Over-the-Counter Medications in Pregnancy

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Pregnant women commonly use over-the-counter medications. Although most over-the-counter drugs have an excellent safety profile, some have unproven safety or are known to adversely affect the fetus. The safety profile of some medications may change according to the gestational age of the fetus. Because an estimated 10 percent or more of birth defects result from maternal drug exposure, the U.S. Food and Drug Administration has assigned a risk category to each drug. Many drugs have not been evaluated in controlled trials and probably will not be because of ethical considerations. Of the commonly used over-the-counter medications, acetaminophen, chlorpheniramine, kaolin and pectin preparations, and most antacids have a good safety record. Other drugs, such as histamine H_2-receptor blockers, pseudoephedrine, and atropine/diphenoxylate should be used with caution. If use of smoking cessation products is desired, the intermediate-release preparations minimize the amount of nicotine while maintaining efficacy. With all over-the-counter medications used during pregnancy, the benefit of the drug should outweigh the risk to the fetus. (Am Fam Physician 2003;67:2517-24. Copyright© 2003 American Academy of Family Physicians.)

See editorial on page 2476.

A common concern about the care of pregnant women involves the use of over-the-counter (OTC) medications. Nonprescription drugs account for about 60 percent of medications used in the United States, and more than 80 percent of pregnant women take OTC or prescription drugs during pregnancy.[1,2] Of the new OTC drugs marketed between 1975 and 1994, 30 percent were previously prescription medications.

It is estimated that up to 60 percent of patients consult a health care professional when selecting an OTC product.[1] Many physicians are cautious in their OTC recommendations because of concern about possible adverse effects on a developing fetus. At least 10 percent of birth defects are thought to result from maternal drug exposures.[3] The issue is complicated by the fact that the safety and efficacy profile of a given medicine often changes during the course of a normal pregnancy.[2]

The medical community's approach to the use of medications during pregnancy has changed dramatically since the early 1970s, largely because of the problems with thalidomide and diethylstilbestrol. Consequently, extensive testing is required before a drug can be labeled for use during pregnancy.

Since 1975, the U.S. Food and Drug Administration (FDA) has assigned pregnancy risk factors to all drugs used in the United States *(Table 1)*.[4] Unfortunately, many drugs have not been adequately researched during pregnancy and, because of ethical considerations, probably will not be in the future.

Pain Medications

The most commonly used OTC pain medications are aspirin, acetaminophen (Tylenol), and nonsteroidal anti-inflammatory drugs (NSAIDs), including ibuprofen (Advil, Motrin), ketoprofen (Orudis), and naproxen (Aleve). The safety of these medications during pregnancy is outlined in *Table 2*.[5,6]

Acetaminophen is widely used during pregnancy. Although there is no known association with teratogenicity, few clinical

TABLE 1
FDA Classification of Drug Safety During Pregnancy

Category A	Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (and there is no evidence of risk in later trimesters), and the possibility of fetal harm appears remote.
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 (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of risk in later trimesters).
Category C	Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) 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 benefit justifies the potential risk to the fetus.
Category D	There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease in which safer drugs cannot be used or are ineffective).
Category X	Studies in animals or human beings have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience, and 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.

FDA = U.S. Food and Drug Administration.

Information from Briggs GG, Freeman RK, Yaffe SJ, eds. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. 5th ed. Baltimore: Williams & Wilkins, 1998:577-8,627-8.

TABLE 2
Use of OTC Pain Medications in Pregnancy

Drug name	*FDA pregnancy risk classification by trimester (1st/2nd/3rd)*	*Drug class*	*Crosses placenta?*	*Use in pregnancy*
Acetaminophen (Tylenol)	B/B/B	Non-narcotic analgesic/antipyretic	Yes	Pain reliever of choice
Aspirin	D/D/D	Salicylate analgesic/antipyretic	Yes	Not recommended except for specific indications*
Ibuprofen (Advil, Motrin)	B/B/D	NSAID analgesic	Yes	Use with caution; avoid in third trimester†
Ketoprofen (Orudis)	B/B/D	NSAID analgesic	Yes	Use with caution; avoid in third trimester†
Naproxen (Aleve)	B/B/D	NSAID analgesic	Yes	Use with caution; avoid in third trimester†

OTC = over-the-counter; FDA = U.S. Food and Drug Administration; NSAID = nonsteroidal anti-inflammatory drug.

