

Drug Transfer across the Placenta

The degree to which the fetus is affected by a given pharmaceutical agent and the nature of that effect depend on multiple factors. The transport of maternal substrates to the fetus and of waste products from the fetus to the mother is established during week 5 of gestation.[1,5,8,13] Drug transfer across the placenta occurs most commonly by simple passive diffusion or by 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 the extent of protein binding. Drugs with a molecular weight of less than 5 kDa readily diffuse. Anionic forms diffuse through the lipid layer more readily than ionized forms. Free drug diffuses more readily than a drug that is bound to plasma proteins. Because fetal pH is slightly more alkalotic than maternal pH, weak organic acids (e.g., salicylate) may become ion trapped in the fetal circulation, increasing fetal exposure.[1,5,8,13]

Drugs may affect the fetus through a variety of mechanisms. Some drugs may alter the availability of substrates, such as vitamins, glucose, oxygen, and amino acids, needed for normal nutrition and growth.[1,5,8,13] Others may directly affect cellular growth and differentiation. The age of the fetus is crucial in determining the impact of any given exposure. During the time of organogenesis (days 21–56 of fetal life), the fetus is much more vulnerable to toxic insults.[1,5,8] The major body organs are formed during this period, and exposure to a terato-

gen at this time may result in major anatomic defects. The central nervous system (CNS) develops over a longer period (10–17 weeks) so that later exposures may affect neurologic development and subsequent function. Exposure after the period of organogenesis may affect the growth and development of the fetus but does not have an impact on organogenesis; however, it most likely affects fetal growth.[1,5,8]

Drug Transfer during Lactation

For the most part, drugs and substances that are ingested or injected by the mother diffuse passively into milk and then back into the maternal circulation for excretion.[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 readily.[14] 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.[14] The interruption of breast-feeding should not be advocated except in rare situations of known drug toxicity to the infant.[15]

Table 178-1 summarizes the compatibility of medications and their effects in pregnancy and lactation.

DRUG THERAPY DURING PREGNANCY

In general, the health of the fetus is directly related to the health of the mother. Physicians should never withhold life-saving 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 that presents maternal benefits that outweigh the risks to the fetus. Included in this category are therapeutic medications for asthma, arrhythmias, status epilepticus, and HIV.

Analgesic Agents

Acetaminophen (paracetamol) is safe throughout pregnancy. It is widely used during pregnancy and has not been associated with an increase in the incidence of congenital malformations when therapeutic doses are used.[16,17] Statements about its safety also apply to acute and chronic overdose conditions.[18,19] However, there is an increase in the incidence of spontaneous abortion and fetal demise, especially when antidote treatment with *N*-acetylcysteine is delayed.[18-20] Acetaminophen is safe during lactation because only a small amount is excreted into breast milk, and the amount that does get through is tolerated by the neonate's sulfhydration pathway.[15,16]

Aspirin appears to be safe throughout pregnancy when used in small doses. Early studies of aspirin use during pregnancy linked it to an increased risk of perinatal and neonatal bleeding, increased risk of postmaturity, significant prolongation of labor, low birth weight, neonatal hypoglycemia, metabolic acidosis in the newborn, and neonatal death.[16,17] However, in the Perinatal Antiplatelet Review of International Studies Collaboration (PARIS) study, low doses of aspirin were actually found to be beneficial and to reduce the risk of preeclampsia, premature birth, and adverse perinatal outcomes.[23] Furthermore, a number of recent meta-analyses in humans failed to demonstrate a teratogenic effect to aspirin, although there was a trend toward a slightly increased incidence of gastroschisis when used in the first trimester.[21,22]

Non-aspirin NSAIDs should be avoided in the first and third trimesters but are considered safe in the second trimester. Use of NSAIDs in the first trimester has been associated with a small increase in cardiac defects, oral clefts, and gastroschisis.[16,17,24] Use of NSAIDs at or near term has been associated with premature closure of the ductus arteriosus, periventricular hemorrhages in the offspring, oligohydramnios, and fetal nephrotoxicity.[16,17] Additionally, a number of population-based cohort studies have found that NSAIDs are associated with an increased risk of spontaneous abortion, preterm birth, and low birth weight.[25] NSAIDs in general appear to be safe during lactation when used for short durations.[16,17]

The short-term use of opiates appears to be safe in pregnancy. Because opiates' sedative effects extend to the fetus, caution should be used when prescribed at term. Chronic use of opiates is discouraged in general because it may result in maternal as well as fetal addiction. Because opiates are poorly concentrated in milk, opiate analgesia may be used safely during breast-feeding.[15]

Antibiotics

First- through fourth-generation penicillins and their derivatives (including procaine, benzathine, clavulanate, sulbactam, and tazobactam) are considered safe for use in pregnancy, as is oral probenecid.[16,17,26,27] Penicillins are considered safe during breast-feeding, but their use may interfere with culture results if a neonatal fever workup is required.[15-17]

First- through fourth-generation cephalosporins appear to be safe for use during pregnancy, although there are no controlled studies examining their safety.[16,17,26-28] Some cephalosporins are excreted into breast milk and may have the same implications on the workup of neonatal sepsis as described for penicillin.[15-17]

Chloramphenicol is safe during pregnancy except at term. No relationship has been found between the use of chloramphenicol and congenital anomalies.[16,17,27,29] Although it is considered safe throughout most of pregnancy, chloramphenicol should be used with caution at term. It has been associated with the development of cardiovascular collapse (the "gray baby" syndrome) in a neonate.[16,17,26,27] The safety of chloramphenicol during breast-feeding is unknown; however, due to its potential toxicity, it is not recommended for use during lactation.[15–17]

The macrolides erythromycin, azithromycin, and clarithromycin are considered to be safe for use in pregnancy and compatible with breast-feeding, although there are no well-controlled studies examining their effects on the fetus.[15–17] Some reports have linked erythromycin to pyloric stenosis, but these studies were not controlled.[16,17,26,27] The estolate salt of erythromycin has also been associated with the development of hepatotoxicity in pregnant women and should be avoided during pregnancy.[16,17,26,27] Clarithromycin has been associated with an increased risk of fetal and embryonic death as well as congenital malformations in animal species. To date, however, this has not been shown in humans. In addition, a prospective controlled multicenter study comparing the outcomes of pregnancies exposed to clarithromycin to matched controls did not find any differences in the types or patterns of malformations between the two groups.[29,30] However, there appeared to be an increased number of spontaneous abortions in exposed women, which may have been due to confounding factors, and further studies are warranted. Azithromycin is poorly

