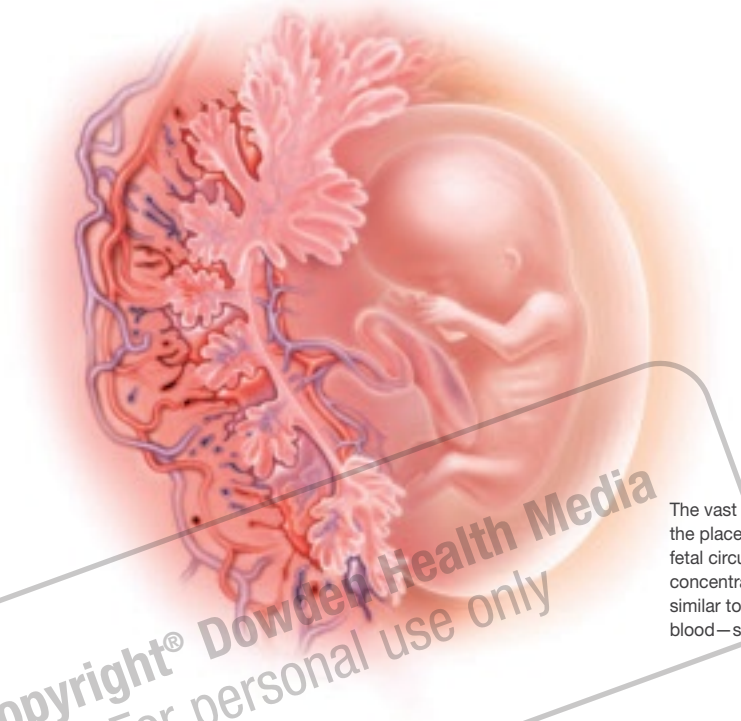
OBG MANAGEMENT

William F. Rayburn, MD
Dr. Rayburn is Seligman Professor and Chair, Department of Obstetrics and Gynecology, at the University of New Mexico Health Sciences Center in Albuquerque. With a background in pharmacology, he has authored many studies reporting drug trials during pregnancy, as well as several texts on the subject.

The author reports no financial relationships relevant to this article.



The vast majority of drugs cross the placenta and enter the fetal circulation, with unbound concentrations in the fetal serum similar to those in the mother's blood—sometimes even higher.

What you need to know about medication safety in pregnancy

Few drugs are major teratogens, but heightened vigilance is crucial to protect your pregnant patient

IN THIS ARTICLE

Fifty years ago, the thalidomide experience—a high incidence of major birth defects following prenatal use of the drug—made clear the devastating potential of drug exposure during pregnancy. Since that disaster, healthcare providers and patients have adopted a conservative approach to medication use during pregnancy, especially during the first trimester and lactation. That is a wise strategy, although very few medications are associated with abnormal fetal development.

In this article, I'll guide you through some of the issues that must be considered when assessing a drug's teratogenicity, help you find information on a host of medications, and familiarize you with some of the challenges involved in counseling the patient. I also present a table listing the adverse effects known to be associated with selected drugs during the first, second, and third trimesters and lactation (**TABLE**, page 76). We are fortunate that a large body of information about medication use during pregnancy and lactation is readily available on the Web and in books and medical journals. This information is far from definitive, however, because much of the evidence concerning prescribed drugs is anecdotal or presented with insufficient warning about their use during pregnancy and lactation.

A discussion of these issues with the patient will help set the risks and

benefits of a particular drug into proper perspective, alleviate fears, and improve compliance. Nonprescription medications should also be discussed, and the patient should be advised that we have very little data concerning their use during pregnancy.

Assignment of risk is an uncertain science

Major structural defects are apparent at birth in about 3% of all pregnancies and in about 4.5% of all children by the age of 5 years.[1] A cause or proposed mechanism for the defects can be determined in fewer than 50% of these cases. Nor can we count on expert consensus about the safety of many medications during pregnancy because it rarely occurs and, in some cases, may be impossible to achieve.

Animal studies are the means of assessing the teratogenicity of most drugs. Animals commonly used to study fetal effects include rodents (fertility, birth defects, birth weight, behavior), rabbits (birth defects), baboons (uterine blood flow), and sheep (uterine blood flow, cardiovascular effects, fetal hypoxia, and acidosis). Dosages are often much higher (in relation to body weight or surface area) to "test the systems" for any possible reproductive harm. Although these studies may be helpful, they do not reliably predict the human response.

