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Baby Safe

Which drugs are safe during pregnancy?

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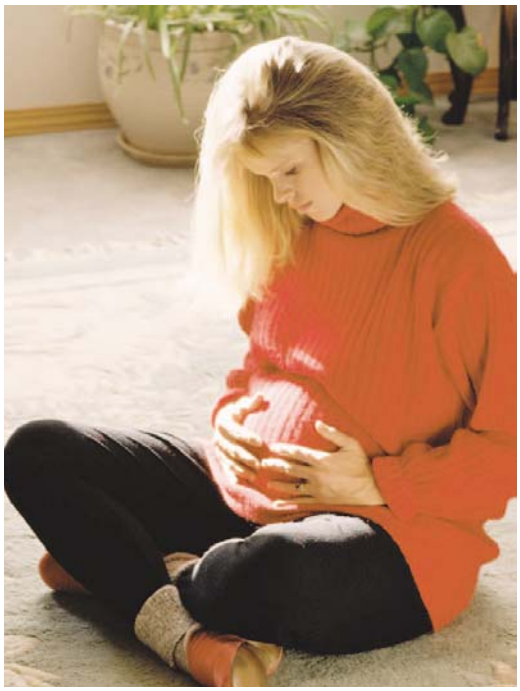

In this article:

Contemplating the prescription or recommendation of a medication for a pregnant woman can be a stressful undertaking for a physician. Most physicians are rightfully wary about the potential harmful effects of prescription or over-the-counter (OTC) medications on the developing fetus. These fears are founded on occasional events in our history during which the use of medications previously thought to be safe for use in pregnancy, such as thalidomide, led to the birth of large numbers of malformed children. Contrary to old beliefs, the placenta does not block transmission of most drugs to the fetus. In fact, almost all medications that are absorbed orally, transdermally, or transbronchially reach the fetal circulation in significant concentrations. In addition, many drugs are still released with little or no experience regarding their use and safety in human pregnancy. On the other hand, physicians must also be wary of "error by omission" and avoid under treatment of pregnant women with serious medical conditions. The fetus is a "passenger" who is reliant on maternal health for its well-being.

How many pregnant women take drugs?

Pregnant women are worried about medication use during pregnancy and need good advice. A recent study noted that women exposed to non-teratogenic medications in early pregnancy estimated the risk of a major fetal abnormality at about 25%.[1] Pregnant women may avoid necessary medications out of fear or poor advice.

In spite of these concerns, data suggest that medication use is common in pregnancy. Recent studies have reported the use of prescription or OTC medication use in 66% to 90% of pregnant women.[2,3] A review from France, which included maternal use of vitamins and supplements, reported intake of at least one "medication" by 99% of French pregnant women, with a mean of 13.6 medications per woman![4] Given this widespread use of medication during pregnancy, it is essential

Drugs and Pregnancy

Table 1
The cause of major congenital malformations in newborns

65%	Multifactorial/unknown cause
25%	Genetic
4%	Maternal condition
3%	Maternal infection
1% to 2%	Mechanical deformations
< 1%	Drugs, chemicals, radiation, hyperthermia

that physicians be equipped with the knowledge and resources to appropriately counsel pregnant women on these issues.

What is teratogenesis?

Teratogenesis is defined as structural or functional dysgenesis of the fetal organs. While it is most commonly thought of as a toxic exposure during early organogenesis leading to structural abnormalities in the developing fetus, teratogenesis may also manifest itself as:

- Pregnancy loss (miscarriage, intrauterine fetal death, stillbirth);
- Intrauterine growth retardation (IUGR);
- Carcinogenesis; and
- Developmental abnormalities.

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Practice Pointer

It is important to point out, when counselling pregnant women on medication use, that < 1% of congenital malformations in infants are due to exposure to medication while in the womb.

It is true that early organogenesis is the period of highest sensitivity to teratogens, and the period of exposure most likely to lead to dysmorphic changes in the fetus. Teratogenic exposures later in fetal development are more likely to cause functional abnormalities of the fetus.

The overall incidence of major congenital malformations among live-born infants is 2% to 3% in the general population. The etiology of these malformations is outlined in Table 1.

Teratogenic effects of medication exposures are an uncommon cause of major congenital malformations. Even in an infant born with a congenital malformation who was exposed to a medication during pregnancy, it is unlikely the malformation is due to the medication exposure (except with known teratogens and characteristic anomalies). This is a very important point to underline when counselling women about medication exposures during pregnancy.

Why is pregnancy an issue?

