The clinical content of preconception care: the use of medications and supplements among women of reproductive age

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The use of prescription and over-the-counter medications and dietary supplements are common among women of reproductive age. For medications, little information about the teratogenic risks or safety is available, as pregnant women are traditionally excluded from clinical trials, and premarketing animal studies do not necessarily predict the effects of treatment in human pregnancy. Even less is typically known about the effects of dietary supplements on pregnancy outcomes, as they are not held to the same rigorous safety and efficacy standards as prescription medications. Congenital anomalies associated with medication use are potentially preventable, because they are linked with modifiable maternal exposures during the period of organogenesis. However, as women of reproductive age experience acute and chronic conditions that can result in adverse outcomes for the woman and her offspring, the benefits of use of a particular medication before or early in pregnancy may outweigh the risks. Resources and principles outlined in this article will aid healthcare providers in selecting appropriate medication regimens for women of reproductive age, particularly those with chronic health conditions, those who are planning a pregnancy, and those who may become pregnant.

Key words: medication, preconception, prescription, teratogen

Medication usage among pregnant women and women of reproductive age is common. A survey of women giving birth in Oklahoma[1] reports that the average number of medications taken during pregnancy ranged from 1.6-2.9 (excluding vitamin and mineral supplements), depending on the trimester. The same survey reported that 54% of all products consumed in pregnancy were over-the-counter (OTC) medications. Another source estimates that more than 80% of pregnant women take OTC or prescription drugs during pregnancy.[2] National surveys among women of reproductive age document that chronic conditions often requiring the ongoing administration of medications for maintenance are not uncommon among women of reproductive age.[3] As maternal age and body mass index increase, it is likely that an even greater proportion of women who are planning a pregnancy or who could become pregnant will have chronic diseases that necessitate prescription medications.

Presently, congenital anomalies are among the leading causes of infant mortality in the United States.[4] It is estimated that approximately 10-15% of congenital anomalies are due to teratogenic maternal exposures. Congenital anomalies caused by teratogenic exposures, such as certain medications, are considered preventable, as they are linked with modifiable maternal exposures during the period of organogenesis.[5] It follows that maternal avoidance of teratogenic exposures would minimize congenital anomalies. However, as women of reproductive age and those who are pregnant experience acute and chronic health conditions that must be medically managed, in many instances avoidance of medications is neither possible nor advisable.

The benefits of medication use during pregnancy are not restricted to the recovery of maternal health, but extend to the protection of the fetus in many instances. Poorly controlled diabetes mellitus is teratogenic, whereas the appropriate management of diabetic pregnant women can prevent diabetic embryopathy.[6] Uncontrolled asthma can decrease oxygen in the fetal blood, possibly impairing fetal growth and survival.[7] Uncontrolled high blood pressure increases the risks of placental problems and fetal growth retardation.[8] The treatment of infectious diseases of the reproductive tract can significantly reduce the prevalence of preterm birth and its effects.[1,9] For all pregnant women infected with HIV, the Center for Disease Control (CDC) recommends the drug zidovudine (AZT) to minimize perinatal transmission.[10] The periconceptional use of folic acid can prevent most neural tube defects[11] and a considerable number of congenital anomalies of the cardiovascu-

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TABLE 1
FDA classification of medication safety during pregnancy

Category	Description
A	Adequate, well-controlled studies in pregnant women have not shown an increased risk of fetal abnormalities.
B	Animal studies have revealed no evidence of harm to the fetus; however, there are no adequate and well-controlled studies in pregnant women; or animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus.
C	Animal studies have shown an adverse effect and there are no adequate and well-controlled studies in pregnant women; or no animal studies have been conducted and there are no adequate and well-controlled studies in pregnant women.
D	Studies, adequate well-controlled or observational, in pregnant women have demonstrated a risk to the fetus. However, the benefits of therapy may outweigh the potential risk.
X	Studies, adequate well-controlled or observational, in animals or pregnant women have demonstrated positive evidence of fetal abnormalities. The use of the product is contraindicated in women who are or may become pregnant.

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lar system, urinary tract, and limb deficiencies.[12,13]

Teratogenicity is a complex process and is dependent on the timing of the exposure in relation to the gestational age, the dose, and route of administration. The developmental stage of the conceptus is particularly critical in determining teratogencity. For example, after 24 weeks' gestation, the antibiotic tetracycline can cause permanent staining of the offspring's teeth. During the second and third trimesters, angiotensin-converting enzyme (ACE) inhibitors can damage the fetal kidneys. The period of greatest sensitivity to most teratogenic exposures is the period of organogenesis, from 18-60 days postconception (approximately 4.5-11 weeks after the last menstrual period).[14] Exposures after the period of organogenesis usually do not result in structural anomalies, although there are exceptions. Rather, teratogenic exposures during the fetal period (after 60 days postconception) typically result in growth restriction or functional disorders of the central nervous system, kidneys, or other organs.