Text continued on p. 2320

Table 178-1 Summary of Medication Safety in Pregnancy and Lactation

MEDICATION	PREGNANCY	LACTATION
Analgesic agents		
Acetaminophen or paracetamol	Safe (B)	Safe
Nonsteroidal anti-inflammatory drugs (NSAIDs)		
Salicylate	Not recommended (D)	Safe for short-term use
Other NSAIDs	Not recommended (D)	Safe
Opiates: Most opiates are considered safe for short-term use but are all reclassified in category D if used for prolonged periods or if used in high doses at term (due to respiratory depression in newborn). Do not use opiates combined with aspirin or NSAIDS.		
Morphine—short-term use	Safe (C)	Safe
Fentanyl—short-term use	Safe (C)	Safe
Methadone	Safe (B/C)	Safe
Meperidine—short-term use	Safe (C)	Safe
Codeine	Possible risk (C)	Not advised if longer than 2 days
Oxycodone—short-term use	Safe (C)	Probably safe
Hydrocodone—short-term use	Safe (C)	Probably safe
Hydromorphone—short-term use	Safe (B)	Probably safe
Oxycodode—short-term use	Safe (B)	Probably safe
Antibiotics: Use of antibiotics near term may interfere with culture results in neonates.		
Penicillins		
First-generation penicillins: penicillin G, benzathine penicillin, bicillin, penicillin VK	Safe (B)	Safe
Second-generation penicillins: oxacillin, dicloxacillin, nafcillin	Safe (B)	Safe
Third-generation penicillins: ampicillin, ampicillin-sulbactam, amoxicillin, amocillin-clavulanate	Safe (B)	Safe
Fourth-generation penicillins: ticarcillin, ticarcillin-clavulanate, piperacillin, piperacillin-tazobactam, carbenicillin	Safe (B)	Probably safe
Cephalosporins		
First generation: cephalexin, cefazolin, cefadroxil	Safe (B)	Safe
Second generation: cefuroxime, cefaclor, cefoxitin, cefprozil	Safe (B)	Safe
Third generation: cefdinir, cefotaxime, ceftazidime, ceftriaxone, cefpodoxime, ceftizoxime	Safe (B)	Probably safe
Chloramphenicol: *Do not* use at term because it can cause "gray baby syndrome."	Safe until term (C)	Possible toxicity
Macrolides		
Erythromycin: *Do not* use estolate salt.	Safe (B)	Safe
Azithromycin	Safe (B)	Safe
Clarithromycin	Probably safe (C)	Probably safe
Sulfonamides: May cause kernicterus in newborn if given in third trimester.	Not recommended near term (C)	Safe, except in premature infants or infants with G6PD deficiency or hyperbilirubinemia
Quinolones		
First generation: nalidixic acid	Moderate risk (C)	Safe
Second generation: ciprofloxacin, norfloxacin, ofloxacin	Small risk (C)	Probably safe
Third generation: levaquin	Small risk (C)	Probably safe
Fourth generation: gatifloxacin, moxifloxacin	Small risk (C)	Probably safe
Aminoglycosides	Not recommended (D)	Safe
Clindamycin	Safe (B)	Safe
Vancomycin	Safe (B)	Safe
Linezolid: Maternal benefit may outweigh risks to fetus or embryo.	Unknown (C)	Safety unknown
Tetracyclines	Not recommended (D)	Not recommended
Nitrofurantoin: May cause hemolytic anemia in newborn if used in third trimester.	Safe (B), except in third trimester	Probably safe
Metronidazole	Contraindicated in first trimester, safe in second and third trimesters (B)	Not recommended
Antifungals		
Nystatin	Safe (B/C)	Safety unknown
Clotrimazole	Safe (B/C)	Safety unknown
Ketoconazole	Probably safe (C)	Probably safe
Fluconazole	Not recommened in high doses (C)	Safe
Terbinafine	Low risk (B)	Not recommended

Table 178-1 Summary of Medication Safety in Pregnancy and Lactation—cont'd

MEDICATION	PREGNANCY	LACTATION
Antituberculous medications in general present a maternal benefit that is much greater than the fetal or embryonic risk and may be prescribed during any stage of pregnancy when indicated.		
INH	Safe (C)	Probably safe
Rifampin	Probably safe (C)	Probably safe
Ethambutol	Safe (C)	Probably safe
Antiviral agents		
Antiherpetic medications		
Acyclovir	Safe (B)	Safe
Valacyclovir	Safe (B)	Safe
Famciclovir	Small risk (B)	Potentially toxic
Anti-influenza agents		
Amantadine	Possible risk (C)	Safety unknown
Oseltamivir	Safe in animals (C)	Safety unknown
Anti-HIV medications in general present a maternal benefit that is much greater than the fetal or embryonic risk and may be prescribed during any stage of pregnancy when indicated.		
Reverse transcriptase inhibitors		
Zidovudine	Caution in first trimester (C)	Not recommended
Lamivudine	Caution in first trimester (C)	Not recommended
Didanosine	Caution in first trimester (B)	Not recommended
Tenovir	Caution in first trimester (B)	Not recommended
Indinavir	Caution in first trimester (C)	Not recommended
Protease inhibitors		
Ritonavir	Caution in first trimester (B)	Not recommended
Nelfinavir	Caution in first trimester (B)	Not recommended
Anticoagulants		
Warfarin	Contraindicated	Safe
Heparin	Safe (B)	Safe
Low-molecular-weight heparin	Safe (B)	Safe
Thrombolytics: Benefits to the mother generally outweigh the risk to the fetus.		
Alteplase	Safe (C)	Probably safe
Reteplase	Safe (C)	Probably safe
Urokinase	Safe (B)	Probably safe
Streptokinase—no human data	Safe in animals (C)	Hold breast-feeding
Tenectaplase—no human data	Safe in animals (C)	Hold breast-feeding
Anticonvulsants: Benefits to the mother outweigh the risks to the fetus and embryo. Monotherapy is recommended. Use of highly teratogenic anticonvulsants is recommended in refractory cases only.		
Carbamazepine	Teratogen (D)	Probably safe
Valproic acid	Teratogen (D)	Probably safe
Phenobarbital	Not recommended (D)	Not recommended
Phenytoin	Teratogen (D)	Safe
Lamotrigine	Small risk in animals (C)	Not recommended
Levetiracetam	Small risk in animals (C)	Safety unknown
Topiramate	Small risk in animals (C)	Safety unknown
Gabapentin	Small risk in animals (C)	Probably safe
Sedative-hypnotics		
Benzodiazepines: Results are inconsistent. There may be a small risk of abnormalities. In the acute short-term treatment of status epilepticus, agitated delirium, and alcohol or benzodiazepine withdrawal, benefits to the mother outweigh risks to the fetus or embryo. Not recommended for long-term use.		
Diazepam—low risk in first and third trimesters	Safe acutely; unsafe for chronic use (D)	Potential toxicity
Lorazepam—low risk in first and third trimesters	Safe acutely; unsafe for chronic use (D)	Potential toxicity
Chlordiazepoxide—low risk in first and third trimesters	Safe acutely; unsafe for chronic use (D)	Potential toxicity
Oxazepam—low risk in first and third trimesters	Safe acutely; unsafe for chronic use (D)	Potential toxicity
Midazolam—low risk in first and third trimesters	Safe acutely; unsafe for chronic use (D)	Potential toxicity
Barbiturates		
Methohexital	Safe (C)	Safety unknown
Thiopental	Safe (C)	Safety unknown
Ketamine: Risk mainly with high doses close to delivery.	Safe (B)	Probably safe after 12 hr
Propofol	Safe (B/C)	Not recommended
Etomidate	Safe (B/C)	Probably safe
Paralytic agents		
Depolarizing agents		
Succinylcholine	Low risk, especially around delivery (C)	Probably safe
Nondepolarizing agents		
Rocuronium	Limited data (C)	Probably safe
Vecuronium	Limited data (C)	Probably safe