Even when humans are the subject of study, conclusions must be viewed with caution. To determine the risk of teratogenesis, it is necessary to know the stage of development during which the exposure occurred, as well as the identity and dose of the medication and the genetic susceptibility of the mother and fetus.

Three critical stages. In utero exposure to a drug occurs in one of three periods of fetal development:

- ovum – from fertilization to implantation
- embryo – from the second through the eighth week of gestation
- fetus – from the eighth completed week until delivery.

An "all-or-none" effect (i.e., spontaneous abortion or not) is believed to arise from exposure during the first period, but the embryo stage is the most critical time because it involves organogenesis. Detrimental effects may occur even beyond this period as cells continue to divide in the hematologic, reproductive, and central nervous systems.

Many fine points of exposure are difficult to clarify

Retrospective and uncontrolled studies, as well as individual case reports or small series, may overestimate the risk to the fetus of exposure to a specific drug or combination of medications. Case reports do not establish causation.

It can also be difficult to differentiate between the risks of a specific drug and the hazards of maternal illness to explain an unfavorable outcome. For example, is a particular case of stillbirth the result of fetal exposure to enoxaparin or maternal thrombophilia, or both? Can fetal growth restriction be attributed to use of azathioprine during pregnancy or to the mother's underlying illness? And so on.

In addition, it is necessary to distinguish between a defect's natural prevalence—i.e., the rate at which it occurs in a population—and the additional risk posed by exposure to a particular drug. Studies in large populations are needed—but usually unattainable—to determine the relative risk from specific potential teratogens.

Finally, it is very difficult to assess neurobehavioral effects of in utero exposure to centrally acting drugs beyond the immediate neonatal period. The dose, offspring's age and gender, and behavioral test system must all be considered.

Few drugs are implicated in restricting fetal growth or reducing organ size. We also lack consistent information about long-term effects such as learning or behavioral problems (i.e., functional teratogenesis) that may re-

***FAST** TRACK*

Detrimental effects can occur beyond the critical embryo stage as cells continue to divide in the hematologic, reproductive, and central nervous systems

Why FDA pregnancy categories have to go

In 1979, the Food and Drug Administration created five pregnancy risk categories to be used by manufacturers to rate their products in the drug formulary for use during pregnancy: categories A, B, C, D, and X, which range from no evidence of damage to the fetus (category A) to clear teratogenicity (D and X).

The D rating is generally reserved for drugs with no safer alternatives, such as secobarbital, doxycycline, and lorazepam. The X rating means there is absolutely no reason to risk using the drug in pregnancy, as in the case of oral contraceptives, benzodiazepines, and misoprostol.

Approximately 2% of drugs fall into category A, 50% in category B, 38% in category C, 3–5% in category D, and 1–5% in category X.[3] These categories do not often accurately reflect the available information on risk to the fetus. A major initiative is under way to declare these categories obsolete and provide more informative drug labeling. Pregnancy labels of the future will likely address three important areas:

- clinical considerations – issues relevant to prescription of a particular drug in pregnancy, including the risk of disease versus no treatment. Also included will be information of use when counseling a patient whose fetus was inadvertently exposed to a medication in early gestation
- summary risk assessment – a narrative text that describes, as comprehensively as possible, the risk of exposure based on animal and human data
- data to support the assessment.

***FAST** TRACK*

During gestation, medications are taken at the same frequency—or more often—as before pregnancy

sult from chronic prenatal exposure to a certain medication.

All drugs cross the placenta

Most medications are easily absorbed during pregnancy, and serum concentrations of albumin for drug binding are lower than in the nonpregnant state. Pharmacokinetic changes during pregnancy include:

- higher volume of distribution
- lower maximum plasma concentration
- lower steady-state serum concentration
- shorter plasma half-life
- higher clearance rate.[1]

The small spatial configuration and high lipid solubility of most medications permit easy transfer of an unbound drug or its metabolite across the placenta or into breast milk. Virtually all drugs and their end products cross the placenta, with unbound concentrations of the drug in the fetal serum similar to the level in maternal serum—sometimes even higher (**FIGURE,** page 72).

A few drugs with high molecular weight do not cross the placenta in significant amounts (e.g., glyburide, interferon, thyroid supplements, insulin).

