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Medication Safety During Pregnancy

The patient asks, "Is it safe to take?" You pause, thinking, the FDA classifies it as a Category C, and everybody seems to use it, but how can anybody be sure? So, you finally respond, "It has been used a lot in pregnant patients and no harmful effects have been observed." But, you say to yourself, am I really confident? What would I do for myself or my spouse if in the same situation?

Most decisions in medicine are balancing benefits versus risks. Few treatments are always effective, and most therapies have some risk. So it is with medicating the pregnant patient. While the benefits can be clinically significant and the risks are small, a bad outcome that is perceived to be from the medication can be troublesome for the physician-patient relationship.

This review should provide some reassurance to the practicing emergency physician — many of the medications we commonly use can be considered "safe" in the pregnant patient.

—J. Stephan Stapczynski, MD, FACEP, Editor

Introduction

The use of any medication during pregnancy is a concern for both the patient and physician because of the potential that the agent may have unanticipated effects on the fetus. Although animal reproductive studies are performed before marketing a drug, these may not predict the same effects in humans. In addition, animal testing may not identify those adverse effects that occur infrequently.[1] Pregnant women are routinely excluded from clinical trials that evaluate medication efficacy and safety; hence there is little objective, scientific data with most medications in this unique patient population. Often the decision to use a particular medication has to be based on the potential risks to the fetus and benefits to the pregnant woman. This is of particular concern in the management of emergency medical conditions and requires that providers have an understanding of the risks and benefits of the use of pharmacologic agents. This paper addresses common emergency medical conditions that may befall pregnant women and the pharmacologic agents used in treatment.

FDA Pregnancy Categorization

Teratogenesis is the abnormal development of fetal organs. Manifestations may include restricted growth, fetal demise, carcinogenesis, or malformations.[2] Birth defects are reported to occur in 3-5% of all newborns. Of these, 1-3% are thought to be attributed to adverse effects from a pharmacologic agent.[3,4] The embryo is most susceptible to drug-induced damage during the peak period of organogenesis, between 4 and 12 weeks of the first trimester. However, after the 12th week of gestation, teratogens still can affect the growth and function of organs.[4] Because of the difficulty in studying the potential effects of medications on fetal development and growth, the teratogenic risk for more than 90% of the U.S. Food and Drug Administration (FDA)-approved medications remains unknown. Much of the evidence available is derived from observational

Executive Summary

- Inhaled beta-2 agonists, inhaled ipratropium, and systemic steroids are considered safe to use in the pregnant patient with acute asthma.
- Ondansetron is considered a safe antiemetic to use in the pregnant patient.
- Intravenous hydralazine is considered safe to treat acute severe hypertension, and methyldopa is considered safe to treat chronic mild to moderate hypertension in the pregnant patient.
- Nitrofurantoin is safe to treat urinary tract infections in the first and second trimesters, but should be avoided in the third trimester.
- Acetaminophen and oxycodone are considered safe for pain management in the pregnant patient when used intermittently.

studies, often with a relatively small number of patients.[5]

In 1979, the FDA developed a five-letter safety categorization system to guide physicians in the interpretation of the teratogenic risk associated with prescription and over-the-counter drugs.[6] This system classifies medications based on the available animal and human data. (*See Table 1.*)

• **Category A:** Adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters).

• **Category B:** Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women.

• **Category C:** Animal reproduction studies have shown an adverse effect on the fetus, there are no adequate and well-controlled studies in humans, and the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks.

• **Category D:** There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks (e.g., if the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective).

• **Category X:** Studies in animals or humans have demonstrated fetal abnormalities, or there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, and the risk of use of the drug in pregnant women clearly outweighs any possible benefit.

Due to the lack of controlled trials in this population for most medications, most drugs considered safe to use in the emergency department on pregnant patients are classified as Category B, reflecting the lack of well-controlled human studies. Medications not recommended during pregnancy and those commonly used during pregnancy are noted in Tables 2 and 3, respectively. It is important to note that some medications may have dual classifications that reflect their safety profiles during different time periods of fetal development.

Pharmacologic Management of Common Disease States

Axioms that the emergency physician should take into account when considering the use of medications in the pregnant patient include:

• All medication should be prescribed with a clear indication.

• Drug exposure should be minimized by using the smallest effective dose for the shortest possible duration.

• Effective drugs that have well-understood safety profiles are preferred to newer pharmacologic agents.

Asthma

Asthma is the most common chronic medical condition to complicate pregnancy, and it is estimated that 3.7-8.4% of pregnant women in the United States are affected.[7] Pregnancy may aggravate symptoms of chronic asthma due to changes in pulmonary physiology, including a reduction in total lung capacity and functional residual capacity.[8] Evidence-based guidelines have concluded that it is safer for pregnant women with asthma to be treated with pharmacologic agents than for them to continue to have asthma-related symptoms. Acute asthma exacerbations and severe or uncontrolled chronic asthma are associated with decreases in fetal oxygenation, preeclampsia, vaginal hemorrhage, complicated labor, preterm birth, low birth weight, and fetal loss.[7] Studies have shown that fetal loss can be reduced to that of the general population in those that continue to be managed with beta-2 adrenergic agonists, theophylline, and corticosteroids.[9,10] Of great concern is poor adherence to pharmacologic treatment in pregnant women due to fears of fetal risk.[11] An analysis of a managed care organization's database found that among 334 women using asthma medications prior to pregnancy, processed claims for beta-2 adrenergic agonists and inhaled corticosteroids decreased by 52% and 36% during pregnancy, respectively.[12] Furthermore the number of these women who had asthma-related emergency department visits increased by 21% during

Table 1: Summary of FDA Pregnancy Categories

Category	Summary
A	Controlled studies in humans show no fetal risk.
B	No evidence of fetal risk in humans with or without adverse findings in animal studies.
C	Evidence of fetal risk in animals, but not studied in humans. Risk cannot be ruled out. Use if benefits outweigh risks to the fetus.
D	Evidence of fetal risk in humans.
X	Contraindicated; benefit does not outweigh risk.
FDA: Food and Drug Administration	

pregnancy.[12]

Albuterol, levalbuterol, and terbutaline have been used safely in pregnancy without an observed increase in the risk of congenital malformations.[4,7] The greatest amount of data is available with albuterol use; therefore this is preferred over other beta-2 adrenergic agonists, although most are rated Category C.[7] Adverse effects from these medications may cause fetal tachycardia as well as transient fetal hyperglycemia. Ipratropium bromide is an anticholinergic agent that is often used during asthma exacerbation as a bronchodilator in combination with albuterol. The combination of these medications is thought to decrease airflow obstruction and reduce the need for hospital admission.[13] As a Category B agent, it is thought to be safe to use during pregnancy as well.