The physiologic changes of pregnancy have important effects on the handling of medications by the body, which may affect the dose, frequency or route of administration of a given medication when given to a pregnant woman.[5]

***Absorption*:** High levels of progesterone, a smooth muscle relaxant, lead to delayed gastric

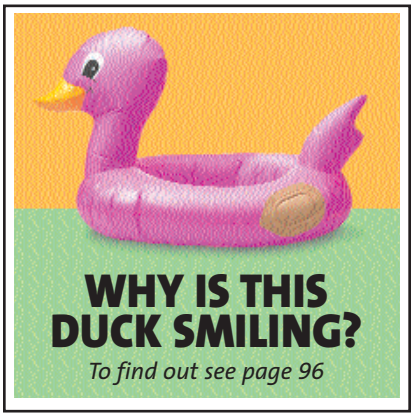
Table 2

Comparison of FDA drug classification and TERIS rating systems

FDA classification	TERIS rating
Category A Controlled studies in women fail to demonstrate a risk to the fetus and the possibility of fetal harm appears remote.	Teratogenic risk "none"
Category B Either animal reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women, or animal reproduction studies have shown an adverse effect that was not confirmed in controlled studies in women.	Teratogenic risk "unlikely"
Category C Either studies in animals have revealed adverse effects on the fetus and there are no controlled studies in women, or studies in women and animals are not available. Drugs should be given only if the potential benefits justify the potential risk to the fetus.	Teratogenic risk "minimal" or "small"
Category D There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk.	Teratogenic risk "moderate"
Category X Studies in animals or human beings have demonstrated fetal abnormalities. The risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.	Teratogenic risk "high"

emptying and reduced small intestine motility during pregnancy. This action may cause reduced or delayed absorption of orally administered medications. Nausea and vomiting in pregnancy may prevent absorption of medications. Conversely, the increased alveolar ventilation and cardiac output seen in normal pregnancy may lead to enhanced alveolar and intramuscular drug absorption.

Distribution: The maternal blood volume increases by half during pregnancy, and extracellular and adipose tissue volumes also expand. This change leads to an increased volume of distribution for many medications. Pregnancy is also characterised by reduced albumin and serum protein levels. These changes lead to reduced total drug levels of some protein-bound medications while free drug levels may increase, decrease, or remain unchanged. Free drug levels should therefore be measured directly whenever possible during pregnancy.



Metabolism and elimination: Some hepatic enzymes are induced during pregnancy, leading to enhanced drug clearance (*i.e.,* phenytoin), whereas other hepatic enzymes are inhibited, causing reduced clearance of other medications (*i.e.,* theophylline). Renal blood flow is markedly increased during pregnancy and the glomerular filtration rate increases by about 50%, leading to enhanced renal clearance of many medications.

Table 3
Clinical resources on medication use during pregnancy

There are several excellent textbooks on medication use during pregnancy, including:

Freeman RK, Yaffe JS, Briggs GG: *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk*. Lipincott, Williams & Wilkins, New York, 2001.

Koren G: Maternal-Fetal Toxicology: A Clinician's Guide. Marcel Dekker, New York, 2001.

Some useful up-to-date articles are:

Koren G, Pastuszak A, Ito S: Drug Therapy: Drugs in Pregnancy. New Engl J Med 1998; 338(16):1128-37.

Wood A, Ito S: Drug Therapy for Breast-Feeding Women. New Engl J Med 2000; 343:118-26.

Bailliere's Best Practice and Research in Clinical Obstetrics and Gynaecology. Vol. 15, No. 6, December 2001. A comprehensive series of articles on drugs in pregnancy by organ system.

To obtain immediate evidence-based information at the point of care, simply access Medline in your office or hospital. Search using the terms "pregnancy [Mesh]" AND [the name of the drug you are researching]. If there are too many results to quickly sort through, it may be useful to limit your search to "clinical trials" or "reviews." If you have online full text access, it may even be possible to quickly obtain a full article addressing your query.

It is also useful to check Motherisk, the Canadian Teratogen Information Service, a counselling and clinical resource for patients and physicians about teratogenesis. They are found at www.motherisk.org.

In difficult cases, particularly following a significant or multiple drug exposure in pregnancy, it may be useful to refer your patient for formal teratogenesis counselling. This service is available in many areas, often through medical genetics departments, and the counsellors are able to provide patients with detailed information and discuss all available options with them.