Medication use tends to increase as pregnancy progresses

The drugs most commonly taken during pregnancy include vitamins, iron preparations, calcium, analgesics, antibiotics, and antacids. Excluding vitamins and mineral supplements, an average of one to two medications are taken during gestation. Over-the-counter formulations account for about half of these drugs, with acetaminophen being the single most commonly used medication during pregnancy. Antibiotics are the most widely prescribed drugs.

Although caffeine, tobacco, alcohol, and illicit substance use tends to diminish as pregnancy progresses, medications are usually taken at the same frequency or more often during gestation.

My colleagues and I found a significantly higher mean number of medications (3.3 and 4.1, respectively) used during the second and third trimesters of gestation than were taken before pregnancy (2.6).[2]

CONTINUED

How to counsel the patient

Counseling a woman before or during pregnancy about the continuation or initiation of a medication should take place in an open, supportive, and informative manner. Most inquiries relate to exposures involving very low levels of relative and absolute risk.

A detailed fetal ultrasonographic examination is often used to accurately date the pregnancy and, if possible, screen for any structural defects. The patient should be advised that first-trimester screening, chorionic villus sampling, maternal serum quadruple screening, amniocentesis, and fetal blood sampling are not very predictive of a drug's fetal effects. Exceptions may be the observation of open neural tube defects (approximate 1% risk associated with valproic acid and carbamazepine) by maternal serum quadruple screening and facial clefting by targeted ultrasonography.

When a patient inquires about a particular drug, it is important to gather the following information:

- When did she take the medication?
- Why did she take it?
- For how long did she take the medication?
- Did she take other medications, or any substances of abuse, at the same time?

A number of sources of information about potential teratogens are available.[3–5] These include national computerized databases that are accessible on the Web:

- National Library of Medicine (http://sis.nlm.nih.gov/enviro.html)
- pregnancy exposure registries (www.fda.gov/womens/registries/default.htm)
- Reproductive Toxicology Center (http://reprotox.org) (access requires a paid subscription)
- LactMed, National Library of Medicine guide to drug safety in lactation (http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT)
- Organization of Teratology Information Specialists (OTIS) (www.otispregnancy.org).

The last source (OTIS) consolidates teratology information nationwide and reports it by state or region. It also publishes a host of fact sheets on various drugs that may be useful to dispense to the patient during counseling. In addition, many teratogen information services or poison control centers (often at children's hospitals) are available throughout the United States to serve specific geographic areas. And teratogen registries at pharmaceutical companies may provide limited information about newer medications.

The *Physician's Desk Reference* (PDR) is a common source of information about the use of prescription drugs in pregnancy.[3] But be aware that, to avoid liability, pharmaceutical manufacturers do not encourage use of their drugs during pregnancy unless the benefit clearly outweighs the risk. It would be unrealistic for them to market a medication for specific use during pregnancy because it would require considerable time and cost, and raise ethical objections, to conduct research in a vulnerable population that is limited in number.

Effects of agents used more than 40 years ago were reported by the Collaborative Perinatal Project or the Boston Collaborative Drug Surveillance Program.[6] Those findings are often inconclusive, reflect bias in study designs, and do not help a clinician evaluate current medications or those less commonly prescribed during pregnancy.

The risks and experience associated with new drugs are usually not well explored in regard to pregnancy. As a result, older medications are more likely to be prescribed as maintenance therapy during gestation for the simple reason that they have a larger body of information regarding their effects. These older drugs may no longer be preferred once the patient delivers.

Most drugs are not teratogens

The **TABLE** on page 76 lists adverse effects in the human fetus known to arise from exposure to specific drugs.