The use of corticosteroids in acute asthma has not been well studied, but information can be extrapolated from chronic corticosteroid usage in pregnant patients. Corticosteroids readily cross the placenta, where they are rapidly converted to less active forms by the fetoplacental unit. Prednisolone, the active metabolite of prednisone, crosses the placenta poorly and with resulting fetal levels that are lower than maternal levels.[8] Inhaled corticosteroids are the preferred route of administration for long-term control in pregnant patients.[7] The routine use of inhaled corticosteroids during pregnancy improves lung function and reduces the risk of acute exacerbation.[7] Observational studies have not found adverse fetal outcomes when inhaled corticosteroids are used as daily maintenance medication during pregnancy. Budesonide (Category B) is considered the drug of choice since there are gestational studies available, while other inhaled corticosteroids are classified as Category C agents. The extent of systemic absorption from inhaled corticosteroids is dependent on the pharmacokinetic properties and lipophilicity of the specific pharmacologic agent, inhaler device, particle size, and deposition site in the lung.[14] Although clinically significant systemic adverse effects are associated with high-dose inhaled corticosteroid use, in general their use can decrease the need for oral corticosteroids.[14] Oral corticosteroids are associated with a small but measurable fetal risk, especially when used during the first trimester. The reported excess risk is 0.2-0.3% compared to the general population.[7] Complications associated with the use of oral corticosteroids during pregnancy include preeclampsia, preterm delivery, and low birth weight. Oral corticosteroids should still be considered in pregnant women with uncontrolled disease due to the higher risk to the fetus of poorly controlled asthma compared to the potential adverse effects of the medication.[7] Systemic corticosteroids have been shown to increase the risk of fetal malformations in certain animal species, but have been used extensively in humans during pregnancy and are not considered teratogenic.[15]

Epinephrine (Category C) may be used in cases of severe acute asthma refractory to selective beta-2 adrenergic agonists and corticosteroids. However, epinephrine has been found to reduce uterine blood flow in animal studies.[16] Epinephrine has also been associated with an increase in fetal malformations when used in early pregnancy.[17]

Cromones are used to inhibit histamine release from mast cells. Both cromolyn and nedocromil are rated Category B, but are not preferred prophylactic therapy because of their limited effectiveness when compared with inhaled corticosteroids.[7] Theophylline has been associated with congenital malformations at high doses in animals. In humans, at recommended doses to maintain a serum concentration of 5 to 12 mcg/mL, it does not seem to have the same fetal risk of congenital malformations; however, data are conflicting regarding an increased risk of preeclampsia and preterm birth.[7,18] Theophylline (Category C) can be used as an alternative to the preferred inhaled corticosteroids.[7]

Dysrhythmias

Premature atrial beats occur in about 50% of women during pregnancy, and most are harmless and transient.[19] Sustained arrhythmias may occur more frequently in pregnancy due to hemodynamic, hormonal, and autonomic changes as well as changes in circulating blood volume, sleep patterns, and emotions during pregnancy. Although sustained arrhythmias are rare, the symptoms of shortness of breath, palpitations, and dizziness may be intensified in 20% of cases.[19]

All antiarrhythmic medications cross the placenta.[20] The choice

Table 2: Medications Not Routinely Recommended During Pregnancy

Condition	Medication
Dysrhythmias	Propranolol Amiodarone Ibutilide Diltiazem
Gastrointestinal	Antacids (sodium bicarbonate-containing products) Nizatidine
Hypertension	ACE inhibitors ARBs Atenolol Diltiazem
Infectious	Nitrofurantoin* Sulfamethoxazole/trimethoprim* Fluoroquinolones (ciprofloxacin, levofloxacin, ofloxacin) Erythromycin estolate Tetracyclines Doxycycline Metronidazole (vaginal) Clindamycin (vaginal) Azole antifungals (oral)
Ear, nose, and throat	Brompheniramine Decongestants (phenylephrine, pseudoephedrine)
Pain	Aspirin NSAIDs (ibuprofen, naproxen, ketorolac) Meperidine
Procedural sedation	Etomidate Ketamine Thiopental Dexmedetomidine
Seizures	Phenytoin Phenobarbital Valproic acid
Thromboembolic disease and anticoagulation	Warfarin Dabigatran Alteplase

ACE: angiotensin-converting enzyme; ARBs: angiotensin receptor blockers; NSAIDs: nonsteroidal anti-inflammatory drugs

* Safe to use in first and second trimester

of antiarrhythmic medication will depend upon the specific arrhythmia being treated, the cardiac condition of the mother or fetus, and the known or anticipated actions of the antiarrhythmic drug being considered. Several agents have a long-standing history of being safe in pregnancy.

Digoxin (Category C) is considered safe during pregnancy when given at appropriate doses, although digitalis toxicity has been associated with miscarriage and fetal death, possibly due to maternal cardiac instability and uterine hypoperfusion.[20] It is important to note that serum digoxin levels may decrease by 50% during pregnancy due to increased renal excretion. Serum levels must be closely monitored during pregnancy, and post-partum digoxin requirements will likely decrease.[20]

Adenosine is effective at terminating atrioventricular node-dependent tachycardias in pregnant women. Likely due to the extremely short half-life of the drug, clinical human experience indicates that there are no teratogenic or adverse fetal effects even at doses reported to be as high as 24 mg.[20]

Class IA antiarrhythmic agents quinidine, procainamide, and disopyramide are considered safe to use in pregnancy (Category C). Of these agents, there is the most experience with quinidine. Lidocaine is a class IB antiarrhythmic drug and is not known to be teratogenic, although it has been reported to increase myometrial tone, decrease placental blood flow, and cause fetal bradycardia. At appropriate doses, the adverse effects of lidocaine are thought to be minor, while large doses have been associated with low Apgar scores and neonatal lidocaine toxicity.[20] Mexiletine (Class IB antiarrhythmic agent) and flecainide and propafenone (Class IC antiarrhythmic agents) cross the placental barrier, but little information is reported on their use in pregnancy, although none are known to be teratogenic.

Beta-blockers have been used often in pregnancy, particularly propranolol. Propranolol (Category C) is not thought to be teratogenic, although there have been rare adverse events linked to propranolol usage during pregnancy. These include intrauterine growth delay, fetal bradycardia, hypoglycemia, polycythemia, hyperbilirubinemia, prolonged labor, and transient respiratory depression at birth.[20] Many of these adverse events are thought to be mediated through beta-2 adrenergic alterations, and it has been hypothesized that the use of beta-1 selective agents may help to minimize these effects.[21]

Amiodarone, a class III antiarrhythmic agent, crosses the placenta to a limited extent; however the drug's high iodine content raises concern. Iodine crosses the placenta freely and is thought to be associated with fetal goiter, neonatal hypothyroidism, and growth retardation. Other adverse effects associated with amiodarone in pregnancy include fetal bradydysrhythmias, prolonged QT interval, prematurity, spontaneous abortion, and death.[20] Based on the potential adverse effects from amiodarone, it should only be used in pregnancy when absolutely necessary and is considered a Category D medication. Sotalol crosses the placenta, and neonatal bradycardia has been reported with its use; however no long-term consequences were noted. Ibutilide has been shown to be teratogenic in animals and is not recommended for use during pregnancy.[20]

Of the calcium channel blockers, the greatest experience is with verapamil. Verapamil can theoretically cause fetal bradycardia, heart block, and hypotension, although clinical experience in pregnant women has not been associated with maternal or fetal adverse effects.[20] In animal studies, diltiazem can cause skeletal abnormalities, decreased fetal weight, fetal death, and delayed delivery. In pregnant women it has been shown to inhibit uterine contractions, and exposure in the first trimester was associated with birth defects. So while diltiazem is a Category C medication, it is not recommended for use during pregnancy.

Gastrointestinal

Nausea and vomiting are common gastrointestinal complaints, occurring in 50-90% and 35-55% of pregnancies, respectively.[22] Vomiting is most common in the first trimester, peaking at 10-15 weeks gestation, and usually subsiding by 20 weeks. Alterations in gastric motility and tone due to elevated levels of progesterone are thought to be possible etiologies for these occurrences. Phenothiazine agents (e.g., promethazine and prochlorperazine) cross the placenta and are eliminated from fetal and neonatal tissue more slowly than in adults, but have not been shown to be teratogenic. The Collaborative Perinatal Project monitored 50,282 mother-child pairs.[23] Of these, 877 had prochlorperazine exposure during the first trimester of pregnancy, and 2,023 had prochlorperazine exposure anytime during pregnancy. There was no evidence of increased malformations or perinatal adverse effects following exposure compared to the general population. Similarly, there was no evidence to suggest a relationship between promethazine exposure and major or minor malformations following the evaluation of 860 exposures during pregnancy.[23] Phenothiazine agents are considered Category C medications.