**—Associated with increased perinatal mortality, neonatal hemorrhage, decreased birth weight, prolonged gestation and labor, and possible teratogenicity.[5]*

†—*Associated with oligohydramnios, premature closure of the fetal ductus arteriosus with subsequent persistent pulmonary hypertension of the newborn, fetal nephrotoxicity, and periventricular hemorrhage.[6]*

Information from Collins E. Maternal and fetal effects of acetaminophen and salicylates in pregnancy. Obstet Gynecol 1981;58(5 Suppl):57S-62S, and Macones GA, Marder SJ, Clothier B, Stamilio DM. The controversy surrounding indomethacin for tocolysis. Am J Obstet Gynecol 2001;184:264-72.

TABLE 3
OTC Decongestants, Expectorants, and Nonselective Antihistamines in Pregnancy

Drug name	*FDA pregnancy risk classification*	*Drug class*	*Crosses placenta?*	*Use in pregnancy*
Chlorpheniramine (Chlor-Trimeton)	B	Antihistamine	Not known	Antihistamine of choice
Pseudoephedrine hydrochloride (Novafed)	B	Sympathomimetic decongestant	Not known	Oral decongestant of choice,[10] possible association with gastroschisis[9]
Guaifenesin (Humibid L.A.)	C	Expectorant	Not known	May be unsafe in first trimester*
Dextromethorphan hydrobromide (Benylin DM)	C	Non-narcotic antitussive	Not known	Appears to be safe in pregnancy
Diphenhydramine (Benadryl)	B	Antihistamine/ antiemetic	Yes	Possible oxytocin-like effects at high dosages
Clemastine fumarate (Tavist)	B	Antihistamine	Not known	Unknown safety profile

OTC = over-the-counter; FDA = U.S. Food and Drug Administration.

**—Possible increased risk of neural tube defects.*

Information from Werler MM, Mitchell AA, Shapiro S. First trimester maternal medication use in relation to gastroschisis. Teratology 1992;45:361-7, and The use of newer asthma and allergy medications during pregnancy. The American College of Obstetricians and Gynecologists (ACOG) and the American College of Allergy, Asthma, and Immunology (ACAAI). Ann Allergy Asthma Immunol 2000;84:475-80.

data are available to support the lack of association.[5] The extensive use of acetaminophen in pregnancy combined with the paucity of documented adverse effects have served to validate the selection of this medication as the pain reliever of choice during pregnancy.

Salicylates have been associated with increased perinatal mortality, neonatal hemorrhage, decreased birth weight, prolonged gestation and labor, and possible birth defects.[5] However, one study[7] found that low-dose aspirin is not associated with an increased risk of abruptio placentae or increased rates of perinatal mortality. Pregnant women should use salicylates only under the guidance of a medical professional.

Indomethacin (Indocin) is the most studied NSAID that is commonly used during pregnancy. Physicians may employ indomethacin during pregnancy to treat pain from degenerating leiomyomata, or as a tocolytic agent. Unfortunately, indomethacin use during pregnancy may result in oligohydramnios, premature closure of the fetal ductus arteriosus with subsequent persistent pulmonary hypertension of the newborn, fetal nephrotoxicity, and periventricular hemorrhage.[6]

Other NSAIDs, such as ibuprofen, have been studied less often during pregnancy. However, an analysis[8] of 50 pregnant patients who overdosed on ibuprofen revealed no evidence of fetal abnormalities. Because of the possibility of adverse effects of NSAIDs on the fetus, it is our opinion that these medications should be used sparingly during pregnancy.