The dose and route of administration of the agent are other important features of potential teratogenicity. Teratogenic effects occur only when the dose of an agent exceeds a threshold.[15] Higher doses and chronic exposures are of more concern than lower doses and single exposures. A teratogenic effect is less likely with the use of dermal agents with minimal systemic absorption. Finally, the way in which the woman or offspring metabolize an agent is influenced by genotype, which ultimately determines the effective "dose" of the exposure. Processes relevant to medication processing that are influenced by genotype include metabolism, receptor binding, drug distribution, placental transport, and cellular sensitivity. In addition, physiologic changes that occur during pregnancy and affect the pharmacokinetics and/or pharmacodynamics include: changes in body weight and body composition; delayed gastric emptying and gastrointestinal transit time; expanded plasma volume; increased cardiac output and blood flow to the uterus, kidneys, skin, and mammary glands; decreased plasma albumin; increased glomerular filtration rate; and changes in the activity of hepatic enzymes.[16] It may be necessary to adjust the dosage and/or frequency of medication used during pregnancy.

For most medications, little information about teratogenic risk or safety is available at the time of marketing, as pregnant women are traditionally excluded from clinical trials. Premarketing animal studies do not necessarily predict the effects of treatment in human pregnancy. Medications for which there were false-negative animal teratology studies include captopril, enalapril, carbimazole, methimazole, and misoprostol. Although comparably more research has been performed on hypertension, depression, and other conditions that commonly occur in women of reproductive age, no areas can be considered well-studied in pregnancy. A review conducted in 2001 concluded that there was not enough information to assess the teratogenic risk or safety during pregnancy of more than 90% of prescription medications approved by the US Food and Drug Administration (FDA) in the previous 20 years.[17] Gaps in information are even more substantial for OTC and dietary supplements.

Given the above, it can be difficult for health care providers and women to decide whether to use a given medication during pregnancy as well as for women who are planning to or who could become pregnant. The decision must be individualized according to the woman and her unique circumstances, considering the balance of risks, benefits, and efficacy of treatment for mother and fetus. There are resources available to aid health care providers and women in their medical decision-making. The US FDA uses a risk classification system for medications based on data from human and animal studies to help interpret the risks associated with use of medications during pregnancy.[18] The current FDA classification system uses the letters A, B, C, D, and X for the 5 categories (Table 1). Drugs for which there is evidence of fetal risk but "the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks" are classified as class D. Drugs that are "contraindicated in women who are or may become pregnant" are classified as class X. Critics of the FDA classification system argue that the risk categories are limited in that they do not indicate the

risk based on time during gestation in which the medication is used and that the letters imply a gradation of risk that does not necessarily exist. In actuality, category X reflects a benefit-risk judgment, but drugs in this category may be no more toxic than those in categories C or D. An understanding of both the value and limitations of the FDA categories of risk is necessary for counseling women of reproductive age who have taken or may need to take a given medication. In response to criticism of the current system of classification, the FDA has proposed to amend its regulations concerning the format and content of the "Pregnancy," "Labor and delivery," and "Nursing mothers" subsections of the "Use in Specific Populations" section of the labeling for human prescription drug and biological products. Specifically, the FDA is proposing to require that labeling includes a summary of the risks of using a drug during pregnancy and lactation, a discussion of the data supporting that summary, and relevant clinical information to help health care providers make prescribing decisions and counsel women about the use of drugs during pregnancy and/or lactation. The proposal would eliminate the current pregnancy categories A, B, C, D, and X.[19]

There are several additional resources that healthcare providers may utilize. The textbook *Drugs in Pregnancy and Lactation*[20] includes a fetal risk summary containing a review of literature about a particular drug to provide more data for decision making by the prescribing health care provider. Complete and up-to-date information regarding medication teratogenic risks can be found on the online REPRORISK system (www.reprotox.org), available from Micromedex, which contains periodically updated, scientifically reviewed resources. In addition, the Organization of Teratology Information Specialists has compiled "fact sheets" on various prescription and OTC medications and supplements (available at http://otispregnancy.org/otis_fact_sheets.asp).

More details about preconception considerations for various prescription and OTC medications and supplements are found below.

Prescription medications

A recent study finds that 1 of every 13 visits made to ambulatory practices by women of reproductive age results in the prescription of a potentially teratogenic (class D or X) medication. The same survey found that contraceptive counseling was provided on less than 20% of visits that documented use of a potential teratogen by a woman of reproductive age, and that women using low-risk drugs (class A or B) received contraceptive counseling as frequently as women using potential teratogens. A table of medications generally accepted to be contraindicated in the preconception period and pregnancy is found in Table 2. A more complete listing of potential teratogens (class D or X) is found as an appendix in the article by Schwarz et al.[21]