Antihistamine agents (e.g., meclizine and dimenhydrinate) are Category B agents and have not been associated with adverse fetal effects.[22] Metoclopramide (Category B) crosses the placenta, but has not been reported to cause teratogenic effects in animals or humans. The 10 major malformations observed in 192 newborns exposed to metoclopramide in the Michigan Medicaid Surveillance Study were not statistically significant when compared to eight fetal malformations that were observed in the general population.[24]

Ondansetron (Category B), a selective 5-HT3-receptor antagonist, has been widely used in pregnant women for hyperemesis and pregnancy-induced nausea without report of teratogenic or fetal adverse effects. Reproduction studies in pregnant rats and rabbits revealed no evidence of impaired fertility or adverse fetal effects at high doses, up to 15 and 30 mg/kg/day.[25]

A 3- to 5-day course of pyridoxine (vitamin B6) alone is considered safe in pregnancy. In randomized, double-blind, placebo-controlled trials pyridoxine has been associated with a decrease in vomiting episodes and nausea scores in pregnant women with severe nausea and vomiting.[26,27]

The frequency of gastroesophageal reflux symptoms is often increased during pregnancy due to the relaxation of the distal esophageal sphincter and increased abdominal pressure from the uterus.[8] Antacids, including magnesium-, aluminum-, and calcium-containing products, are considered safe and effective treatment during pregnancy.[24] Sucralfate (Category B) is not systemically absorbed and is known to be safe in pregnancy.[8] Sodium bicarbonate-containing antacids should be avoided due to the potential for maternal or fetal metabolic acidosis and fluid volume derangements.[24]

In pregnant patients with gastroesophageal reflux refractory to antacid agents, histamine-2 receptor antagonists may be used. Cimetidine, ranitidine, famotidine, and nizatidine are all considered Category B agents. There has been extensive experience with cimetidine and ranitidine exposure during the first trimester of pregnancy and continuing through delivery without suggestion of adverse fetal effects.[28] In the Michigan Medicaid Surveillance Study, cimetidine was not associated with an increased number of congenital defects among 460 newborns exposed.[24] Reports of intrauterine growth delay and malformations have been reported in association with nizatidine.[8]

Proton-pump inhibitors do cross the placenta. Omeprazole, the first proton-pump inhibitor, has been associated with toxicity in rabbits and rats at high doses causing embryo damage, fetal resorption, and pregnancy disruption.[28] Omeprazole is classified as a Category C agent, while the other proton-pump inhibitors (lansoprazole, esomeprazole, pantoprazole, and rabeprazole) are Category B. The Swedish Medical Birth Registry evaluated a cohort of 955 infants of mothers exposed to omeprazole, with 863 during the first trimester, and did not report a difference in birth weights, congenital malformations, perinatal death, or Apgar scores compared to the general population.[29] A recent, large, cohort study evaluating exposure to all proton-pump inhibitors during the first trimester of pregnancy

evaluated 840,968 live births.[30] Exposure was most common to omeprazole; however, other agents such as lansoprazole, esomeprazole, pantoprazole, and rabeprazole were reported. There was no statistically significant difference in birth defects reported when evaluating those exposed to proton-pump inhibitors compared to those who were not, 3.4% and 2.6%, respectively.[30]

Hypertension

Hypertension complicates 5-10% of pregnancies, and hypertensive disorders of pregnancy are a leading cause of maternal and perinatal morbidity and mortality.[31] Pregnancy hypertension is defined as a sustained diastolic blood pressure ≥ 90 mm Hg, and some professional societies include a systolic blood pressure ≥ 140 mm Hg in the definition.[31] Severe maternal hypertension is defined as a systolic blood pressure ≥ 170 mm Hg or a diastolic blood pressure ≥ 110 mm Hg and should be treated immediately to avoid maternal stroke, eclampsia, or death.[31] Even mild chronic hypertension that is untreated increases the risk of fetal injury. Care must be taken not to overtreat the condition and cause maternal hypotension and ischemia.[8]

Centrally acting alpha-2 adrenergic agonists (e.g., methyldopa and clonidine) decrease systemic vascular resistance without decreasing cardiac output.[31] Methyldopa (Category B) is the drug of choice for chronic management of mild to moderate hypertension in pregnant women due to the availability of favorable long-term pediatric follow-up data.[32] Clonidine (Category C) does cross the placenta, but adverse fetal effects with its use have not been reported. Caution should be exercised with its use due to the potential for rebound hypertension following sudden discontinuation.

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) should be avoided during pregnancy. The use of ACE inhibitors in the second and third trimesters has been associated

Table 3: Medications Considered Safe During Pregnancy

Condition	Medications	Pregnancy Category
Asthma	Albuterol	C
	Terbutaline	B
	Ipratropium bromide	B
	Prednisone	B
	Methylprednisolone	C
	Epinephrine	C
Dysrhythmias	Digoxin	C
	Adenosine	C
	Lidocaine	B
	Sotalol	B
	Verapamil	C
Gastrointestinal	Promethazine	C
	Prochlorperazine	C
	Metoclopramide	B
	Ondansetron	B
	Antacids (magnesium-, aluminum-, calcium-containing products)	C
	Sucralfate	B
	Histamine-2 receptor antagonists (cimetidine, ranitidine, famotidine)	B
	Omeprazole	C
	Other proton-pump inhibitors (lansoprazole, esomeprazole, pantoprazole, rabeprazole)	B
Hypertension	Methyldopa	B
	Clonidine	C
	Labetalol	C
	Metoprolol	C/D*
	Verapamil	C
	Amlodipine	C
	Hydrochlorothiazide	B
	Furosemide	C
	Hydralazine	C
Infectious	Beta-lactams (amoxicillin, ampicillin)	B
	Cephalosporins	B
	Aminoglycosides (gentamicin, tobramycin, amikacin)	C
	Nitrofurantoin	B**
	Macrolides (azithromycin, erythromycin base, erythromycin ethylsuccinate)	B
	Acyclovir	B
	Valacyclovir	B
	Metronidazole (oral)	B
	Clindamycin (oral)	B
	Azole antifungals (vaginal)	C

* C: manufacturer, D: 2nd and 3rd trimester, expert analysis
** Safe to use in 1st or 2nd trimester

(*Table continued*)

Table 3: Medications Considered Safe During Pregnancy (*continued*)

Condition	Medications	Pregnancy Category
Ear, nose, and throat	Diphenhydramine	B
	Chlorpheniramine	B
	Dextromethorphan	C
	Codeine	C/D+
Pain	Acetaminophen	B
	Morphine	C/D+
	Hydrocodone	C/D+
	Oxycodone	B/D+
	Methadone	C/D+
	Fentanyl	C/D+
	Nalbuphine	B/D+
Procedural sedation	Benzodiazepines, intermittent use	D
	Propofol	B
	Ketamine	D++
	Methohexital	B
Thromboemoblic disease and anticoagulation	Unfractionated heparin	C
	Low molecular weight heparin (enoxaparin, dalteparin)	B
	Fondaparinux	B

+ Category D with prolonged use or high doses at term

++ Safe to use in 3rd trimester

with fetopathy characterized by oligohydramnios, fetal distress and death, renal and cranial structural defects, pulmonary hypoplasmia, joint contractures, and intrauterine growth restriction. The teratogenic risk is not evident in the first trimester; therefore, drug exposure during this time period is not normally considered an indication for elective termination of the pregnancy.[31] ACE inhibitors and ARBs by relation are considered Category C agents for the first trimester and Category D agents for the second and third trimesters of pregnancy.