Continued

Table 178-1 Summary of Medication Safety in Pregnancy and Lactation—cont'd

MEDICATION	PREGNANCY	LACTATION
Antiarrythmics: In cases of refractory arrhythmias, the benefits to the mother may outweigh risks to the fetus or embryo.		
Adenosine	Safe (C)	Safe
Amiodarone	Not recommended (D)	Contraindicated
Digoxin—caution in third trimester (oxytocic)	Safe (C)	Safe
Disopyramide	Caution in third trimester (B)	Probably safe
Encainide	Limited data (C)	Probably safe
Flecainide	Limited data (C)	Not recommended
Quinidine	Safe (C)	Not recommended
Procainamide	Safe (C)	Not recommended
Ibutilide	Risk in animals	Not recommended
Lidocaine	Safe (B)	Probably safe
Sotalol	Probably safe (C)	Not recommended
Antihypertensives		
Angiotensin antagonists		
Angiotensin-converting enzyme inhibitors	Not recommended (D)	Some are safe
Angiotensin II receptor antagonists	Not recommended (D)	Safety unknown
Beta-blockers		
Labetalol	Probably safe (C)	Probably safe
Atenolol	Caution in second and third trimesters (D)	Potential toxicity
Esmolol	Caution in third trimester (C)	Safety unknown
Metoprolol	Caution in second and third trimesters (D)	Potential toxicity
Propranolol	Caution in second and third trimesters (D)	Probably safe
Calcium channel blockers		
Diltiazem—tocolytic	Probably safe (C)	Probably safe
Verapamil	Probably safe (C)	Probably safe
Amlodipine	No data (C)	No data
Nifedipine—not sublingual	Probably safe (C)	Probably safe
Diuretics: Caution for dehydration and electrolyte abnormalities.		
Furosemide	Low risk (C)	Probably safe
Bumetanide	Low risk (C)	Probably safe
Ethacrynic acid	Low risk (B)	Probably safe
Torsemide	Low risk (B)	Probably safe
Hydrochlorothiazide—contraindicated in gestational HTN	Safe (B)	Safe
Nitrates		
Nitroprusside	Some risk (C)	Potential toxicity
Nitroglycerin	Probably safe (C)	Probably safe
Vasodilators		
Hydralazine	Safe (C)	Safe
Alpha effectors		
Clonidine	Caution in third trimester (C)	No data
Other		
Methyldopa	Safe (B)	Safe
Fenoldopam	No data (B)	No data
Medications used in the treatment of asthma, allergies, and upper respiratory infection: For asthmatic patients, maternal benefits outweigh risks to fetus or embryo.		
Beta-adrenergics considered safe for short-term use		
Epinephrine	Risk (C)	Potential toxicity
Metaproterenol	Safe (C)	Probably safe
Salmeterol	Limited data (C)	Probably safe
Albuterol	Safe (C)	Probably safe
Terbutaline	Low risk (C)	Probably safe
Anticholinergic agents		
Ipratropium	Safe (B)	Probably safe
Mast cell stabilizers		
Cromolyn sodium	Safe (B)	Probably safe
Leukotriene inhibitors		
Zafirlukast	Risk (B)	No data
Zileuton	Risk (C)	Not recommended
Montelukast	Risk (B)	No data; probably compatible

Table 178-1 Summary of Medication Safety in Pregnancy and Lactation—cont'd

MEDICATION	PREGNANCY	LACTATION
Corticosteroids safe for short-term use: Human data suggest an increased risk of orofacial clefts.		
Prednisolone	Risk (C)	Safe
Prednisone	Risk (C)	Safe
Methylprednisolone	Risk (C)	Safe
Antihistamines		
Chlorpheniramine	Safe (B)	Not recommended
Diphenhydramine	Safe (B)	Not recommended
Dimenhydramine	Safe (B)	Not recommended
Doxylamine	Safe (B)	Not recommended
Hydroxyzine	Risk (C)	Not recommended
Meclizine	Safe (B)	Not recommended
Cetirizine	Probably safe (B)	Not recommended
Fexofenadine	Class C	Safe
Loratadine	Probably safe (B)	Safe
Decongestants		
Pseudoephedrine	Risk (C)	Probably safe
Antiemetics		
Dopamine antagonists		
Promethazine	Safe (C)	Not recommended
Prochlorperazine	Safe (C)	Potential toxicity
Metoclopramide	Safe (B)	Potential tocxicity
5-HT_3 antagonists—generally safe		
Dolasetron	Low risk (B)	Probably safe
Granisetron	Low risk (B)	Probably safe
Ondansetron	Safe (B)	Probably safe
Medications used in the treatment of diabetes		
Insulin	Safe (B)	Safe
Sulfonylureas		
Glipizide	Low risk (C)	Probably safe. Caution: Nursing infants should be monitored.
Glyburide	Low risk (C)	Probably safe. Caution: Nursing infants should be monitored.
Metformin	Moderate risk (C)	Probably safe
Pioglitazone	Moderate risk (C)	Probably safe
Rosiglitazone	Moderate risk (C)	Probably safe
Antacids		
H_2 blockers		
Famotidine	Low risk (B)	Probably safe
Ranitidine	Safe (B)	Probably safe
Nizatidine	Low risk (B)	Probably safe
Cimetidine	Safe (B)	Safe
Proton pump inhibitors		
Omeprazole	Low risk (C)	Safety unknown
Esomeprazole	Low risk (B)	Safety unknown
Lansoprazole	Low risk (B)	Safety unknown
Pantoprazole	Low risk (B)	Safety unknown
Antidotes and toxicology: When indicated, the benefits to the mother will outweigh the possible risks to the fetus.		
Antidote: acetaminophen overdose		
N-acetylcysteine	Safe (B)	Safe
Universal antidote		
Charcoal	Safe (B)	Safe
Antidote: iron toxicity		
Deferoxamine	Probably safe (C)	No data
Antidote: digitalis		
DIG Fab	No data (C)	No data
Antidote: benzodiazepines		
Flumazenil	No data (C)	No data
Antidote: toxic alcohols		
Fomepazole	No data (C)	No data
Antidote: cyanide poisoning		
Hydroxycobalamine	Safe (B)	Safe
Antidote: methemoglobinemia		
Methylene blue	Risk noted (C)	Not recommended

Continued

Table 178-1 Summary of Medication Safety in Pregnancy and Lactation—cont'd

MEDICATION	PREGNANCY	LACTATION
Antidote: narcotics		
Naloxone	Safe (B)	Safe
Universal antidote		
PEG-ELS	Safe (B)	Safe
Antidote: anticholinergics		
Physostigmine	No data	No data
Antidote: organophosphates		
Pralidoxime	No data	No data
Antidote: isoniazid overdose		
Pyridoxine	Safe (B)	Safe
Antidote: lead poisoning		
Succimer	No data	No data

G6PD, glucose-6-phosphate dehydrogenase; PEG-ELS, polyethylenegycol-electrolyte lavage solution.

concentrated in breast milk and may be the preferred agent in lactating mothers.[15-17,27]

Sulfonamides are safe for use in the second trimester and possibly safe in the first trimester, but they should be avoided at term. The primary use of sulfonamides in the emergency department is in the treatment of uncomplicated urinary tract infection, and in this circumstance, sulfamethoxazole is combined with trimethoprim. Trimethoprim is a folate antagonist and has traditionally been contraindicated in pregnancy because of an increased risk of neural tube defects. The sulfonamides readily cross the placenta to the fetus during all stages of gestation. Fetal levels may reach 90% of maternal plasma concentrations. Although sulfamethoxazole has been associated with an increase in congenital malformations in animals, most reports of sulfonamide exposure during pregnancy in humans have failed to demonstrate such an association.[16,17] Sulfonamides are contraindicated in pregnancy near term because they theoretically compete with bilirubin for protein-binding sites, leaving large amounts of free bilirubin to diffuse, be deposited in the infant's brain, and cause kernicterus.[16,17,31,32] To date, however, this complication has not been reported in neonates, presumably because free bilirubin is effectively cleared by the placental circulation. In contradistinction, kernicterus has occurred in newborns exposed to sulfonamides after birth.[16,17] Sulfonamides are excreted into breast milk in low concentrations and are generally tolerated by a healthy neonate. They should be avoided, however, in ill or premature infants and in infants with hyperbilirubinemia or glucose-6-phosphate dehydrogenase deficiency.[15]

Aminoglycosides should be avoided during pregnancy. These drugs readily cross the placenta and their use in pregnancy has been linked to fetal ototoxicity and nephrotoxicity, especially when high doses are used.[16,17] Gentamicin is secreted in small amounts in breast milk and is poorly absorbed from the gastrointestinal tract. It is compatible with lactation.[15-17]