Decongestants, Expectorants, and Antihistamines

Women commonly use cold medications during pregnancy. These medications, like most of the other OTC drugs, have not been studied well in pregnancy *(Table 3)*.[9,10] As a result, some physicians are disinclined to rec-

Because of potential adverse effects on the fetus from use of salicylates and nonsteroidal anti-inflammatory drugs, acetaminophen is the preferred pain reliever during pregnancy.

ommend any treatment for the common cold. The most commonly used cold medications include decongestants and expectorants such as pseudoephedrine (Novafed), guaifenesin (Humibid L.A.), and dextromethorphan (Benylin DM), and the antihistamines diphenhydramine (Benadryl), chlorpheniramine (Chlor-Trimeton), and clemastine fumarate (Tavist).

The use of vasoconstrictive agents such as pseudoephedrine may activate alpha-adrenergic receptors, elevating blood pressure or causing vasoconstriction in the uterine arteries, and potentially adversely affecting blood flow to the fetus. This process could explain the reported association between the use of pseudoephedrine in the first trimester and the development of gastroschisis.[9] This theory is debatable; evidence suggests that this effect is negligible at typical dosages.[11]

Diphenhydramine is widely used in pregnancy as a sedative, an antihistamine, and an anti-nausea drug, although few data confirm its safety during pregnancy. The drug has been shown to have oxytocin-like effects, especially in high dosages.[12] In addition, adverse drug interactions that do not occur in nonpregnant patients may occur in pregnant patients. For example, one study[13] showed a significant increase in fetal morbidity when diphenhydramine was taken in combination with temazepam (Restoril).

In 2000, the American College of Obstetricians and Gynecologists and the American College of Allergy, Asthma, and Immunology released a position statement[10] regarding the use of asthma and allergy medications, including antihistamines and oral decongestants. Chlorpheniramine and tripelennamine (PBZ) were recommended as antihistamines of choice. Pseudoephedrine was recommended as the oral decongestant of choice, based on animal studies and a large prospective human experience with the drug during pregnancy. However, because pseudoephedrine may be associated with gastroschisis and because other choices are available, it may be prudent to avoid using this medication during the first trimester unless the benefit outweighs the risk.

Dextromethorphan has been associated with birth defects in chicken embryos. The Collaborative Perinatal Project[14] monitored 50,282 pregnant women, 300 of whom were exposed to dextromethorphan in the first trimester. Birth defects did not increase above the baseline rate. Another study[15] of 59 women who had used dextromethorphan in the first trimester documented one malformation. Thus, sufficient evidence indicates a lack of adverse effects of dextromethorphan use during pregnancy.

When used during the first trimester in the presence of a febrile illness, guaifenesin has been associated with an increased risk of neural tube defects.[16] It is unclear whether this increased risk derives from the medication use, the illness, or both.

A MEDLINE search using the keywords "clemastine," "clemastine and pregnancy," and "clemastine and teratogen" found no studies addressing the safety or potential teratogenicity of clemastine fumarate in pregnancy.

Antidiarrheal Agents

The most commonly used antidiarrheal medications include kaolin and pectin preparations (such as Kaopectate), bismuth subsalicylate (Pepto Bismol), loperamide (Imodium),[4] and atropine/diphenoxylate (Lomotil). The safety of the various agents is outlined in

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Table 4.[4] Kaolin and pectin preparations are not absorbed. A possible association has been identified between the ingestion of clays containing kaolin and the development of iron deficiency anemia.[17] Use of bismuth subsalicylate can result in absorption of salicylate and should be avoided in pregnancy. Loperamide has not been found to be teratogenic in animals. However, at least one study[4] involving first-trimester exposure in humans showed a possible increase in fetal cardiac malformation. Atropine/diphenoxylate has been found to be teratogenic in animals; however, there is insufficient evidence of teratogenicity in human pregnancy.[18]

Because kaolin and pectin preparations are not absorbed, they are preferred over bismuth subsalicylate and atropine/diphenoxylate products during pregnancy.