Beta-blockers as a drug class do not appear to be teratogenic based on limited human data. Labetalol (Category C) has been the most studied as a parenteral agent in clinical trials of acute severe hypertension with minimal effects on fetal hypotension. It has also been shown to increase fetal surfactant, which may be beneficial among premature infants.[8] Newborns of mothers taking chronic beta-blockers should be monitored for neonatal bradycardia, respiratory depression, and hypoglycemia for the first 24 hours after birth.[20] Atenolol (Category D) is a cardioselective beta-blocker that may increase the risk of intrauterine growth retardation when started in the first trimester.[33] The reason for this effect is unknown, but given the availability of other beta-blocker agents, atenolol should be avoided in pregnancy.

Calcium channel antagonists (Category C) should be used as a last resort during pregnancy.[8] The non-dihydropyridines (verapamil and diltiazem) have been discussed previously in the section on dysrhythmias. Dihydropyridine agents, particularly nifedipine, have been readily used in pregnancy. This subclass of calcium channel antagonists produces a reflex increase in vascular tone, and immediate-release preparations have been associated with maternal hypotension, fetal distress, and ischemic events in those patients with concomitant coronary artery disease or diabetes mellitus. Due to the possibility of severe hypotension with immediate-release nifedipine, extended-release preparations or longer-acting agents, such as amlodipine, are preferred.

Thiazide diuretic agents (e.g., hydrochlorothiazide, Category B) and loop diuretic agents (e.g., furosemide, Category C) are not considered teratogenic. An increased risk of perinatal mortality and congenital defects has been associated with these classes of drugs, possibly due to decreased maternal plasma volume and subsequent placental hypotension.[34] Controversially, other data suggest that the changes in plasma volume have not been shown to have a negative effect on fetal growth.[35]

Direct vasodilators such as hydralazine (Category C) appear to be safe in pregnancy and often require combination therapy to minimize the associated reflex sympathetic activation. Hydralazine is considered the drug of choice for parenteral treatment in acute severe hypertension during pregnancy. However, data are available that demonstrate more frequent significant hypotension when compared to labetalol or short-acting (oral or sublingual) nifedipine.[31]

Infections

Urinary Tract Infections. Urinary tract infections (UTI) are the most common infection to occur during pregnancy, with an incidence of 2-7%.[36] Asymptomatic bacteriuria is present in 1.9-9.5% of pregnant women, and there is a 20- to 30-fold increased risk of developing pyelonephritis during pregnancy if untreated compared to pregnant women without bacteriuria.[8,37] Adequate treatment decreases the risk of pyelonephritis from 20-35% to 1-4%.[37] Pyuria is present with asymptomatic bacteriuria in 30-70% of pregnant women.[37] Bacterial pathogens responsible for UTI in pregnant patients are similar to those in the general population. *Escherichia coli* is the most common and is isolated in about 75% of cases. *Klebsiella pneumoniae*, *Proteus mirabilis*, group B streptococci, *Staphylococcus saprohyticus*, and enterococci may also be causative organisms.

All antibiotics cross the placenta; still, many have been used for years without reports of adverse fetal effects. Cephalosporins are the most commonly prescribed antibiotics and are considered to be safe in pregnancy (Category B). First-generation cephalosporins (e.g., cephalexin) will provide adequate coverage for the typical gram-negative bacteria identified in UTIs. It is important to note that the half-life of these agents may be decreased in pregnancy due to increased renal clearance.[36] All other beta-lactam antibiotics (e.g., amoxicillin and ampicillin) are considered safe in pregnancy (Category B). Due to the high incidence of *E. coli* resistance with ampicillin (reported 30-50%), this agent is usually not recommended for empiric treatment. If enterococci are isolated, a cephalosporin should not be used and ampicillin is the drug of choice.

Aminoglycosides (e.g., gentamicin, tobramycin, amikacin) are considered Category C agents and may be used to treat gram-negative infections in pregnant patients. Gentamicin is the most widely used aminoglycoside in pregnancy. It rapidly crosses the placenta, with peak cord levels approximately 40% of maternal levels in 1-2 hours.[36] Aminoglycosides should be reserved for resistant gram-negative infections, where less toxic options are not available. This is due to the potential for aminoglycoside-induced maternal renal dysfunction. Although this is a well-known adverse effect of aminoglycoside agents, there have been no reports of neonatal nephrotoxicity or ototoxicity following in-utero exposure.[36]

Nitrofurantoin (Category B) is regularly used in pregnancy. In the third trimester, it has been reported to cause neonatal hyperbilirubinemia and should therefore be avoided during this time period.[8]

The combination of sulfonamides and trimethoprim is a common regimen in non-pregnant patients. Sulfonamides are considered safe in early pregnancy, but are contraindicated during the third trimester due to the competition with bilirubin for albumin binding sites resulting in kernicterus. Trimethoprim is a bacterial folate antagonist and can theoretically cause decreases in maternal folate. In studies involving approximately 300 pregnant women with exposures to trimethoprim, there was no association with teratogenic or adverse fetal effects.[36] Sulfonamide/trimethoprim combination agents should not be used routinely in pregnancy for empiric treatment since there is increasing *E. coli* resistance and there are more appropriate antibiotics available. Fluoroquinolones (e.g., ciprofloxacin and levofloxacin) are contraindicated in pregnancy due to reports of irreversible arthropathy in immature animals.[36]

Treatment duration of 3-7 days is recommended for cystitis or asymptomatic bacteriuria.[37] Single-dose regimens are not recommended for use in pregnant patients. Longer courses of 10-14 days are advised in patients with diabetes mellitus or those with pyelonephritis.[37] Treatment of pregnant patients with pyelonephritis is often initiated in the inpatient setting.[8]

Respiratory Tract Infections. The risk of pneumonia is not increased in pregnancy, but pregnant patients with pneumonia are often treated in the inpatient setting since functional residual lung capacity is reduced, leaving less respiratory reserve.[8] Macrolide antibiotics (e.g., azithromycin, erythromycin) are safe alternatives to fluoroquinolones in pregnancy (Category B). The antimicrobial coverage is similar and effective against the common causative pathogens in pneumonia: *Streptococcus pneumoniae*, *Moraxella catarrhalis*, *Haemophilus influenzae*, and atypical pathogens. Tetracyclines and doxycycline, both Category D agents, are not recommended for use in pregnancy since they are associated with genitourinary and limb malformations. Tetracyclines are also known to chelate calcium and may stain teeth and bones if given after 5 months of gestation.[36]

Antihistamines and decongestants are commonly used for symptomatic relief during upper respiratory infection. Brompheniramine (Category C) is a commonly used antihistamine that is associated with fetal malformations and is contraindicated in pregnancy. Diphenhydramine and chlorpheniramine, both Category B, have been considered the parenteral and oral antihistamines of choice, respectively, in pregnancy. One retrospective case-controlled study reported an association between diphenhydramine exposure in the first trimester and cleft palate; however, subsequent studies have not established this correlation.[38] In the Collaborative Perinatal Project, there were no differences in major malformations or congenital anomalies among 595 children of women who were exposed to diphenhydramine in the first four months of pregnancy.[17]