Tetracycline should be avoided during pregnancy because it has been associated with the development of fatal fatty liver in pregnant women.[16,17,26,27] It readily crosses the placenta and reaches the fetus, where it chelates calcium, causing abnormalities in bone growth and staining of decidual teeth. Tetracycline has also been associated with fetal genitourinary anomalies, inguinal hernias, and limb abnormalities.[16,17,26,27] Doxycycline does not bind to calcium and is associated less with stained teeth than is tetracycline. Also, it does not appear to cause an increase in any type of congenital malformation. Despite these findings, doxycycline is not advocated for long-term use in pregnancy.[16,17,26,27]

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.[15-17] Because it does not bind to breast milk calcium, doxycycline is present in greater quantities in breast milk and is not recommended for use for prolonged periods.[15-17,26,27]

Fluoroquinolones have been linked to numerous toxic effects on bone and cartilage growth in animal models and have been discouraged from use during pregnancy, particularly during the first trimester.[15-17,26,27] A 1998 prospective multicenter study, however, found no increase in premature birth, fetal distress, low birth weight (<2500 g), birth weight, or motor development when fluoroquinolones were used during pregnancy.[33] The American Academy of Pediatrics (AAP) considers fluoroquinolones to be compatible with breast-feeding, because breast-fed infant plasma levels are low.[15,27]

Clindamycin has not been associated with birth defects in humans, and animal studies have failed to link clindamycin to congenital abnormalities in the offspring.[16,17,26,27] The AAP considers clindamycin to be compatible with breast-feeding.[15]

Vancomycin has not been linked to birth defects in humans.[16,17,26,27] Reports of auditory abnormalities and renal insufficiency in neonates of mothers treated with vancomycin are believed to be false positives.[34] Vancomycin is excreted into milk but not well absorbed by the GI tract. Its effects on the nursing infant have not been studied.[16,17]

Linezolid has been linked to embryonic death, decreased weight, and abnormalities in cartilage and ossification in animal studies, but there is no information regarding its effects in humans. Its use in pregnant women should be limited to cases in which the maternal benefit will outweigh possible risk to the fetus.[16,17]

Nitrofurantoin has not been linked to birth defects in animals or humans. However, there are rare reports of hemolytic anemia in the newborn when the drug is used near term, independent of glucose-6-phosphate dehydrogenase deficiency.[16,17,35]

Human data on the use of metronidazole during pregnancy are mixed.[16,17,27] Because metronidazole is mutagenic and carcinogenic in mice, many physicians avoid prescribing it during pregnancy. An analysis of pooled data from case-control and cohort studies, however, did not reveal any increased incidence of congenital malformations even when metronidazole was used in the first trimester.[36] It is therefore considered safe for use in the second and third trimesters, but because of its potential mutagenic effects it is not recommended for use in the first trimester.[16,17,27] Furthermore, the AAP recommends using metronidazole with caution during lactation.[15-17]

Antifungal Medications

Nystatin has a long safety profile during pregnancy and lactation. It is poorly absorbed from skin, mucous membranes, and the GI tract, and it is considered the antifungal agent of first choice for treatment of mucocutaneous fungal infections.[16,17,27] Clotrimazole, miconazole, and ketoconazole seem to be safe during pregnancy and lactation because they have not been associated with major birth defects. However, in a case-control study, a minor increase in the incidence of hypoplastic left ventricle was reported. In addition, ketoconazole is teratogenic in rats. For these reasons, clotrimazole, miconazole, and ketoconazole are considered second-line treatment of fungal infections in pregnancy.[16,17,27] 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.[16,17,27,37] These anomalies were not noted when lower doses were used or with single-dose (150 mg) therapy for vaginal candidiasis.[16,17]

Ketocanazole, fluconazole, and itraconazole are excreted into breast milk. Based on the safe use of ketocanazole in neonates and the lack of negative reports, it is considered compatible with breast-feeding.[15-17]

Antituberculous Agents

Untreated tuberculosis places the mother and fetus at greater risk than does the use of antituberculous medications. In addition, in a review of antituberculous treatment during pregnancy, no association was found between these medications and congenital malformations.[16,17,27,38] Rifampin crosses the placenta and occasionally has been implicated in case reports of congenital anomalies and with hemorrhagic disease of the newborn.[16,17] Because there are no controlled studies documenting these effects, rifampin continues to be recommended as first-line therapy along with isoniazid for treatment of pregnant women with tuberculosis. Ethambutol crosses the placenta but has not been associated with any congenital defects.[16,17,27] All three antituberculous medications are considered compatible with breast-feeding.[15-17]

Antiviral Agents

Antiherpetic Drugs

Acyclovir is a purine analogue commonly used in the treatment of herpesvirus infections. During pregnancy, acyclovir is indicated 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.[16,17,27,39] The Centers for Disease Control and Prevention also recommends treatment of the first episode of genital herpes during pregnancy with oral acyclovir.[39,40] In humans, acyclovir readily crosses the placenta and reaches higher concentrations in fetal circulation than in maternal circulation. There are no reports of teratogenicity or adverse effects in the fetuses or newborns of mothers using acyclovir or valaciclovir.[16,17,27,39-41] Famciclovir was associated with congenital cardiovascular anomalies, hepatotoxicity, and death.[16,17] Acyclovir is concentrated in milk, in which levels may be higher than in plasma. Because there are no reported adverse outcomes in infants of mothers taking acyclovir or infants treated with acyclovir for disseminated herpes, it is considered safe during breast-feeding.[15-17]

Anti-influenza Drugs

Amantadine appears teratogenic in some animals but not others. Its use in pregnant women is very limited, and one cannot draw any conclusions.[16,17]

Oseltamivir has no effect on embryonic or fetal development in animal studies. There appear to be no reports of its use in pregnancy, but based on its safety in animals, it may be used in human pregnancy, albeit cautiously.[16,17]

Anti-HIV Drugs

Anti-HIV drugs may be indicated immediately after a needlestick injury or sexual contact with an infected individual. No specific pattern of birth defects has been described with the use of these drugs, but there are a number of unanswered questions relating to the drugs' mutagenesis and carcinogenesis and their long-term effects on the liver, heart, and reproductive system.[15-17]

Animal and human data suggest that didanosine, lamivudine, stavudine, zidovudine, and zalcitabine present some risk, albeit small, of structural malformations and mitochondrial dysfunction in the developing fetus. However, even if a negative association is proven, the risk of morbidity and mortality from HIV infection far outweighs the risk of toxicity of most of these substances.[15-17,40,42] Similarly, no specific pattern of birth defects has been described with protease inhibitors such as ritonavir and nelfinavir. When indicated, the benefits of treatment outweigh the drugs' toxicities.[15-17,42]

Anticoagulants

Warfarin (Coumadin) is a known human teratogen and affects 4 or 5% of exposed fetuses. The risk from exposure is greatest during 6 to 9 weeks of gestation and seems to be dose dependent.[16,17,27] The fetal warfarin syndrome is associated with multiple abnormalities, such as hypoplasia of the nasal bones, midline dysplasia including agenesis of the corpus callosum, optic atrophy and blindness, mental retardation, seizures, and stippling of the bones with scoliosis and shortening of limbs.[16,17,27,43] Because warfarin is so highly protein bound, only a little is secreted into milk, and use by breast-feeding mothers is acceptable.[16,17] Caution should be used in breast-feeding premature infants because they may be at increased risk for intraventricular hemorrhage.[16,17]

Unfractionated heparin is a highly charged heterogeneous molecule with a molecular weight between 5 and 35 kDa. It does not cross the placenta and does not present a direct risk to the fetus. Early reports on the use of heparin for the prevention or treatment of venous thromboembolism during pregnancy concluded that the risks to the fetus from prematurity, stillbirth, and hemorrhage might affect one third of infants. Recently, however, the increased risks previously associated with heparin were determined to be related to underlying maternal medical problems rather than heparin.[16,17,26,27] When anticoagulation during pregnancy is required, heparin is considered the agent of choice.[16,17,44] Its use is sometimes associated with maternal osteopenia and immune-mediated thrombocytopenia.[16,17,27] Patients need careful monitoring for these adverse effects. The risk of maternal hemorrhage at delivery is significant. Because of its high molecular weight, heparin is not excreted in breast milk and is compatible with breast-feeding.[15-17]

Low-molecular-weight heparin may be used during pregnancy and in the postnatal period for therapeutic or prophylactic anticoagulation.[16,17,27] All currently available low-molecular-weight heparin products have been used safely

during pregnancy. Data are limited, however, because of their relatively recent introduction.