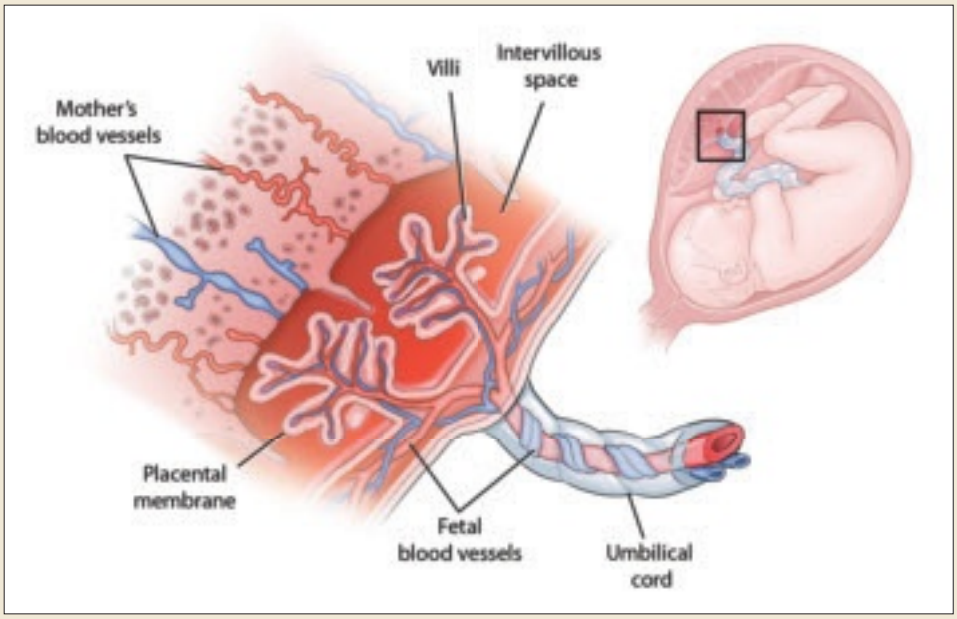
CONTINUED

***FAST** TRACK*

First-trimester screening, CVS, maternal serum quadruple screening, amniocentesis, and fetal blood sampling are not predictive of a drug's fetal effects

FIGURE

An elaborate nutrient (and drug) delivery system



The placenta and umbilical cord deliver the nutrients and oxygen the fetus needs for normal growth—as well as most medications used by the mother.

***FAST** TRACK*

When reviewing or planning maintenance drug therapy, follow the same principles as in a nonpregnant patient

The information comes largely from the Reprotox database, which was reviewed as recently as 2006, describes human data only, and is reported by first trimester (anomalies, abortion) and the second and third trimesters (fetal growth restriction, stillbirth, low birth weight, preterm delivery, immediate neonatal problems).[7] Typical dosages of most drugs are not anticipated to increase the risk of congenital anomalies.

Most human data come from small series or case reports. Although these types of studies are helpful, they tend to be biased or reflect the pregnancy's background risk of birth defects rather than the risk posed by a specific drug. In addition, case reports of malformation after prenatal exposure to a certain drug may involve exposures to other agents and a lack of uniformity of abnormalities, making the association between adverse effects and a single agent unlikely. Dissimilarities in the dosage and route of delivery also limit interpretation. For example, short-term intravenous or sublingual administration of a drug may pose a different risk than taking that medication orally or vaginally, in a lower dose, for a longer period, or at a different period of gestation.

Randomized controlled trials of drugs are rare during pregnancy, as are prospective cohort investigations. Because a control population is often impossible to identify, it becomes difficult to separate any heightened risk identified during use of the medication from the underlying disease. When the gravida has significant medical problems, it is important to assess the potential risk of a drug—or its omission—in her as well as her fetus. The lowest effective dose is preferred, but keep in mind that inadequate treatment may lead to minimal benefit and potentially greater risk to the pregnancy.

When reviewing or planning maintenance drug therapy, follow the same principles as you would in a nonpregnant patient. Be familiar with more than one medication for each disorder. Also be aware that some drugs may need to be prescribed at a higher dose or greater fre-

quency to attain a therapeutic concentration in the expanded intravascular volume of pregnancy. In addition, side effects such as nausea, fatigue, and gastrointestinal disturbance may mimic symptoms arising from physiologic changes of pregnancy.

Assessing the risks associated with over-the-counter medications and natural food products is even harder. The *PDR for Nonprescription Drugs, Dietary Supplements, and Herbs*[8] contains little or no information about the reproductive hazards of most of these products. Many agents contain multiple ingredients, both active and inactive, thereby complicating counseling about their risks during pregnancy. Although the recommended dosage is usually low, many product labels do not specify what it should be.

Most drugs enter breast milk

The amount of drug that an infant consumes from breast milk depends on the medication's chemical properties as well as the dosage, frequency, and duration of exposure.[2] Contraindications and cautions are usually either theoretical or based on findings from case reports that often conflict or confuse. In theory, it is safer for the mother to take the medication just after infant feeding or just before the infant's longest sleep period.

The **TABLE** on page 76 also lists the effects of drugs in the breastfed human infant. Again, the information comes from the Reprotox database, access to which requires a subscription. For additional information, try the free LactMed site at http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT.

Nearly all drugs are excreted in breast milk, usually in small amounts (often less than 5% of the weight-adjusted maternal daily dose). The amount of drug or metabolite in an infant's serum also is determined by the volume of breast milk, age of the infant, and other exposures.