How to know what is safe

Unfortunately, rigorous studies on humans about medication use in pregnancy are rarely done because they are difficult and expensive. At present, most precautionary information relates only to anatomic defects noted in newborns. Some other potential toxicities, such as developmental or behavioural effects, may not be apparent for years and are seldom looked for. Studies on drug safety in pregnancy are made even more difficult by the fact that even the most teratogenic agents are safe for the majority of pregnancies, and therefore, large numbers of exposures are necessary to evaluate for a harmful effect. In fact, it is estimated that about 220 fetal exposures and a similar number of control pregnancies, would be needed to evaluate for an increased relative risk of 2.5 for a malformation occurring in 3% of the general population.[6]

Animal studies: Since most new medications have minimal data on safety in human pregnancy at the time of their release, data from animal studies is typically used to form initial guidelines. Unfortunately, it is apparent that animal data cannot always be confidently extrapolated to humans. There is a considerable variability between species, and even between strains of a species, as to the effects of a medication on a developing fetus. While almost all human teratogens have some teratogenic effect in animals, these effects are certainly not uniform across species and may not be noted prior to release of the medication for human use.

Another limitation is that subtler behavioural and intellectual effects of medications are difficult to recognise in animals.

Case reports and case registries: Case reports are the usual starting point for concerns about potential harmful effects of a medication. They are an essential first step in identifying harmful drug effects, but may raise false concerns about medication effects due to publication bias (as only bad outcomes are usually reported). Case reports and case series are also tainted by recall bias, as women who have a difficult pregnancy outcome are more likely to recall medication use during pregnancy.

Population studies: These studies typically involve retrospective comparisons between infants of mothers exposed to a medication and those who were not. While there is less potential for bias by this methodology, a major concern is that these studies do not examine why the medication was administered. "Medication effects" observed in this manner may reflect the reason the mother was on the medication, such as a serious underlying medical condition, rather than an effect of the medication itself.

Clinical trials: Evaluation of fetal effects among women randomised to various medications during pregnancy would avoid much of the potential bias and confusion of the other study methods. Unfortunately, randomised treatment trials involving pregnant women are uncommon and often involve a small numbers of subjects.

What are the drug risk classifications?

The Food and Drug Administration (FDA) drug classification system is widely available and used to assess the risk of medication use in pregnancy for many drugs. The system ranks medications based on the amount of data available about safety during pregnancy in animal and human models, and the degree of fetal risk identified. The scale ranges from A to D, plus X (Table 2).

Unfortunately, the FDA classification is flawed as it implies a gradient of risk for medication use in pregnancy, when in reality it is often a gradient of evidence. For instance, newer drugs (without a

Table 4
Preferred drugs for use in pregnancy by selected indication

Indication	Medication
Asthma	Inhaled beta-agonists: Short-acting, safe, very limited human data on long-acting beta-2 agonists (salmeterol) Inhaled corticosteroids: Minimal systemic absorption, only 10% of maternal dose reaches fetus. Systemic corticosteroids: Small increased risk of cleft/lip palate in first trimester exposure, should be used for significant exacerbations. Cromolyn: Very reassuring safety data.
Commom colds	Acetaminophen Pseudoephedrine: Preferred over ephedrime or penylephrine, possible association with gastroschisis. Ipratropium or cromolyn nasal sprays: Mildly effective, reassuring safety data. First generation antihistamines (chlorpheniramine, brompheniramine, diphenhydramine): sedating, but minimal human pregnancy data on second generation agents.
Depression	Tricyclic antidepressants: Extensive human pregnancy exposure, not teratogenic, normal neurodevelopment in preschool children exposed to TCAs or fluoxetine.[9] Fluoxetine: Most human safety data among SSRIs, neurodevelopment data as above.
Headaches	Acetaminophen Metoclopramide: Intrinsic headache reducing-properties, effective for nausea of migraine, combine with other analgesics. Codeine, other narcotics: Avoid prolonged use near-term, risk of neonatal depression or withdrawal, frequent use may lead to analgesic-withdrawal headaches. Caffeine: Safe adjunct to simple analgesics in low-moderate doses.
Hypertension	Alpha-methyldopa: Best safety data including normal childhood development. Labetalol: Widely used, safe, used IV may cause fetal/neonatal bradychardia. Nifedipine: Safe and well-tolerated, may cause hypotension when administered with MgSO4.
Nausea & vomiting	Diclectin: Only drug licensed for treatment of nausea & vomiting during pregnancy in Canada. Metoclopramide: Not teratogenic, caution regarding risk of dystonic reactions, particularly if combined with other dopamine-blocking agents. Prochlorperazine: See metoclopramide above.
Pneumonia	Amoxicillin Erythromycin: Avoid use of estolate ester, risk of sub-clinical hepatoxicity. Azithromycin: More expensive than erythromycin, widespread use, but only small amount of human pregnancy data.

TCA: tetracyclic antidepressant
SSRIs: selective serotonin reuptake inhibitors

proven record of safety or experience in human pregnancy) are typically rated fairly high (Class B or C), whereas older medications (with controlled safety data) are typically rated lower. The system also implies that drugs within a class are of similar teratogenic risk when this is often incorrect.