Thrombolytic agents have been used successfully in pregnant women in cases of life-threatening pulmonary embolus or myocardial infarction. Experience with these agents during pregnancy, however, remains limited. To date, no teratogenic effects have been reported in humans, but maternal hemorrhage occurred when alteplase was used during the intrapartum period.[16,17,45] Most thrombolytics are thought to be compatible with breast-feeding because of their short half-life.[16,17]

Anticonvulsants

The occurrence of generalized seizures during pregnancy has been associated with an increased risk of spontaneous abortion, hypoxic injury to the fetus, and impaired neuropsychological functioning.[16,17] Anticonvulsants are known teratogens, however, and 30% of neonates exposed to commonly used anticonvulsants exhibit congenital anomalies.[16,17,27,46] The risks for birth defects increase with the duration of exposure and with the number of agents used.[16,17,27,46] In an observational study of 25 epilepsy centers, it was noted that valproate use during pregnancy was 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).[47] Despite the risks, most practitioners believe that it is important to control seizures during pregnancy. Monotherapy is the most appropriate option and is recommended at the lowest effective anticonvulsant dose. Dividing the daily dose to decrease peak plasma levels may be considered. Adjustment of the dosage upward is often required to maintain adequate seizure control.[16,17]

Phenytoin is a human teratogen that readily crosses the placenta. The parent compound and all metabolites have been identified in fetal tissues. Of chronically exposed fetuses, 5 to 10% develop the fetal hydantoin syndrome.[16,17,27,48] 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 cardiovascular anomalies, including atrial septal defects, ventricular septal defects, coarctation of the aorta, and endocardial cushion defects. Phenytoin has also been associated with hemorrhagic disease of the newborn, presumably because it competitively inhibits placental transport of vitamin K.[16,17,27,48] To avoid this rare complication, some clinicians have advocated the use of vitamin K during the last month of pregnancy, but evidence does not support its use.[47] Phenytoin has been linked to a variety of tumors in infants. Phenytoin use is considered safe in breast-feeding.[15-17]

Carbamazepine use during pregnancy is associated with a syndrome similar to fetal hydantoin syndrome, which is thought to be secondary to a toxic, teratogenic metabolite and not the parent compound.[16,17,27,49] In one study, carbamazepine was associated with a twofold increase in major congenital abnormalities in exposed fetuses compared with nonexposed fetuses.[16,17,27,49] These abnormalities include craniofacial defects, fingernail hypoplasia, neural tube defects, and developmental delay. Carbamazepine has also been reported to induce hemorrhagic disease of the newborn.[39] The use of carbamazepine is considered compatible with breast-feeding.[15-17]

Valproic acid, a class D medication that should not be used in pregnancy, is an eight-carbon, branched-chain carboxyl acid that has been approved for the treatment of absence seizures since 1978.[16,17,27,50] It is teratogenic in laboratory animals and in humans. It readily crosses the placenta and concentrates in the fetus. Many authors have described a syndrome of defects associated with the use of valproic acid. The characteristics of the syndrome include multiple minor facial anomalies, low birth weight, delayed neurologic development, congenital heart defects, neural tube defects, hypospadias, strabismus, nystagmus, tracheomalacia, afibrinogenemia, and hyperglycemia.[16,17,27,50] Valproic acid is present in breast milk in low levels and is considered safe during breast-feeding.[15-17]

Phenobarbital is considered a class D medication in pregnancy. It is associated with a slightly increased risk of congenital abnormalities, including congenital heart disease and cleft lip or palate and some minor malformations associated with the fetal hydantoin syndrome.[16,17,46] It is occasionally associated with hemorrhagic disease in the newborn and may result in neonatal withdrawal. Breast-fed infants of mothers taking phenobarbital have developed toxicity characterized primarily by sedation. These infants must be monitored closely for sedation while breast-fed and after breast-feeding for symptoms of withdrawal.[15-17]

Newer Anticonvulsant Medications

No adequate studies of human teratogenicity have been published regarding felbamate, levetiracetam, gabapentin, and lamotrigine, but they appear to be safe during pregnancy. Lamotrigine has been associated with a slightly increased incidence of cardiovascular, craniofacial, gastrointestinal, and genitourinary birth defects.[16,17,51] Safety in lactation is unknown.

Cardiovascular Medications

Antidysrhythmics

Adenosine is a naturally occurring compound that is metabolized quickly in the body. It has been used safely throughout pregnancy and is the drug of choice for terminating maternal supraventricular tachycardia,[52] despite the absence of large-scale studies.[16,17,27,48] Adenosine has also been used safely in terminating incessant tachycardia in the fetus.[53] Adenosine is likely safe in lactation.[16,17]

Amiodarone, a class D agent, is not recommended in pregnancy, except in refractory cases of supraventricular and ventricular tachycardias of the mother or the fetus.[54,55] It contains large amounts of iodine and has been associated with congenital goiter and transient neonatal hyperthyroidism and hypothyroidism.[16,17,56,57] In addition, amiodarone use during pregnancy has been linked to many congenital abnormalities, including growth retardation, structural cardiac abnormalities, corneal deposits, and developmental delay.[16,17,54] Because of its high iodine content, its excretion into milk, and its long elimination half-life, amiodarone should not be used in nursing mothers.[16,17]

Digoxin, disopyramide, and quinidine are all considered safe for use during pregnancy and lactation.[16,17] None have been linked to congenital defects in humans or animals. Of the three agents, digoxin and quinidine have the longest safety records in pregnancy and are first-line agents for the treatment of significant maternal dysrhythmias.[16,17] They have also been successfully used in fetal tachycardia.[58,59] However, maternal overdoses of digoxin resulting in fetal death have occurred.[60] Although considered safe during pregnancy, disopyramide has been associated with premature uterine contractions and labor.[61]

Lidocaine is a weak base. It rapidly crosses the placenta and becomes ion trapped in the fetus. There is no evidence of a

link between lidocaine and any fetal malformations.[16,17] High doses used near term are associated with neonatal CNS depression, apnea, hypotonia, seizures, and bradycardia. Lidocaine is considered compatible with breast-feeding.[15-17]

Procainamide is also well tolerated and should be considered a first-line treatment of wide-complex tachydysrhythmias during pregnancy.[55,58] The use of procainamide in nursing mothers is controversial because it and its metabolite, *N*-acetyl procainamide, have been found in breast milk.[15-17]

Encainide and flecainide are newer class IC antiarrhythmic agents that are structurally related to procainamide. Both have been used safely to terminate maternal and fetal tachycardia.[16,17] A few negative fetal effects have been noted with the use of flecainaide, including hyperbilirubinemia, hepatotoxicity, and loss of fetal heart rate variability.[62,63] Both encainide and flecainide are found in breast milk. Although experience with encainide is limited, the AAP considers flecainide compatible with breast-feeding.[16,17]