Suspect a drug-related effect

A medication may be the cause in any newborn manifesting signs of anemia, hepatitis, hepatotoxicity, hepatorenal dysfunction, and hyperbilirubinemia. This includes breastfed infants. An adverse drug-related effect should also be suspected when an infant exhibits signs of jaundice, floppiness, jitteriness, poor suck, diarrhea, or growth restriction. ■

Prescribing strategies for your pregnant patient

Avoid prescribing multiple medications, if possible, and choose "safe" drugs from among the options in categories that include a number of teratogenic medications, such as anticonvulsants.

Determine the best method to monitor therapy. For example, use a peak flow meter for asthma, a portable blood pressure monitor for hypertension, and so on.

Focus on keeping the patient healthy. The healthiest mother is most likely to deliver the healthiest infant.

Keep the underlying disorder in mind, as well as the drug, when choosing a drug.

Know which drugs are clearly linked to birth defects. These include phenytoin, warfarin, alcohol, methotrexate, diethylstilbestrol, *cis*-retinoic acid, valproic acid, and carbamazepine.

Pay special attention to the first trimester. Too little is known about the first-trimester effects of the vast majority of drugs for them to be considered safe.

References

1. American College of Obstetricians and Gynecologists. Teratology. ACOG Educational Bulletin #236. Washington, DC: ACOG; 1997.
2. Splinter M, Nightingale B, Sawgraves R, Rayburn W. Medication use during pregnancy by women delivering at a tertiary university hospital. South Med J. 1997;90:498–502.
3. Physician's Desk Reference. 61st ed. Montvale, NJ: Medical Economics; 2007.
4. Briggs GG, Freeman RK, Yaffee FJ. Drugs in Pregnancy and Lactation: Reference Guide to Fetal and Neonatal Risk. 7th ed. Baltimore: Williams & Wilkins; 2005.
5. Briggs GG, Freeman RK, Yaffee FJ. ReproTox Database. Vol. 13. No. 1. Bethesda, Md: Reproductive Toxicology Center; 2000.
6. Heinonen OP, Sloan ED, Shapiro S. Birth Defects and Drugs in Pregnancy. Boston: John Wright PSG; 1973.
7. Reproductive Toxicology Center. Bethesda, Md. Available at http://reprotox.org. Accessed Oct. 5, 2007.
8. PDR for Nonprescription Drugs, Dietary Supplements, and Herbs. 28th ed. Montvale, NJ: Medical Economics; 2007.

CONTINUED

***FAST** TRACK*

Suspect a drug-related effect when a newborn shows signs of anemia, hepatitis, hepatotoxicity, hepatorenal dysfunction, and hyperbilirubinemia

Extensive **LISTING**

See the table of drug effects on the pages that follow

How selected drugs affect the human fetus and breastfed infant

DRUG	FIRST-TRIMESTER EFFECTS	EFFECTS DURING SECOND AND THIRD TRIMESTER	SAFETY DURING BREASTFEEDING
ANALGESICS			
Acetaminophen	None known	Hepatotoxicity/nephrotoxicity	Safe
Ibuprofen	Gastroschisis (?)	Closure of ductus	Small amount passed; no other information
Narcotics	None known	Depression, withdrawal	Not recommended if dosing is repetitive
Salicylates	None known	Prolonged pregnancy and labor, hemorrhage, altered hemostasis, intracranial hemorrhage	Use with caution; may have adverse effects in newborn
ANESTHETICS			
General	Anomalies (?), abortion (?)	Depression	
Local	None known	Bradycardia, seizures	
ANTI-ASTHMATICS			
Metaproterenol, salmeterol, albuterol	None known	None known	No information available
Terbutaline	None known	Tachycardia, hypothermia, hypocalcemia, hypoglycemia, and hyperglycemia	Compatible
Theophylline	None known	Jitteriness, tachycardia	May produce jitteriness, poor feeding, vomiting, cardiac arrhythmias
ANTICOAGULANTS			
Warfarin	Nasal hypoplasia, ophthalmic abnormalities, epiphyseal stippling	Hemorrhage, stillbirth	Safe
Heparin, low molecular weight	None known	Hemorrhage (?), stillbirth (?)	Safe
ANTICONVULSANTS			
Barbiturates	Malformations (?)	Bleeding, withdrawal	Not recommended
Carbamazepine, oxcarbazepine	Craniofacial, neural tube (?)	Bleeding, withdrawal, growth restriction	Probably safe
Clonazepam	None known	Withdrawal, depression	Not recommended (potential for apnea, cyanosis, or hypotonia); serum levels should be monitored
Ethosuximide	None known	None known	Compatible
Gabapentin	Unknown	None known	Unknown
Phenytoin*	Craniofacial abnormalities, mental retardation, hypoplasia of phalanges	Hemorrhage, depletion of vitamin K-dependent clotting factors	Probably safe
Primidone	Orofacial clefts	Hemorrhage, depletion of vitamin K-dependent clotting factors, intrauterine growth restriction	May produce significant adverse effects in infants; use with caution
Trimethadione*	Mental retardation, facial dysmorphogenesis, cardiovascular effects	Hemorrhage, depletion of vitamin K-dependent clotting factors, intrauterine growth restriction	No information available
Valproic acid*	Spina bifida, facial dysmorphogenesis	Perinatal distress, behavioral abnormalities	Safe
ANTI-EMETICS			
Diphenhydramine	None known, clefting unlikely	None known	Safe, but may cause drowsiness
Doxylamine (with pyridoxine)	None known	None known	Unknown; probably sedating
Meclizine	None known	Retrolental fibrosis in premature infant	Unknown