Antacid Preparations

Several antacids are available in OTC forms, including preparations that contain alginic acid, aluminum, magnesium, and calcium. All of these preparations generally are regarded as safe in pregnancy *(Table 5)*. There have been sporadic reports of fetal maldevelopment and injury associated with prolonged use of high dosages of aluminum-containing antacids during pregnancy.[19] Data are insufficient to determine if these associations are significant. Magnesium compounds contain magnesium sulfate, a known tocolytic agent. Despite the minimal magnesium absorption that occurs with antacid ingestion, some clinicians prefer the use of calcium-containing preparations. Simethicone (Mylanta Gas) is not absorbed.

The histamine H_2-receptor blockers are effective in treating symptoms of heartburn and gastroesophageal reflux disease in pregnancy,[20] but these drugs readily cross the placenta.[21] Their use is recommended in pregnant women whose symptoms cannot be adequately controlled with lifestyle modification and antacids.[22]

The most studied H_2 blockers are cimetidine (Tagamet) and ranitidine (Zantac). Stud-

TABLE 4
OTC Antidiarrheal Medications in Pregnancy

Drug name	*FDA pregnancy risk classification by trimester (1st/2nd/3rd)*	*Drug class*	*Crosses placenta?*	*Use in pregnancy*
Kaolin and pectin (Kaopectate)	B/B/B	Antidiarrheal	No	Antidiarrheal of choice (not absorbed)
Bismuth subsalicylate (Pepto Bismol)	C/C/D	Antidiarrheal	Yes	Not recommended (salicylate absorption)
Loperamide (Imodium)	B/B/B	Antidiarrheal	Not known	Probably safe*
Atropine/diphenoxylate (Lomotil)	C/C/C	Antidiarrheal	Not known	Not recommended (adverse animal studies)

OTC = over-the-counter; FDA = U.S. Food and Drug Administration.

**—Possible increase in fetal cardiac malformation with first-trimester use.[4]*

Information from Briggs GG, Freeman RK, Yaffe SJ, eds. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. 5th ed. Baltimore: Williams & Wilkins, 1998:577-8,627-8.

TABLE 5
OTC Antacids, Simethicone, and H_2-Receptor Selective Antihistamines in Pregnancy

Drug name	*FDA pregnancy risk classification*	*Drug class*	*Crosses placenta?*	*Use in pregnancy*
Aluminum hydroxide/ magnesium hydroxide (Maalox)*	B	Antacid	Not known	Generally regarded as safe
Calcium carbonate (Tums)	C	Antacid	Not known	Generally regarded as safe
Simethicone (Mylanta Gas)	C	Antiflatulent	No	Generally regarded as safe
Cimetidine (Tagamet)	B	Antihistamine	Yes	Preferred after antacids; generally regarded as safe
Ranitidine (Zantac)	B	Antihistamine	Yes	Preferred after antacids; generally regarded as safe
Nizatidine (Axid)	C	Antihistamine	Yes	Not recommended (adverse animal studies)
Famotidine (Pepcid)	B	Antihistamine	Yes	Probably safe, data needed

OTC = over-the-counter; FDA = U.S. Food and Drug Administration.

—Contains magnesium sulfate.

ies of these agents generally have shown significant improvement of symptoms with no significant adverse effects. Animal studies also fail to show an increased fetal risk with the use of these medications in pregnancy, the notable exception being nizatidine (Axid).[22]

Nizatidine has been associated with an increased risk of fetal death, spontaneous abortion, and decreased fetal weight in rabbits.[22] These studies used the common prescription-strength doses. The OTC doses are one half of the prescription strength. Although studies have indicated that there is probably no increased risk of fetal morbidity or mortality, few studies have evaluated first-trimester use of H_2 blockers. Therefore, most investigators recommend avoiding these drugs in the first trimester.[22,23]

Antifungals

The most common antifungal medications available as OTC drugs include the imidazole agents clotrimazole (Mycelex), butoconazole (Femstat), miconazole (Monistat), and tioconazole (Vagistat-1). *Table 6*[23,24] describes the safety of various OTC antifungal agents in pregnancy. One of the largest studies[24] to date investigated the teratogenicity of clotrimazole. The population-based, case-control study of 18,515 case pregnancies and 32,804 control pregnancies did not show an association between fetal malformations and the use of clotrimazole.