Ibutilide is a class III antiarrhythmic used to terminate atrial fibrillation and flutter. Although there are no reports of its use in pregnancy in humans, when used in high doses, ibutilide was found to be teratogenic in rats.[16,17] Ibutilide may be used in refractory cases in which the benefits of therapy outweigh any fetal risk.[16,17]

Sotalol does not appear to have teratogenic effects in animals.[16,17] It has been used in pregnant women to treat hypertension. In these cases, bradycardia in the newborn was noted, which persisted for 24 hours. Sotalol has also been used successfully to terminate in utero fetal supraventricular tachycardia.[64]

Isoproterenol is indicated for refractory high-grade atrioventricular block and for torsades de pointes associated with prolonged QT interval. Data from animal studies have not shown any association between isoproterenol and developmental toxicity. It is also considered compatible with breast-feeding.[16,17]

Vasopressors

Dobutamine is an inotrope used in the setting of cardiac dysfunction and sepsis. Data from animal studies have not revealed any untoward reproductive effects. Effects in humans are not known, but one case report did not reveal any effects on the fetus.[16,17,65]

Dopamine and other vasopressors offer a maternal benefit that far outweighs the possible deleterious effects on the fetus and should not be withheld if indicated. Dopamine has been associated with increased uterine vascular resistance in animal studies, but no significant fetal side effects directly related to the drug have been reported. In addition to its use in maternal shock, dopamine has been successfully used in low doses to improve cardiac and urine output in patients with preeclampsia and oliguria.[66]

Epinephrine has been used to treat shock from any cause during pregnancy. However, it has been associated with anoxic injury to the fetus, intracranial hemorrhage, and an increased incidence of inguinal hernias.[16,17,67] Safety during breast-feeding has not been studied.

Norepinephrine is associated with an increased incidence of cerebral hemorrhage, skeletal abnormalities, and a significant decrease in placental blood flow and fetal oxygenation in animal studies.[16,17,68] Its safety during breast-feeding has not been studied.

Antihypertensives

Hypertension complicates 12% of pregnancies and accounts for 18% of maternal deaths in the United States.[69] Previously, the most commonly used drug in hypertensive emergencies was hydralazine, but other medications currently available, such as labetolol and nifedipine, appear to be as effective and possibly safer than hydralazine.

Angiotensin-converting enzyme (ACE) inhibitors are classified as category D drugs and are contraindicated for use during pregnancy. ACE inhibitors are embryocidal in animals and increase the rate of stillbirths in some species. Although they seem to be safe in humans during the first trimester of pregnancy, many adverse fetal effects have been noted with their use during the second and third trimesters, precluding their use.[16,17,37,70] Reported adverse neonatal effects include oligohydramnios, anuria, renal agenesis resulting in death, increased risk of stillbirth, intrauterine growth retardation (IUGR), fetal skull abnormalities, pulmonary hypoplasia, respiratory distress syndrome, and fetal and neonatal hypotension. Captopril and enalapril are considered compatible with breast-feeding.[15-17]

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, IUGR, persistent patent ductus arteriosus, abnormal ossification, and death.[16,17] Their safety in lactation is unknown.

Beta-blockers have become a first-line treatment for hypertension in pregnancy.[71,72] All beta-adrenergic blocking agents cross the placenta. The most experience with beta-blockers has been with women requiring treatment during the last trimester of pregnancy, at which time they seem to be safe. Long-term in utero exposure and first-trimester exposure have not been studied.[16,17,37] Labetalol is the antihypertensive of choice during pregnancy.[71,72] It has not been associated with any teratogenic effects in animal studies. Human reports of its use in the treatment of hypertension during pregnancy have not revealed any significant effect on the fetal birth weight or fetal heart rate.[16,17,37] Transient neonatal hypotension and bradycardia may be observed when used at term. However, compared with traditional therapies for pregnancy-induced hypertension, labetolol appeared to reduce the blood pressure more smoothly than either hydralazine or diazoxide.[16,17,71,73] Furthermore, it was associated with fewer cesarean sections than either of the two drugs.[73] Atenolol and metoprolol are considered safe in pregnancy but only when used for short periods of time.[16,17,73] There are reports of fetal harm when atenolol is used in the first trimester. Atenolol has also been associated with IUGR when used for prolonged periods during pregnancy, and when given near term, it is associated with persistent beta blockade in the newborn.[16,17,73] Similarly, propranolol is associated with fetal and neonatal adverse effects, especially when doses exceeding 160 mg/day are used. These adverse effects include IUGR, hypoglycemia, bradycardia, respiratory depression at birth, and hyperbilirubinemia. Esmolol has also been associated with fetal bradycardia, neonatal bradycardia, and hypotonia as well as fetal distress requiring emergent cesarean section.[74] It should therefore be used only if the benefits to the mother outweigh the risks to the fetus and if other options have failed. Beta-blockers are reportedly safe in breast-feeding, but close monitoring of the infant for adverse effects is recommended.[15-17]

Calcium channel blockers are indicated in the treatment of hypertension and a number of supraventricular rhythm disturbances during pregnancy.[16,17,71] Nifedipine and cardizem have also been used as tocolytic agents. In addition, verapamil has been used to terminate maternal as well as fetal tachycardia.[75] Despite negative reproductive studies in animals, the calcium channel blockers are used extensively during the second and

third trimesters in humans and are considered safe for use during these stages of pregnancy.[16,17,37,76] Whereas cardizem appears to be safe at all stages of pregnancy, nifedipine was associated with fetal distress secondary to maternal hypotension when it was used sublingually.[16,17] In addition, when used in conjunction with magnesium, nifedipine appeared to potentiate the neuromuscular blocking effects of magnesium, resulting in profound muscle weakness, difficulty in swallowing, and paradoxical respirations.[77] Calcium channel blockers are considered safe for use during breast-feeding.[15-17]

Thiazide diuretics have been used successfully for the treatment of hypertension in pregnancy but may result in electrolyte abnormalities in neonates when given near term.[16,17,71] An increase in perinatal mortality and congenital defects possibly caused by volume depletion has been reported.[16,17] First-trimester use has been associated with an increase in congenital anomalies.[16,17] Diuretics are not recommended for the treatment of pregnancy-induced hypertension because of the maternal hypovolemia characteristic of this disease. Other risks to the pregnancy include higher rates of uterine inertia and meconium staining.[78] In the neonate, there is a higher incidence of hypoglycemia, thrombocytopenia, hyponatremia, hypokalemia, and death from maternal complications.[16,17] Moreover, thiazide diuretics may have a direct effect on smooth muscle and inhibit labor. Bendroflumethiazide, chlorthalidone, and hydrochlorothiazide are considered safe during breast-feeding.[16,17] Loop diuretics are generally not used in pregnancy unless indicated for congestive heart failure. They have not been found to cause major adverse outcomes in the fetus.