* Proven teratogen.
Unknown = no studies to investigate fetal effects; none known = no malformations reported in human studies or no consistent malformations in animal studies; (?) = conflicting information
Source: Reprotox data from humans, last reviewed in 2006.

How selected drugs affect the human fetus and breastfed infant

DRUG	FIRST-TRIMESTER EFFECTS	EFFECTS DURING SECOND AND THIRD TRIMESTER	SAFETY DURING BREASTFEEDING
Metoclopramide	None known	None known	Potential central nervous system effects
Ondansetron	Unknown	Unknown	Unknown
Promethazine	None known	None known	Compatible
Scopolamine	None known	Fetal heart rate changes	Compatible
ANTIBACTERIALS			
Aminoglycosides	None known	Nephrotoxic (?), ototoxic (?)	Depends on level of exposure and renal function of infant
Azithromycin	None known	None known	Compatible
Cephalosporins	None known	None known	Probably compatible
Chloramphenicol	None known	Vascular collapse	Contraindicated
Ciprofloxacin	Toxic to developing cartilage (?)	Toxic to developing cartilage (?)	Compatible
Clindamycin	Unknown	Unknown	Compatible, but potential modification of bowel flora, interference with culture interpretation after fever work-up in infants
Erythromycin	None known	None known	Compatible
Isoniazid	Malformations (?)	Behavioral abnormality	Compatible
Metronidazole	None known	None known	Use with caution because of mutagenic and carcinogenic effects in some species; abstain from breastfeeding for 12–24 hours after single dose
Nitrofurantoin	None known	Hemolysis (?)	Compatible
Penicillins	None known	None known	Compatible
Rifampin	Risk of malformation not greater than in general population	None known	Compatible
Sulfonamides	None known	None known	Generally compatible, but avoid in infants with hyperbilirubinemia, premature infants, and infants with G6PD deficiency
Tetracyclines	None known	Stained deciduous teeth (enamel hypoplasia)	Compatible
Trimethoprim	Cleft palate, micrognathia, limb shortening	Unknown	Compatible
ANTIFUNGALS			
Amphotericin-B	Unknown	Unknown	Unknown
Fluconazole	None known	None known	Compatible
ANTIRETROVIRALS			
Class of drugs in general	None known	None known	Contraindicated (HIV)
ANTIVIRALS			
Acyclovir	None known	None known	Compatible
Interferon	None known	Intrauterine growth restriction (?)	Likely safe
CANCER CHEMOTHERAPY			
Alkylating agents	Abortion, anomalies	Hypoplastic gonads, growth restriction and delay	Contraindicated
Antimetabolites			
• Folic acid analogues (methotrexate)	• Abortion, intrauterine growth restriction, cranial anomalies	• Hypoplastic gonads, growth restriction and delay	• Contraindicated
• Purine analogues	• Same as above	• Same as above, plus transient anemia	• Contraindicated
• Pyrimidine analogues (cytosine arabinoside, 5-fluorouracil)	• Same as above	• Same as above	• Contraindicated

TABLE CONTINUED

How selected drugs affect the human fetus and breastfed infant (continued)