Decongestant medications (e.g., phenylephrine, pseudoephedrine, and phenylpropranolamine) have been associated with tetatogenicity in animals and minor fetal malformations and are Category C agents that should be used with caution during pregnancy. Dextromethorphan and codeine are considered safe to use for cough suppression during pregnancy (Category C).[8]

Genitourinary Tract Infections. Sexually transmitted diseases are common complications in pregnancy and can cause significant maternal or fetal adverse effects when left untreated. *Chlamydia trachomatis* and *Neisseria gonorrhoeae* are common causes of cervicitis, and more than 40% of pregnant women with gonococcal infections will have concomitant chlamydial infection.[39] Treatment of *C. trachomatis* with azithromycin or amoxicillin (Category B) is recommended.[40] Erythromycin base or erythromycin ethylsuccinate are considered safe alternative agents. Cephalosporins such as ceftriaxone or cefixime are safe for the treatment of *N. gonorrhoeae* in pregnancy. In the case of cephalosporin allergy, azithromycin as a single 2 gram oral dose or spectinomycin can be used.[40] Doxycycline and fluoroquinolones are contraindicated in pregnancy.

The *Treponema pallidum* spirochete readily crosses the placenta

and can cause detrimental effects to the fetus at all gestational ages. Treatment with parenteral agents is preferred to oral therapy. Penicillin G benzathine (Bicillin® L-A) has a 98% maternal cure rate and prevents congenital disease.[41] Skin desensitization and subsequent treatment with penicillin G benzathine (Bicillin® L-A) is recommended in pregnant patients with an allergy to penicillin.[40]

Herpes simplex virus during pregnancy is associated with a 50% neonatal infection rate with a vaginal delivery during a primary maternal outbreak.[8] Oral or intravenous acyclovir (Category B) is recommended for treatment of the first episode of genital herpes and severe recurrent herpes, respectively. Valacyclovir is the prodrug to acyclovir and a common alternative treatment for genital herpes simplex virus. There are limited human data available evaluating adverse fetal effect when used during pregnancy. Animal reproductive studies performed with valacyclovir doses to achieve plasma concentrations 10 times that of the usual human dose revealed no evidence of teratogenicity. The Acyclovir Pregnancy Registry collected prospective voluntary data on 1129 pregnant patients with acyclovir or valacyclovir exposure (712 in the first trimester) between 1984 and 1999.[42] Registry findings did not show an increase in the number of birth defects when compared to those expected in the general population. No data support the use of antiviral therapy among herpes simplex virus seropositive women without a history of genital herpes.[40]

Human papilloma virus infection during pregnancy may obstruct the vaginal canal and increase the risk of hemorrhage during delivery. However, the risk of neonatal transmission is low, 1 in 10,000.[41] Treatment with podophyllin, podofilox, imiquimod, or sinecatechin ointment are not recommended in pregnancy. Current treatment recommendations in this patient population include carbon dioxide ablation, liquid nitrogen cryotherapy, or surgical excision.[41]

Vaginal infections with *Trichomonas vaginalis* or bacterial vaginosis may be associated with premature rupture of the membranes, preterm labor, and chorioamnionitis. Oral metronidazole (Category B) is the recommended treatment for symptomatic *T. vaginalis* and bacterial vaginosis infections during pregnancy. Multiple studies and meta-analyses have not shown an association between metronidazole use during pregnancy and fetal teratogenic or mutagenic effects.[40] Tinidazole as an alternative agent for *T. vaginalis* is not recommended for use during pregnancy. Oral clindamycin may be used as an alternative to metronidazole in symptomatic bacterial vaginosis. Intravaginal clindamycin cream administered at 16 to 32 weeks gestation was associated with an increase in low birth weight and neonatal infections.[40] Therefore, regardless of the antimicrobial agent used, oral therapy is preferred because of the possibility of untreated subclinical upper genital tract infection.

Vulvovaginal candidiasis occurs frequently in pregnancy. Topical azole therapies, including clotrimazole, miconazole, and nystatin, are safe to use during pregnancy. Oral azole antifungal agents are associated with fetal malformations and should be avoided.[8,40]

Pain

Analgesic agents are among the most commonly prescribed medication classes in the emergency department. Aspirin (Category D) is the most studied analgesic medication in pregnant women. The Collaborative Perinatal Project evaluated more than 50,000 pregnancies and found no increases in stillbirth, reduced birth weight, teratology, or perinatal death in those exposed to low-dose aspirin.[8,17] Similarly, the results from the Michigan Medicaid Surveillance Study investigated more than 1,700 pregnancies and found no increases in congenital malformations from aspirin use during the first trimester.[43] Since aspirin irreversibly blocks the formation of thromboxane A2, producing an inhibitory effect on platelet aggregation, use in late pregnancy may increase the risk of peripartum hemorrhage.[44] Furthermore, aspirin-associated prostaglandin inhibition may also cause constriction or premature closure of the fetal ductus arteriosus.[8] Consequently, its use is not recommended in the third trimester of pregnancy.

Other nonsteroidal anti-inflammatory agents (NSAIDs), such as ibuprofen, naproxen, and ketorolac, are primarily prostaglandin inhibitors. Prostaglandins modulate the patency of the fetal ductus arteriosus and NSAIDs have been associated with premature closure of the ductus, causing infantile pulmonary hypertension.[8,44] The Michigan Medicaid Surveillance Study evaluated more than 3,000 first-trimester exposures to ibuprofen and found an association with oligohydramnios.[43] The adverse effects of NSAIDs on the ductus and amniotic fluid volume do appear to be reversible with drug discontinuation, yet NSAID use is not recommended in the third trimester of pregnancy.[8]

Acetaminophen (Category B) is the analgesic of choice during pregnancy. Although it provides similar analgesia to NSAIDs, it does not inhibit prostaglandin synthesis or affect platelet function.[44] Caution should be taken to maintain a dose less than 4 g daily to minimize the risk of maternal and fetal hepatotoxicity.

There is no evidence to suggest a relationship between exposures to any of the opioid agonists or agonist-antagonists during pregnancy and fetal malformations.[44] The Collaborative Perinatal Project monitored more than 50,000 mother-child pairs. Of these, 563 had first-trimester exposure to codeine and 686 had first-trimester exposure to propoxyphene.[17,44] There was no evidence of a causative relationship to major or minor malformations. The same results were observed in those with exposures to hydrocodone, meperidine, methadone, morphine, or oxycodone. Furthermore, there have been no reports to link

the use of fentanyl, remifentanil, oxymorphone, butorphanol, or nalbuphine with congenital defects.[44] Meperidine is well-known to be extensively metabolized to the metabolite normeperidine. The long half-life of normeperidine and the risk of accumulation causing excitation of the central nervous system and subsequent seizures do not make this agent a good choice for pain control in the pregnant patient in the emergency department. All of the opioid analgesics are considered Category B or C when used in intermittent doses, but all are considered Category D if used for prolonged periods or at high doses near term. Chronic maternal opioid use, including methadone use for opioid addiction, can cause symptomatic withdrawal in infants beginning 48 hours up to 14 days postpartum. Slow opioid weaning, described as a 10% reduction every 3 days, may be utilized to prevent withdrawal symptoms.[44]