Several small trials have indicated that butoconazole and miconazole are likely to be safe during the second and third trimesters. Insufficient data are available regarding the safety of tioconazole in pregnancy.[25]

Many clinicians use oral fluconazole (Diflucan) to treat vulvovaginal candidiasis. A study[26] of 226 women exposed to fluconazole during the first trimester of pregnancy revealed that patients taking fluconazole were no more likely than unexposed control patients to experience miscarriage, stillbirth, or congenital anomalies. Ketoconazole (Nizoral), flucytosine (Ancobon), and griseofulvin (Grisactin) may be teratogenic or embryotoxic in animals.[25]

The Centers for Disease Control and Prevention recommends using only topical vaginal antifungal agents (including butoconazole, clotrimazole, miconazole, and the prescription medications terconazole [Terazol] and nystatin [Mycostatin]) in pregnancy.[27] Because imidazole agents are likely to be safe when used during pregnancy and may be more effective than nystatin,[28] they should be considered as first-line therapy in pregnant patients.

Smoking Deterrents

Nicotine replacement therapy presents an interesting clinical dilemma. Researchers believe that nicotine and its metabolic byproduct, cotinine, are harmful to the developing fetus because smoking is known to cause harmful fetal effects, including intrauterine growth retardation, premature birth, hyperviscosity in the newborn, spontaneous abortion, fetal neurotoxicity, and pulmonary defects, and an increased risk of sudden infant death syndrome.[29] For these reasons, the FDA classifies nicotine as a Pregnancy Category D drug. The primary mechanism of these deleterious effects is believed to be uteroplacental insufficiency. Reduced perfusion of oxygenated blood through the placenta at various stages of development may cause the various manifestations of fetal maldevelopment and injury.

Physicians should educate pregnant patients about the harmful effects of smoking to themselves and the developing fetus, and help these patients develop a plan for smoking cessation. The safety of nicotine replacement products in pregnancy has not been adequately studied. However, smoking is likely to be more harmful than nicotine replacement therapy, particularly because cigarette smoke contains more than 3,000 different chemicals that can potentially harm humans, and one of the main components of cigarette smoke is carbon monoxide, a known fetal toxin. Therefore, it is reasonable to consider the use of nicotine replacement products in patients who cannot maintain smoking abstinence without pharmacologic intervention.

If pregnant women require nicotine replacement to quit smoking, the amount of nicotine administered should be minimized as much as possible while still maintaining efficacy. Until further research is available, physicians should consider recommending the intermediate-release nicotine preparations (nicotine gum, nicotine spray, and nicotine inhaler) rather than the continuous-release method (nicotine patches).[30]

Histamine H_2-receptor blockers should not be used during the first trimester unless symptoms cannot be controlled with lifestyle modification and antacids.

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TABLE 6
OTC Topical Vaginal Antifungal Medications in Pregnancy

Drug name	*FDA pregnancy risk classification*	*Drug class*	*Crosses placenta?*	*Use in pregnancy*
Butoconazole (Femstat)	C	Imidazole antifungal	Not known	Probably safe
Clotrimazole (Lotrimin)	C	Imidazole antifungal	Not known	Safe in second and third trimesters (human trials),[24] first trimester probably safe[23]
Miconazole (Monistat)	C	Imidazole antifungal	Not known	Probably safe
Tioconazole (Vagistat-1)	C	Imidazole antifungal	Not known	No data

OTC = over-the-counter; FDA = U.S. Food and Drug Administration.

Information from Lagace E. Safety of first trimester exposure to H_2 blockers. J Fam Pract 1996;43:342-3, and Czeizel AE, Toth M, Rockenbauer M. No teratogenic effect after clotrimazole therapy during pregnancy. Epidemiology 1999;10:437-40.

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