Table 5
Drugs to avoid during pregnancy by selected indication

Indication	Medication
Asthma	Leukotriene inhibitors: Minimal human pregnancy data, generally not essential for asthma control.
Common colds	Intranasal decongestants: Vasoactive, risk of adverse effects on uterine blood flow in setting of overuse, inflammed nasal mucosa or if placentation marginal. No clear teratogenic effect but most agents are in need of further study. ASA/NSAIDs: Not teratogenic but toxic effects on the fetal kidneys may lead to reversible decreases in amniotic fluid volume. Risk of premature closure of the ductus arteriosis in the third trimester. Cough supressants: Minimally effective, many syrups contain alcohol. Narcotic use near term may cause neonatal depression, frequent maternal use could lead to neonatal withdrawal.
Depression	New SSRIs: No apparent increase in malformation rates, but no data on neurodevelopment (data available for TCAs and fluoxetine).[10]
Headaches	NSAIDs: Same as above. Ergotamines: Vasoactive, may decrease placental blood flow. Triptans: Vasoactive, preliminary human data reassuring but limited. Anticonvulsants (prophylaxis): Teratogens, other options generally effective.
Hypertension	Atenolol: Risk of intrauterine growth restriction, neonatal bradychardia and hypoglycemia. ACE inhibitors and angiotensin receptor blockers: Toxic to developing kidneys in second and third trimester.
Pneumonia	Quinolones: Risk of arthropathy in animal model.[11] Tetracyclines: Staining of bone and teeth. Clarithromycin: Teratogenic in some animals.

ASA: acetylsalicylic acid
SSRIs: selective serotonin reuptake inhibitors
ACE: angiotensin-converting enzyme
NSAIDs: nonsteroidal anti-inflammatory drugs
TCA: tetracyclic antidepressant

Lastly, the FDA categories are based largely on unpublished data from pre-marketing animal studies, and are assigned through a structured regulatory process and negotiations with the drugs' sponsors. In contrast, the Tetratogen Information System (TERIS) ratings system is a drug safety evaluation tool in which medication ratings are determined by a consensus of opinion among an independent group of experienced clinical teratologists, based on data from published human studies. Teratogenic risk is rated as "none," "unlikely," "minimal," "small," "moderate," "high," or "undetermined" (Table 2). Unfortunately, a recent study showed that 91.2% of new drugs approved by the FDA and released between 1980 and 2000 still have "undetermined" teratogenic risk according to TERIS.[7] There is also substantial discordance between TERIS and FDA category rankings for some drugs. For other resources concerning medication use during pregnancy, consult Table 3.

Drugs and Pregnancy

How to talk to your patients

In discussing potential medication use in pregnancy it is important to work with the patient to make a judgment, based on both the available data and the indication of a particular agent. By working with the patient, physicians can determine whether the available information justifies or warrants the risk inherent in the use of the medication in pregnancy. One suggested guideline is to use the "four questions approach."

Question 1: Is the medication necessary or is the symptom to be treated self-limited and/or amenable to nonpharmacologic management?

Question 2: If the medication is **not** administered, what are the possible outcomes for the mother and fetus? Recognise here that fetal well-being is dependant on maternal health.

Question 3: What data is available on the safety of this medication in pregnancy and is there a similar drug with better safety data available that could be used instead? Physicians should remain particularly cautious about newer agents, as many fetal toxicities have been identified several years after the release of new medications.

Question 4: How is the patient's (and the provider's) understanding and value system affecting decisions about the use of this medication during pregnancy? Remember that women usually overestimate the teratogenic risk of medication exposures during pregnancy and therefore, may avoid prescriptions or exhibit non-compliance with recommended therapy.

Take-home message

Pregnant women are frequently exposed to OTC and prescription medications. They are worried about these exposures and often need reassurance. More importantly, they need evidence-based advice about potential risks of medication exposures and guidance regarding which medications are safest for use in pregnancy. Unfounded fear may lead pregnant women to withhold needed medications, thereby jeopardising their health (and also the health of the fetus). When possible, "symptoms" should be treated non-pharmacologically during pregnancy. When pharmacologic treatment is clearly indicated, the "safest" effective therapy should be chosen. Physicians should seek to counsel patients with the best evidence-based information available.

What are the treatment options?

Discussion of all possible treatment options for all conditions is beyond the scope of this article. Recommended medications for specific common medical conditions, and those to avoid, are outlined briefly in Tables 4 and 5 respectively. CME

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Drugs and Pregnancy