Procedural Sedation

Use of sedatives and analgesic agents may be necessary for the care of the patient during potentially uncomfortable procedures. Administration of pharmacologic agents commonly used for the general population may be concerning for the provider to administer to the pregnant patient. Benzodiazepine use for procedural sedation has been a mainstay in the emergency department. Exposure during pregnancy is concerning because benzodiazepines act on gamma-aminobutyric acid (GABA) receptors, and the GABA neurotransmitter is thought to be related to palatal development.[45] Early animal and retrospective human studies reported that diazepam was associated with clefting.[45] More recent studies have produced unclear results. One study evaluated 272 women with chronic exposure to alprazolam, lorazepam, or clonazepam. Of the 186 liveborns, 15 were reported to have malformations.[45] These were most commonly cardiac defects and inguinal hernias and thought to be from the muscle relaxant properties of benzodiazepines. Another study prospectively evaluated 460 pregnancies exposed to benzodiazepines in the first trimester and found no increase in total malformations, but more cardiac defects compared to the control group.[46] Midazolam (Category D) is one of the most common benzodiazepines used for procedural sedation due to its quick onset and short duration of action compared to other benzodiazepine agents. Reproduction studies in animals reported no teratogenic effects or malformations with the use of midazolam at 10 times the human dose.[45] Benzodiazepines should only be used if safer therapy is unavailable or contraindicated.

Propofol (Category B) is ideal for use during procedural sedation due to the quick onset of action, easy titration, and short duration of action. Propofol does cross the placenta and induces vasodilation of isolated vessels, but has not been shown to alter fetal placental vascular resistance.[47] Animal studies demonstrate no evidence of impaired fertility or harm to the fetus with propofol doses equivalent to those used in humans.[48] Although human data is limited, there is no evidence that propofol is associated with fetal adverse effects.[49,50]

Ketamine (Category D) has traditionally been used more in the pediatric population than the adult population, although use in the latter group has increased over recent years. The sedative and analgesic properties at relatively low doses and few side effects make this agent appealing for use during procedural sedation. Animal reproductive data have not shown an association between ketamine and fetal malformations with both intravenous and intramuscular administration.[51,52] In humans, intrauterine pressure is increased with ketamine usage in the first trimester, but not in the third trimester.[53] Increases in pressure were equal to that of ergometrine.

Etomidate (Category C) is a nonbarbiturate sedative hypnotic agent that is desirable for use in procedural sedation owing to its rapid onset, short duration of action, and minimal hemodynamic effects. Etomidate is lipid soluble and readily crosses the placenta in high amounts. Fetal elimination is as rapid as maternal elimination; therefore, accumulation is not evident.[54] Animal reproductive studies report no teratogenicity; however, decreased pup survival was noted in rats and rabbits in doses ranging from one to 16 times the usual human dose.[55] Human reproductive data is limited, although experience is great with its use in induction of patients undergoing cesarean section. Induction doses of etomidate have been associated with reduction in plasma cortisol; however, the clinical sequelae of this are unclear and have not been reported or evaluated in the pregnant patient.

Barbiturates (e.g., methohexital and thiopental) have fallen out of favor for use in procedural sedation in the emergency department given the availability of newer agents with a more favorable side-effect profile (e.g., propofol). Methohexital (Category B) does cross the placenta; however, it has not been associated with fetal malformations in animals or humans. Thiopental (Category C) crosses the placenta with a peak concentration at 10 minutes following administration. In spite of this, concentration in the fetal brain in rats has been reported to be 10 times less than that of the maternal brain concentration, and in humans, intrauterine pressure was not increased.[51,56] Reproductive studies in animals with exposure to thiopental to evaluate fetal development have not been performed.

Dexmedetomidine (Category C) is a selective alpha-2 adrenergic agonist that causes sedation and mild analgesic effects without respiratory depression. Its use in procedural sedation is limited and has been reported mostly in children.[57,58] Current limitations to its use in the emergency department for procedural sedation include the incidence of hypotension and bradycardia, longer sedation recovery times when compared to propofol, and high medication cost.[58]

Reproductive animal data report placental transfer, fetal and embryocidal toxicity, delayed motor development, and increased frequency and amplitude of myometrial contractions at doses less than the maximum recommended in humans.[59] At 10 times the recommended dose in humans, dexmedetomidine was associated with post-implantation losses and fetal death.[59,60] Human data are limited, although one case report found no negative sequelae when used for sedation during cesarean section.[61]

Seizures

Seizure disorders affect approximately 1.1 million women of childbearing age in the United States. Five percent to 25% of pregnant women who have underlying epilepsy may experience an increase in their baseline seizure activity.[62] The management of pregnant women with seizures is important since seizures alone can increase the risk of miscarriage and fetal hypoxic injury.[8] Antiepileptic medications also increase the risk of fetal malformations. Decreased patient compliance with these medications is sometimes seen because of concerns of danger to the developing fetus. Treatment must be carefully weighed to minimize both the risks of increasing seizure frequency of the mother and that of potential adverse effects of antiepileptic medication to the fetus. Clearly, this is the situation to consider monotherapy, if at all possible, and use of the minimum effective dose.[62]

The risk of fetal malformations with the use of antiepileptic medication is reported to be 6-8%, or a two- to three-fold increase compared to the general population.[62] Phenytoin (Category D) is a known human teratogen. Fetal hydantoin syndrome, consisting of craniofacial anomalies, distal digital hypoplasia, epicanthal folds, hypertelorism, low-set ears, and developmental delay was first described in 1973 and is reported in 3-10% of infants following maternal exposure to phenytoin during pregnancy.[34] Those that require phenytoin treatment during pregnancy are often treated with vitamin K and folic acid to decrease the respective risks of neonatal coagulopathy and neural cord defect caused by phenytoin-induced deficiencies of these substances.[8,34]

Phenobarbital and primidone (both Category D) may also contribute to folic acid deficiency and neonatal coagulopathy.[34] The antiepileptic drug pregnancy registry reported 77 patients who received phenobarbital monotherapy during pregnancy; major malformations were reported in 6.5% of fetuses, compared to the general population rate of 1.6%.[63] Primidone is converted to phenobarbital in vivo; therefore, the fetal effects are expected to be the same.

Valproic acid and valproate sodium (Category D) are teratogenic in humans and have been associated with neural tube defects in approximately 1-2% of infants exposed in utero, which is up to 10 times that of the general population.[8]

Carbamazepine and oxcarbamazepine are Category C medications. Carbamazepine has been associated with craniofacial abnormalities, hypoplastic nails, and developmental delays.[8,34] Furthermore, neural tube defects are reported in 0.5% to 1% of infants, and there is an increased risk of cardiac anomalies. Fetal echocardiogram is recommended at 20 to 22 weeks gestation.[62] Animal studies with oxcarbamazepine have reported teratogenic effects; however, human data are lacking. Due to the structural similarity to carbamazepine, one would expect similar human teratogenic effects. Trimethadione (Category X) is rarely used in the treatment of seizures and is associated with malformations and fetal loss 87% of the time.[8]

Felbamate, gabapentin, lamotrigine, levetiracetam, and topiramate (Category C) are newer antiepileptic agents with little human data in pregnancy. Registry data are currently being collected to provide more robust information on the incidence of fetal adverse effects following exposure.[64] From reproductive animal data, gabapentin and topiramate have been reported to be teratogenic, and levetiracetam is associated with developmental toxicities. Lamotrigine has been reported to decrease folate concentrations in animals, and preliminary registry data report an increased incidence of cleft lip or cleft palate following first-trimester exposure.[65] Case reports of hypospadias following in vitro exposure have been reported with topiramate use.[66]

Thromboembolic Disease and Anticoagulation

Pregnancy is traditionally thought to be a hypercoagulable state.[67] Fibrin generation is increased, fibrinolytic activity is decreased, levels of coagulation factors II, VII, VIII, and X are all increased, free protein S levels are decreased, and acquired resistance to activated protein C is common.[68] The incidence of venous thromboembolism, most commonly pulmonary embolism or deep vein thrombosis, is estimated at 0.76 to 1.72 per 1000 pregnancies.[69,70] This is four fold greater than the occurrence in the non-pregnant population.