DRUG	FIRST-TRIMESTER EFFECTS	EFFECTS DURING SECOND AND THIRD TRIMESTER	SAFETY DURING BREASTFEEDING
Antibiotics			
• Actinomycin	• Abortion, intrauterine growth restriction, cranial anomalies	• Hypoplastic gonads, growth restriction and delay	• Contraindicated
• Vinca alkaloids (vincristine)	• Same as above	• Same as above	• Contraindicated
CARDIOVASCULAR DRUGS			
ACE inhibitors	None known	Oliguria, skull defects, death	Compatible
Adenosine	None known	No effects on fetal heart rate	Unknown
Beta-sympathomimetics	None known	Tachycardia, hypothermia, hypocalcemia, hypoglycemia, and hyperglycemia	Compatible
Calcium channel blockers	Unknown	None known	Compatible
Digitalis	None known	Lower heart rate	Compatible
Hydralazine	Skeletal defects (?)	Tachycardia, thrombocytopenia, fetal distress	Compatible
Methyldopa	None known	Hemolytic anemia, tremor, hypotension	Compatible
Propranolol, labetalol	Unknown	Lower heart rate, intrauterine growth restriction (?), hypoglycemia, respiratory distress	Compatible; hypoglycemia (?)
Reserpine	None known	Lethargy, respiratory distress	Unknown
COLD AND COUGH PREPARATIONS			
Antihistamines	None known	None known	Reduced milk (?); drowsiness
Cough suppressants	None known	None known	Compatible
Decongestants	None known	None known	Compatible
Dextromethorphan	None known	None known	No information
Expectorants	Fetal goiter (?)	None known	Compatible
Loratadine	Likely none	Likely none	Compatible
DIURETICS			
Furosemide	Unknown	Death from sudden hypoperfusion, electrolyte imbalance	Found to suppress lactation
Thiazides	None known	Thrombocytopenia, hypokalemia, hyperbilirubinemia, hyponatremia	Compatible
FERTILITY DRUGS			
Clomiphene	Meiotic nondisjunction (?), neural tube defects (?)	Unknown	No data available
GASTROINTESTINAL AGENTS			
Bisacodyl	Unknown	Unknown	No reports of adverse effects
Cholestyramine	None known	None known, but fat-soluble vitamins are depleted	Unknown
Colestipol	Unknown	Unknown, but minimal absorption	No data available
Docusate	None known	None known	Compatible
H_2-histamine receptor blockers	None known	Anti-androgen effect (cimetidine)	Compatible
Magnesium hydroxide (Milk of Magnesia)	None known	None known	Compatible
Mineral oil	Decreased maternal vitamin absorption	Decreased maternal vitamin absorption	Compatible
Proton pump inhibitors	None known	None known	Unknown
Sulfasalazine	None known	None known	Caution with ill infants
HORMONES			
Androgens*	Virilization of female fetus	Adrenal suppression	No adverse effects reported

TABLE CONTINUED

How selected drugs affect the human fetus and breastfed infant (continued)