Hydralazine is safe in pregnancy. It was previously considered the drug of choice for the parenteral treatment of acute severe hypertension during pregnancy.[71] However, it has been associated with higher rates of maternal hypotension compared to labetolol, which may affect perinatal outcome.[16,17,37,71] It is also associated with a lupus-like syndrome, which has been reported in both mother and neonate.[16,17,37,79] Because other agents, particularly labetalol, are safer and just as effective, hydralazine is no longer recommended as a first-line agent in the treatment of hypertensive emergencies in pregnant women.[71] Hydralazine is safe in lactation.[16,17,79]

Methyldopa is considered safe in pregnancy, and most reviews have not linked it to any adverse effects on the pregnancy.[16,17] Many clinicians still use it as first-line therapy to treat hypertension during pregnancy. Methyldopa is compatible with breast-feeding.[31]

Clonidine has been safely used throughout pregnancy, but experience during the first trimester is very limited.[80] A few insignificant adverse fetal effects attributable to clonidine have been reported. Transient neonatal hypertension has been reported in neonates with in utero exposure to clonidine.[16,17,37,80] Its effects on breast-feeding neonates are unknown, but it is considered to be compatible with breast-feeding.[15-17]

Nitroglycerin has not been shown to cause fetal harm in animal studies. Limited reports in humans do not show 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.[16,17,81] It appears to be effective in relieving intrapartum fetal distress related to uterine hyperactivity.[81]

Nitroprusside use for the treatment of hypertensive emergencies in pregnancy has the same advantages and disadvantages seen in nonpregnant patients.[16,17,71] Advantages include its rapid onset, rapid metabolism, and rapid excretion. Disadvantages of nitroprusside include the need for constant monitoring and cumbersome administration. During prolonged administration of high doses, nitroprusside may result in cyanide toxicity. 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 major risk of toxicity, but with the availability of safer alternatives, notably labetalol, nitroprusside is considered a second-line agent.[16,17,37] When used, it is recommended to monitor plasma and red blood cell cyanide and maternal pH. Nitroprusside is considered a category C medication. No data are available on its use during breast-feeding.

Asthma, Allergy, and Upper Respiratory Infection Medications

Pregnant women with asthma are at risk of neonatal death, preterm birth, low-birth-weight infants, preeclampsia, and small-for-gestational-age infants.[71,82] Asthmatic mothers may also have a higher rate of chorioamnionitis, hypertensive disorders of pregnancy, cesarean section, and prolonged hospital stay compared to control mothers.[82,83] Better asthma control has been associated with an improved outcome.[71]

The beta-adrenergic medications albuterol, metaproterenol, and terbutaline are safe for use in pregnancy. None have been linked to congenital anomalies.[16,17] Beta-adrenergic agents have also been used during the last trimester to treat premature labor. Adverse reactions are related to the drugs' cardiovascular and metabolic effects, which are transient and generally well tolerated by the fetus.[16,17,83,84] Transient hyperglycemia followed by insulin secretion may also occur, resulting in neonatal hypoglycemia, especially in diabetic patients.[16,17] Long-term use of albuterol has not been associated with adverse effects. Albuterol is compatible with breast-feeding.[15-17] Long-acting beta-agonists also appear to be safe during pregnancy.[16,17,83]

Ipratropium has not been found to be teratogenic in numerous animal models. Although there are few human data, ipratropium seems to be safe for use during pregnancy and lactation.[15–17]

Cromolyn sodium is safe in pregnancy. Cromolyn has not been associated with any significant risk of birth defects or negative perinatal outcomes.[16,17,82,83]

Corticosteroids are commonly used during pregnancy for the treatment of various disorders, including autoimmune diseases, hyperemesis gravidarum, and asthma. 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.[16,17,37,85] 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.[16,17,37,85] Other authors have also raised concerns about the development of congenital adrenal hyperplasia in newborns.[16,17] Prednisone is considered safe during breast-feeding.[15-17]

Data on the use of leukotriene antagonists in pregnancy are limited. One study did not find an association with congenital abnormalities, but there was a slight increase in intrauterine growth restriction. However, these results should be interpreted with caution because of the small sample size of the study.[86] Zileuton is mutagenic in animal studies and should be avoided during pregnancy and lactation.[16,17]

Antihistamines have been safely used in the treatment of allergic reactions during pregnancy and as antiemetics in the treatment of nausea and vomiting during pregnancy. Antihis-

tamines have been linked to the development of retrolental fibroplasia (retinopathy of prematurity) in premature infants when given during the last 2 weeks of pregnancy.[16,17] A meta-analysis that reviewed 24 studies involving more than 200,000 patients confirmed the safety of antihistamines, including chlorpheniramine, diphenhydramine, doxylamine, hydroxyzine, and meclizine, during pregnancy.[87] The newer generation antihistamines, such as cetirizine and loratadine, also appear safe during pregnancy.[88] They may be acceptable alternatives for severe allergies if the first-generation antihistamines are not tolerated.[16,17] First-generation antihistamines are not recommended during breast-feeding because they may inhibit lactation. In addition, neonates receiving antihistamines appear to develop serious adverse CNS effects, including seizures, especially when premature.[15-17]

Decongestants are not recommended during pregnancy.[16,17] Decongestants with strong vasoconstrictive properties, such as phenylpropanolamine and pseudoephedrine, cause placental vasoconstriction, resulting in an increased incidence of abnormalities typically associated with placental vascular disruption, such as gastroschisis and intestinal atresia.[16,17,83]

Gastrointestinal Medications

Phenothiazines, such as promethazine, chlorpromazine, perphenazine, and metoclopramide, are dopamine antagonists commonly used in the treatment of nausea and vomiting during pregnancy, and they have not been linked to congenital abnormalities. Caution should be used with chlorpromazine because it may cause hypotension and also with promethazine at term because it may cause respiratory depression.[16,17,89]

Ondansetron, a serotonin 5-HT_3 receptor antagonist, has not been linked to any fetal malformations, but it may not offer any additional antiemetic activity compared to the phenothiazines.[16,17,89] Newer 5-HT antagonists, such as dolasetron and granisetron, also appear to be safe during pregnancy, although experience is limited.[16,17,89] These agents are most likely compatible with breast-feeding.[15-17]

The H_2 receptor antagonists ranitidine, famotidine, and cimetidine have not been linked to any congenital malformations and appear to be safe for long-term use during pregnancy and lactation.[15-17] However, one report has linked the use of antacids during pregnancy to an increased incidence of asthma during childhood.[90]

Diabetes Medications

Insulin has been used safely during pregnancy and lactation for many years and is the drug of choice for glucose control in pregnancy. Sulfonylurea drugs traditionally have not been used during pregnancy. They are regarded as possibly teratogenic and less effective than insulin in the control of gestational diabetes.[16,17] Sulfonylurea drugs have also been associated with neonatal hypoglycemia when used at term.[16,17] In reality, there is little information about their use during pregnancy, and in a randomized study, glyburide proved to be as effective and safe during pregnancy as insulin.[16,17,91] Glyburide and glipizide are highly protein bound and are not likely to pass into breast milk; nursing infants should be monitored.[16,17]

Metformin has not been associated with fetal malformations in animals, and there are no controlled studies analyzing its effect in humans.[16,17] Metformin has been associated with serious adverse effects in adults, including severe life-threatening metabolic acidosis and hepatotoxicity. Because of its potential for serious effects in adults, metformin is not recommended for use in lactating mothers.[16,17,92]

Anesthetics and Sedatives

The short-term use of benzodiazepines during pregnancy appears to be safe. However, the safety of benzodiazepines during pregnancy has been debated because data on the fetal effects of these drugs have been inconsistent. Some case reports have linked their use during the first trimester of pregnancy to increased risk of oral clefts, but in a meta-analysis of pooled data from the cohort studies, no association was found between fetal exposure to benzodiazepines and the risk of oral clefts.[93] Different benzodiazepines also have been linked to different effects and risks. Lorazepam, for example, has been linked to anal atresia; clonazepam has been associated with congenital cardiac abnormalities; and oxazepam and diazepam have been linked to specific dysmorphic features, CNS abnormalities, and growth defects.[16,17] Midazolam, on the other hand, has not been linked to any developmental abnormalities. Neonates exposed to benzodiazepines may exhibit signs of toxicity, including apnea, cyanosis, unresponsiveness, hypotonia, poor feeding, and withdrawal symptoms characterized by irritability and tremulousness.[16,17] Because of the reported risk of apnea, it is recommended that neonates exposed to benzodiazepines through breast-feeding be monitored closely.[15-17]