Oral anticoagulation with warfarin is contraindicated in pregnancy (Category X). Warfarin is known to cross the placenta and has been linked to abnormal fetal development.[71] These are characterized as midface hypoplasia, stippled chondral calcification, scoliosis, short proximal limbs, and short phalanges. Warfarin will affect 5% of fetuses that are exposed between 6 and 9 weeks of gestation.[72] The use of warfarin in the second and early third trimesters is associated with fetal intracranial hemorrhage and schizencephaly.[67] Likewise, a new class of pharmacologic agents available, the oral direct thrombin inhibitors (e.g., dabigatran), was shown to increase fetal death, increase vaginal/uterine hemorrhage, and increase the incidence of delayed or irregular ossification of fetal skull bones and vertebrae in animals.[73] To date, there are no human data available during pregnancy, and dabigatran is considered a Category C agent.

Table 4: Immunization and Pregnancy

Vaccine or Immune Globulin	Recommendation During Pregnancy	Type of Vaccine
Hepatitis A	Yes, if at high risk for disease	Inactivated
Hepatitis B	Yes, if at high risk for disease	Inactivated
Hepatitis B immune globulin (HBIG)	Yes	N/A
Influenza TIV	Yes	Inactivated
Pneumococcal (PPV23)	Yes	Inactivated
Rabies (human diploid cell)	Yes	Inactivated
Rabies immune globulin	Yes	N/A
Tetanus & diphtheria (Td)	Yes	Inactivated
Tetanus, diphtheria, acellular pertussis (Tdap)	Yes	Inactivated
Tetanus immune globulin	Yes	N/A
Varicella zoster immune globulin (VZIG)	Yes	N/A
Human papillomavirus (HPV)	No	Inactivated
Influenza LAIV	No	Live, attenuated
Measles, mumps, rubella (MMR)	No	Live, attenuated
Polio IPV	No	Inactivated
Polio OPV	No	Live, attenuated
Varicella	No	Live, attenuated

TIV: trivalent inactivated vaccine; LAIV: live, attenuated influenza vaccine; PPV23: pneumococcal polysaccharides vaccine 23-valent; IPV: inactivated polio vaccine; OPV: oral polio vaccine

Unfractionated heparin and low-molecular-weight heparin (LMWH) do not cross the placenta, and and treatment of venous thromboembolism during pregnancy is primarily with these agents. In the non-pregnant population being treated for a pulmonary embolism, unfractionated heparin and LMWH have been shown to have equivalent efficacy.[74] On the other hand, LMWH has been shown to be more effective and associated with a lower risk of hemorrhagic complications and mortality compared to unfractionated heparin in the non-pregnant population for the initial treatment of deep vein thrombosis.[75,76] Data are available from several systematic reviews and large case series that report the efficacy and safety of LMWH for the treatment of deep vein thrombosis and pulmonary embolism during pregnancy.[71] Therefore, LMWHs are considered pregnancy Category B agents. Although there are two different weight-based dosing strategies for LMWH products, once-daily and twice-daily administration, expert opinion recommends twice-daily administration because of increased renal excretion and a decreased half-life of the drug during pregnancy.[67] Routine measurement of peak anti-Xa activity is not recommended in pregnancy and is only recommended in women at the extremes of body weight and those with altered renal function.[67,71] Regular adjustments to the calculated weight-based medication dose should be made throughout the patient's pregnancy. Long-term use of LMWH may increase the incidence of cutaneous allergic reactions compared to short-term use in non-pregnant patients.[67] Fondaparinux (Category B), a direct factor Xa inhibitor, may be an alternative. In vitro models found that fondaparinux does not cross the placenta; however, clinical experience suggests that use results in low levels of anti-factor Xa activity in the umbilical cord blood.[67]

There is limited experience, mostly as case reports or case series, with the use of thrombolytic agents during pregnancy. Although it is known that streptokinase crosses the palcenta, the incidence with recombinant products (e.g., alteplase) is unknown.[77] There have been 172 pregnant patients treated with thrombolytic therapy in the literature, most commonly with streptokinase. Problems associated with treatment have been reported as non-fatal maternal bleeding complications (2.9%) and fetal death (1.7%).[77] No maternal deaths have been reported. Based on the mechanism of action of the medication, there is concern for placental abruption and the risk of antepartum hemorrhage.[8,67] Overall, the data

suggest that the maternal bleeding complication rate is between 1% and 6%.[71] This is no different from the rate seen in the non-pregnant population and is most often associated with bleeding around catheter and puncture sites.[68] In pregnant patients with a massive pulmonary embolism and severe hemodynamic compromise, streptokinase use may be lifesaving.[71,78]

Immunizations

Benefits of vaccinating pregnant women usually outweigh the risks when possible exposure is likely. There is no evidence of increased fetal harm when inactivated viral or bacterial vaccines are given to pregnant women.[79] Live vaccines should be avoided in pregnancy due to the theoretical risk of transmission of the vaccine virus to the fetus.[79] Avoidance of immunization administration during the first trimester of pregnancy is preferred, since high fevers during this time period have been associated with neural tube defects, and vaccination may cause fevers.[8]

Vaccines that are safe in pregnancy include hepatitis A, hepatitis B, inactivated influenza pneumococcal (PPV23), human diploid cell rabies vaccine, tetanus and diphtheria (Td), and tetanus, diphtheria, acellular pertussis (Tdap). Health-care providers may choose to administer Tdap instead of Td in situations where the pregnant patient is at a high risk for pertussis infection. These include pregnant adolescents, pregnant health-care providers, child care providers, and pregnant women employed in an institution or living in a community with increased pertussis activity.[79] Although the inactivated polio vaccine (IPV) is commonly used in the United States compared to the oral polio vaccine (OPV), neither is recommended for use in pregnant patients.

There are no known risks associated to the fetus from passive immunization of pregnant women with immune globulin preparations.[79] Therefore, the use of hepatitis B, rabies, tetanus, and varicella zoster immune globulins is considered safe in pregnancy. Pregnant women should not be vaccinated with human papillomavirus (HPV), live attenuated influenza (LAIV), measules, mumps, and rubella (MMR), or varicella vaccines due to the live formulation of the vaccine or theoretical risk to the fetus. A summary of vaccine and immune globulin recommendations during pregnancy is available in Table 4.

Summary

The use of medications in the pregnant population can be daunting to the emergency physician. General considerations should include minimizing the risk to the fetus with the choice of appropriate and necessary pharmacologic agents, limiting exposure to the smallest effective dose prescribed for the shortest necessary duration, and using medications that have been in use for long periods of time with well-understood safety profiles.