DRUG	FIRST-TRIMESTER EFFECTS	EFFECTS DURING SECOND AND THIRD TRIMESTER	SAFETY DURING BREASTFEEDING
Corticosteroids	Orofacial cleft in animals, not in humans	No adverse effects in humans	No data available
Danazol	Virilization of female fetus (?)	None known	No information available
Estrogens	Cardiovascular anomalies (?)	None known	No reported adverse effects
Progestins	Limb and cardiovascular anomalies (?), VACTERL syndrome (?), masculinization of female fetus (?)	None known	No reported adverse effects
DIABETES CARE			
Glucagon	None known	None known	Compatible
Glyburide	None known	Not thought to cross the placenta in significant amounts; no neonatal hypoglycemia	Compatible
Insulin	None known	None known	Safe
Metformin	None known	Neonatal hypoglycemia	Unknown
Sulfonylureas	Anomalies (?)	Suppressed insulin secretion	Compatible
MIGRAINE REMEDIES			
Ergotamine	None known	May stimulate contractions	Use with caution
Sumatriptan	None known	None known	Compatible
PSYCHOACTIVE DRUGS, ANTIDEPRESSANTS			
Amphetamine	Inconsistent; likely none	Reduced weight	Contraindicated
Benzodiazepines	Facial dysmorphism (?)	Depression, floppy infant, hypothermia, withdrawal	Some concern about central nervous system toxicity with long-term use
Fluoxetine	None known	None known	Symptoms of colic
Hydroxyzine	None known	None known	No information
Lithium	Facial clefts; cardiovascular anomaly	Lithium toxicity (neurologic and hepatic dysfunction)	Contraindicated
Meprobamate	Cardiac anomalies (?), major malformations (?)	None known	Unknown
Phenothiazines	None known	Muscle rigidity, hypothermia, tremor	Unknown
Sedatives	None known	Depression, slow learning	Not recommended
Thalidomide*	Phocomelia in 20% of cases	None known	No information
Tricyclics	None known	None known	Unknown/caution
Zolpiden	Unknown	Withdrawal or floppy infant (?)	Compatible
RADIOLABELED DIAGNOSTICS			
Albumin	None known	None known	No information available
I^{131} (diagnostic)	None known	None known	Not recommended during exposure; may continue 24 hours after exposure
Technetium	None known	None known	Not recommended during exposure; may continue 24 hours after exposure
SMOKING CESSATION			
Bupropion	Likely none	None known	Compatible
Nicotine	Spontaneous abortion (?)	Impaired growth (?)	Consistent with passive smoking
THYROID MEDICATION			
I^{131} (therapeutic)	Goiter, abortion, anomalies	Goiter, airway obstruction, hyperthyroid, mental retardation	Contraindicated
Methimazole	Aplasia cutis (?), goiter	Goiter, airway obstruction, hyperthyroid, mental retardation, aplasia cutis (?)	Compatible, but monitor fetal thyroid function

TABLE CONTINUED

How selected drugs affect the human fetus and breastfed infant (continued)

DRUG	FIRST-TRIMESTER EFFECTS	EFFECTS DURING SECOND AND THIRD TRIMESTER	SAFETY DURING BREASTFEEDING
Propylthiouracil	Goiter	Same as above	Safe, but monitor baby's thyroid status
Thyroid USP	None known	None known	Compatible
Thyroxine	None known	None known	Compatible
TOCOLYTICS			
Beta-sympathomimetics	None known	Tachycardia, hypothermia, hypocalcemia, hypoglycemia, hyperglycemia	—
Indomethacin	None known	Oligohydramnios (>48 hours of use)	—
Magnesium sulfate	None known	Hypermagnesemia, respiratory depression	—
Nifedipine	Unknown	None known	—
VACCINATIONS			
Influenza	None known	Passive immunization	Compatible
Pneumovaccine	None known	Passive immunization	Compatible
Tetanus toxoid	None known	Passive immunization	Compatible
VAGINAL PREPARATIONS			
Antifungal agents	None known	None known	Compatible
Podophyllin	Mutagenesis (?)	Central nervous system effects (?)	Contraindicated
VITAMINS (high dose)			
A	Urogenital and craniofacial anomalies (?)	None known	No data available
C	None known	Scurvy after delivery	Compatible
D	Supravalvular aortic stenosis (?)	None known	Compatible
E	Unknown	None known	Compatible
K	Unknown	Hemorrhage, if deficiency	Compatible
"STREET" DRUGS			
Cocaine	Placental abruption, vascular disruption, urinary tract anomalies	Withdrawal, placental abruption, vascular disruption, growth restriction	Contraindicated
Heroin	None known	Depression, withdrawal, growth restriction	Contraindicated
LSD	None known	Withdrawal, behavioral effects	Contraindicated
Marijuana	None known	Behavioral effects, growth restriction	Contraindicated
Methadone	None known	Withdrawal, growth restriction	Contraindicated
Methamphetamine	None known	Withdrawal, growth restriction	Contraindicated
Pentazocine	None known	Withdrawal, growth restriction	Contraindicated
Phencyclidine	None known	Withdrawal, neurobehavioral effects, growth restriction	Contraindicated
OTHER DRUGS			
Azathioprine	Abortion	Anemia, thrombocytopenia, lymphopenia, growth retardation	Not recommended
Bromocriptine	None known	None known	Compatible
Caffeine	Anomalies (?) in high doses, abortion (?)	Jitteriness	Not recommended
Immune gamma globulin	None known	None known	Compatible
Isotretinoin*	Central nervous system, cardiac, facial anomalies	Stillbirth, mental retardation (?)	Contraindicated
Misoprostol	Abortion; variety of anomalies (cranium, limb, oral cleft); Mobius sequence	None with low dose for cervical ripening; placental abruption	Contraindicated, especially if diarrhea occurs
Spermicides	None known	None known	No information