Ketamine is a rapidly acting dissociative anesthetic that is commonly used in pediatric procedural sedation and may be used in rapid sequence intubation (RSI). It has not been associated with any developmental malformations.[16,17,94] Ketamine has a dose-related oxytocic effect, and in high doses it has been associated with uterine tetany, increases in maternal blood pressure and heart rate, and increased neonatal muscle tone. Neonatal depression has also been reported.[16,17,94] Ketamine may remain in breast milk for 12 hours.[16,17]

Propofol is a rapidly acting sedative anesthetic that rapidly crosses the placenta. It has not been linked to any congenital defects when used in pregnancy.[16,17,94] When high doses are used at term, it can cause neonatal respiratory and CNS depression. Propofol is excreted in breast milk in negligible amounts.[16,17]

Thiopental is an ultra-short-acting barbiturate that may be used during RSI or for persistent status epilepticus. It has not been linked to any congenital defects when used during pregnancy, but a slight reduction in birth weight has been noted when high doses are used.[16,17,94]

Etomidate is an ultra-short-acting hypnotic agent that is commonly used for procedural sedation or RSI. No reports on developmental effects of etomidate have been published. However, newborns of mothers undergoing cesarean section with etomidate were found to have significant reductions in serum cortisol concentrations 1 hour after delivery.[16,17,95] The significance of this effect remains to be elucidated. No data on breast-feeding were found.

Paralyzing Agents

Succinylcholine is a depolarizing neuromuscular blocking agent used in RSI for its rapid onset of action and short duration of paralysis. It has not been associated with any congenital defects, although there is limited experience with its use in early pregnancy in humans.[16,17,94] In addition, it does not appear to have any effects on the newborn, except in rare cases of neonates with pseudocholinesterase deficiency.[96] As occurs in adults with the same condition, newborns with cholinesterase deficiency exhibit prolonged respiratory depression and paralysis.[96] Succinylcholine in lactation has not been

studied; however, it is probably safe because it is hydrolyzed quickly.[16,17,96]

Rocuronium and vecuronium are nondepolarizing neuromuscular blocking agents used in RSI. The effects of neuromuscular blocking agents on organogenesis are not known, but these agents are not thought to pose a significant teratogenic risk.[16,17,94] Because of their chemical properties, very little of either drug crosses the placenta, and very little is excreted in milk.[16,17,94] Their effects on lactation are unknown but probably would be minimal.[16,17]

Antidotes

N-acetylcysteine has been used successfully and without untoward effects in pregnant women who have overdosed on acetaminophen.[18,19] No teratogenic effects have been reported.

Deferoxamine is indicated for iron toxicity occurring from iron overdose or from multiple transfusions in thalassemia patients. It has been associated with developmental effects on ossification in some animal species.[16,17] Experience in humans is limited, but it does not appear to affect the fetus.[99] The effects of deferoxamine on the nursing infant are not known.

Dimercaprol or British antilewisite is a metal chelating agent that is used as an antidote for acute mercury, lead, arsenic, and gold poisoning. It has also been used in Wilson's disease. It is teratogenic in mice and has been associated with increased mortality, growth retardation, cleft facial features, cerebral herniation, and abnormal digits, but experience in humans is limited.[16,17,97] In certain cases of heavy metal poisoning, the maternal benefits of dimercaprol use outweigh its potential risks to the unborn fetus. Breast-feeding is not recommended for patients poisoned by heavy metals.

Flumazenil is a benzodiazepine antagonist. No teratogenic effects have been reported in animals, and data on humans are very limited.[16,17] Its use in pregnancy depends on the potential maternal benefit compared to possible risks to the fetus.

Fomepazole is a competitive inhibitor of alcohol dehydrogenase indicated in cases of methanol and ethylene glycol poisoning. Its use during pregnancy has not been studied in animals or humans. Its safety during pregnancy is not known.[16,17] In cases of toxic alcohol poisoning, the benefits of treatment of the mother outweigh the possible risks to the fetus. Use of ethyl alcohol in these situations may also be considered.

Activated charcoal is not absorbed and is probably safe for use in pregnancy and lactation, although there are no published studies regarding the effects of charcoal use during pregnancy.[16,17]

Digoxin fragment (DIG Fab) therapy is indicated for life-threatening digoxin overdose and is being studied for treatment of preeclampsia. There are very few case reports of the use of DIG Fab immune globulin during pregnancy. A conclusion on the effects of DIG Fab cannot be made based on these reports. However, in cases of life-threatening digitalis overdose with arrhythmias, the benefits of treatment of the mother may outweigh the risk to the fetus. DIG Fab is not likely to be excreted in large amounts in milk, and it is probably safe for use during lactation.[16,17]

Hydroxycobalamin is a vitamin that is indicated in the treatment of cyanide toxicity. Studies in animals do not reveal an association with any developmental abnormality.[16,17]

Methylene blue is used in the treatment of methemoglobinemia. In the past, it was injected into the amniotic sac to identify twins and to detect rupture of the membranes, but these practices were associated with hemolytic disease in the newborn, hyperbilirubinemia, and deep blue staining of the newborn.[16,17,98] Methylene blue in pregnancy has also been associated with an increased incidence of intestinal obstruction and atresia in the newborn.[99] The effects on nursing infants are unknown but probably minimal.[16,17]

Naloxone, used to reverse the effects of opiates in an overdose, readily crosses the placenta. Naloxone has not been associated with reproductive abnormalities; however, its use in opiate-addicted mothers may precipitate withdrawal in both mother and term fetus.[16,17] It is compatible with breast-feeding.[15]

Physostigmine is an anticholinesterase agent indicated in cases of severe anticholinergic poisoning associated with delirium. Experience with the medication during pregnancy is limited, and its effects on the developing fetus are unknown.[16,17] Use of physostigmine at term was associated with only mild decreases of Apgar scores at 1 and 5 minutes.[100]

Polyethylene glycol (PEG) is not absorbed systemically. It is probably safe for use in pregnancy and lactation, although there are no reports on the effects of PEG in pregnancy.[16,17]

Pralidoxime is indicated for organophosphate/cholinergic poisoning because it is able to reactivate cholinesterase. Experience with pralidoxime in pregnancy is limited, and its effects on fetal development are not known.[16,17] In cases of organophosphate poisoning, the benefits to the mother generally outweigh the possible risk to the fetus.

Pyridoxine is a vitamin required for good maternal health and good fetal development. It is indicated in isonizid poisoning and in gyromytrin mushroom poisoning. Its use has been advocated in some for nausea and vomiting of pregnancy and gestational hypertension and diabetes. It has not been associated with any adverse developmental effects, and it is safe in lactation.[16,17]

Succimer is a lead chelator that is indicated in lead poisoning. It has been linked to congenital defects in animal models, possibly due to effects on zinc and copper metabolism.[16,17] Experience with the use of succimer in pregnancy is limited to case reports of women poisoned with lead. No conclusions can be drawn on its teratogenic effects.[101]

KEY CONCEPTS

- Chemically induced birth defects are believed to be responsible for approximately 1 to 3% of anomalous births.
- The age of the fetus is crucial in determining the impact of any given exposure; during the time of organogenesis (days 21–56 of fetal life) when major body organs are formed, exposure to a teratogen may result in major anatomic defects.
- Certain medications, such as anticonvulsants, warfarin derivatives, NSAIDs, sulfonamides, fluoroquinolones, ACE inhibitors, and oral hypoglycemic agents, are known teratogens or cause potential toxic effects in the newborn and should be avoided, if possible, during pregnancy.

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