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Physician CME Questions

31. The time of greatest susceptibility of the embryo to organ malformations occurs at:
    A. 1-3 weeks
    B. 4-12 weeks
    C. 13-27 weeks
    D. 28-40 weeks

32. A medication that is contraindicated in pregnancy, where the risk of using the drug clearly outweighs the benefit, is described as United States FDA Pregnancy Category:
    A. B
    B. C
    C. D
    D. X

33. Considerations that emergency physicians should take into account with the use of medications in the pregnant population include:
    A. Each drug should have a clear indication.
    B. Drug exposure should be minimized using the smallest effective dose for the shortest possible duration.
    C. Effective drugs with a well-known safety profile are preferred to newer pharmacologic agents.
    D. All of the above

34. Antacids containing which product should be avoided in pregnancy?
    A. aluminum
    B. magnesium
    C. sodium bicarbonate
    D. calcium

35. Asymptomatic bacteriuria increases the risk of developing pyelonephritis during pregnancy if untreated compared to pregnant women without bacteriuria.
    A. true
    B. false

36. Which antibiotic is safe to use throughout pregnancy?
    A. ciprofloxacin
    B. doxycycline
    C. azithromycin
    D. sulfamethoxazole/trimethoprim

37. Which sedative agent is considered safe to use during pregnancy and is a Category B agent?
    A. midazolam
    B. propofol
    C. ketamine
    D. thiopental

38. Which of the following medications/medication classes has not been associated with fetal adverse effects in humans?
    A. warfarin
    B. low molecular-weight heparins (LMWH)
    C. phenytoin
    D. angiotensin-converting enzyme inhibitors (ACE inhibitors)

39. Acute asthma exacerbations, uncontrolled hypertension, untreated infection, and seizure activity may cause detrimental fetal and maternal adverse effects.
    A. true
    B. false

40. Which vaccine is *not* safe to administer during pregnancy?
    A. tetanus, diphtheria, acellular pertussis (Tdap)
    B. tetanus and diphtheria (Td)
    C. varicella
    D. influenza (TIV — trivalent inactivated vaccine)

In Future Issues

Ultrasound-guided Procedures

CME Answer Key

31. B; 32. D; 33. D; 34. C; 35. A; 36. C; 37. B; 38. B; 39. A; 40. C

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- discuss the differential diagnosis of the particular medical problems discussed in the publication;
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Medication Safety During Pregnancy

Summary of FDA Pregnancy Categories

Category	Summary
A	Controlled studies in humans show no fetal risk.
B	No evidence of fetal risk in humans with or without adverse findings in animal studies.
C	Evidence of fetal risk in animals, but not studied in humans. Risk cannot be ruled out. Use if benefits outweigh risks to the fetus.
D	Evidence of fetal risk in humans.
X	Contraindicated; benefit does not outweigh risk.
FDA: Food and Drug Administration	

Medications Considered Safe During Pregnancy

Condition	Medications	Pregnancy Category
Asthma	Albuterol	C
	Terbutaline	B
	Ipratropium bromide	B
	Prednisone	B
	Methylprednisolone	C
	Epinephrine	C
Dysrhythmias	Digoxin	C
	Adenosine	C
	Lidocaine	B
	Sotalol	B
	Verapamil	C
Gastrointestinal	Promethazine	C
	Prochlorperazine	C
	Metoclopramide	B
	Ondansetron	B
	Antacids (magnesium-, aluminum-, calcium-containing products)	C
	Sucralfate	B
	Histamine-2 receptor antagonists (cimetidine, ranitidine, famotidine)	B
	Omeprazole	C
	Other proton-pump inhibitors (lansoprazole, esomeprazole, pantoprazole, rabeprazole)	B
Hypertension	Methyldopa	B
	Clonidine	C
	Labetalol	C
	Metoprolol	C/D*
	Verapamil	C
	Amlodipine	C
	Hydrochlorothiazide	B
	Furosemide	C
	Hydralazine	C
Infectious	Beta-lactams (amoxicillin, ampicillin)	B
	Cephalosporins	B
	Aminoglycosides (gentamicin, tobramycin, amikacin)	C
	Nitrofurantoin	B**
	Macrolides (azithromycin, erythromycin base, erythromycin ethylsuccinate)	B
	Acyclovir	B
	Valacyclovir	B
	Metronidazole (oral)	B
	Clindamycin (oral)	B
	Azole antifungals (vaginal)	C
* C: manufacturer, D: 2nd and 3rd trimester, expert analysis ** Safe to use in 1st or 2nd trimester		

(*Table continued*)

Medications Considered Safe During Pregnancy (*continued*)

Condition	Medications	Pregnancy Category
Ear, nose, and throat	Diphenhydramine	B
	Chlorpheniramine	B
	Dextromethorphan	C
	Codeine	C/D[+]
Pain	Acetaminophen	B
	Morphine	C/D[+]
	Hydrocodone	C/D[+]
	Oxycodone	B/D[+]
	Methadone	C/D[+]
	Fentanyl	C/D[+]
	Nalbuphine	B/D[+]
Procedural sedation	Benzodiazepines, intermittent use	D
	Propofol	B
	Ketamine	D[++]
	Methohexital	B
Thromboemoblic disease and anticoagulation	Unfractionated heparin	C
	Low molecular weight heparin (enoxaparin, dalteparin)	B
	Fondaparinux	B
[+] Category D with prolonged use or high doses at term [++] Safe to use in 3rd trimester		

Medications Not Routinely Recommended During Pregnancy

Condition	Medication
Dysrhythmias	Propranolol Amiodarone Ibutilide Diltiazem
Gastrointestinal	Antacids (sodium bicarbonate-containing products) Nizatidine
Hypertension	ACE inhibitors ARBs Atenolol Diltiazem
Infectious	Nitrofurantoin* Sulfamethoxazole/trimethoprim* Fluoroquinolones (ciprofloxacin, levofloxacin, ofloxacin) Erythromycin estolate Tetracyclines Doxycycline Metronidazole (vaginal) Clindamycin (vaginal) Azole antifungals (oral)
Ear, nose, and throat	Brompheniramine Decongestants (phenylephrine, pseudoephedrine)
Pain	Aspirin NSAIDs (ibuprofen, naproxen, ketorolac) Meperidine
Procedural sedation	Etomidate Ketamine Thiopental Dexmedetomidine
Seizures	Phenytoin Phenobarbital Valproic acid
Thromboembolic disease and anticoagulation	Warfarin Dabigatran Alteplase

ACE: angiotensin-converting enzyme; ARBs: angiotensin receptor blockers; NSAIDs: nonsteroidal anti-inflammatory drugs
* Safe to use in first and second trimester

Immunization and Pregnancy

Vaccine or Immune Globulin	Recommendation During Pregnancy	Type of Vaccine
Hepatitis A	Yes, if at high risk for disease	Inactivated
Hepatitis B	Yes, if at high risk for disease	Inactivated
Hepatitis B immune globulin (HBIG)	Yes	N/A
Influenza TIV	Yes	Inactivated
Pneumococcal (PPV23)	Yes	Inactivated
Rabies (human diploid cell)	Yes	Inactivated
Rabies immune globulin	Yes	N/A
Tetanus & diphtheria (Td)	Yes	Inactivated
Tetanus, diphtheria, acellular pertussis (Tdap)	Yes	Inactivated
Tetanus immune globulin	Yes	N/A
Varicella zoster immune globulin (VZIG)	Yes	N/A
Human papillomavirus (HPV)	No	Inactivated
Influenza LAIV	No	Live, attenuated
Measles, mumps, rubella (MMR)	No	Live, attenuated
Polio IPV	No	Inactivated
Polio OPV	No	Live, attenuated
Varicella	No	Live, attenuated

TIV: trivalent inactivated vaccine; LAIV: live, attenuated influenza vaccine; PPV23: pneumococcal polysaccharides vaccine 23-valent; IPV: inactivated polio vaccine; OPV: oral polio vaccine

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