Recommendations by other groups

Several professional organizations have issued recommendations regarding the use of drugs related to their specialty in pregnancy. Specifically, there are established practice guidelines for use of medications to manage diabetes,[22] hypertension,[23] seizure disorders,[24] thyroid disorders,[25] disorders requiring anticoagulation,[26] asthma,[27] gastrointestinal disorders,[28] tuberculosis,[29] sexually transmitted infections including HIV,[9,10] migraine headaches,[30] the management of acne using isotretinoin, and psychiatric and psychologic disorders (including depression and bipolar disorders).[31,32] Recently, the FDA has changed the labeling of paroxetine (Paxil) from class C to D based on the results of recent studies suggesting that the drug increases the risk of birth defects, particularly heart defects, when women take it during the first 3 months of pregnancy.[33]

Recommendation. All women of reproductive age should be screened for the use of teratogenic medications and should receive counseling about the potential impact of chronic health conditions and medications on pregnancy outcomes for mother and child. Whenever possible, potentially teratogenic medications should be switched to safer medications before conception. For women with chronic conditions with serious morbidity (to mother and infant), the fewest number and lowest dosages of essential medications that control maternal disease should be used. For women not desiring pregnancy, a plan for contraception should be addressed and initiated. *Strength of recommendation*: A; *quality of evidence*: II-2.

OTC medications

Commonly used OTC medications among women of reproductive age include analgesics; cough, cold, and allergy remedies; and remedies for gastrointestinal upset.[34,35] The safety of commonly used examples of these OTC medications are given in Table 3.

Related recommendations by other groups

As part of a preconception care visit, the American College of Obstetricians and Gynecologists (ACOG) recommends that women inform their health care provider of their use of OTC medications. The ACOG also recommends that women who are pregnant talk to their doctor before using any OTC medication during pregnancy.

Recommendation. Health care providers should educate women of reproductive age about the need to discuss the use of OTC medications with their provider when planning a pregnancy. Women should be specifically advised not to use aspirin if they are planning a pregnancy or become pregnant. *Strength of recommendation*: A; *quality of evidence*: III.

Dietary Supplements

The 1994 Dietary Supplement Health and Education Act (DSHEA) defined dietary supplements (DSs) as vitamin, mineral, herb/botanical, amino acid, enzyme, protein, probiotic, glandular, or hormone-like substances. Various national surveys have estimated that 18-52% of the US population uses dietary supplements and many women use dietary supplements before and during pregnancy.[36-38] In the United States, dietary supplements are not regulated in the same way as prescription medications and do not necessarily undergo clinical trials for safety and efficacy, especially in pregnancy. However, concerns about safety, effectiveness, quality control, contamination, adverse events, and

TABLE 2
Medications contraindicated (class X) in pregnancy

Agent	Comments
Angiotensin-converting enzyme inhibitors (antihypertensive), and angiotension II receptor blockers	May cause kidney abnormalities in fetus when used in 2nd or 3rd trimesters.
HMG-CoA reductase inhibitors (statins)	A range of abnormalities has been reported for exposures during the 4th-9th week of gestation.
Androgens and testosterone derivatives	Cause masculinization of female fetus.
Carbamazapine (anticonvulsant)	Risk of fetal death, mental retardation, and malformed hearts, genitals, cleft palates, and arteries. Should be switched to another, less teratogenic agent before conception whenever possible. Use should be reserved only for cases where benefit outweighs risk.
Coumadin derivatives	Risk of bone and cartilage deformities, mental retardation, and vision problems. Should be switched to heparin before conception whenever possible.
Folic acid antagonists	Risk of spontaneous abortion and malformations.
Leflunomide, thalidomide	Risk of limb deformities. Use only with strict pregnancy prevention protocols.
Lithium (antidepressant)	Associated with increased risk of cardiovascular anomalies.
Phenytoin (anticonvulsant)	Risk of fetal hydantoin syndrome, including intrauterine growth restriction with small head circumference, dysmorphic facies, orofacial clefts, cardiac defects, and distal digital hypoplasia. Use should be reserved only for when benefit outweighs risk.
Streptomycin and kanamycin (antiinfective)	Risk of ototoxicity.
Tetracycline (antiinfective)	Risk to developing bones and teeth causing discoloration of teeth and skeletal abnormalities.
Valproic acid (anticonvulsive)	Risk of central nervous system dysfunction, spina bifida, development delay, intrauterine growth retardation, and cardiac anomalies. Should be switched to another, less teratogenic agent before conception whenever possible. If benefit of use outweighs risk, should be administered in 3-4 divided doses and should not be combined with carbamazapine and phenobarbitol.
Isotretinoin, known as Accutane (antiacne)	Elevated risk of spontaneous abortion and many anomalies.

Information from Briggs et al.[19]

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interactions with medications have been raised in the literature about dietary supplements.[39] Although many health care professionals will recommend certain dietary supplements before and during pregnancy (eg, folate, iron, and calcium), the safety and efficacy of many dietary supplements (eg, botanicals and weight loss products) has not been well established before or during pregnancy.[40] Most of the data available have been based on case reports, animal studies, and retrospective studies. Clinical trials evaluating the safety and efficacy of dietary supplements before and during pregnancy are needed especially for vitamin D, fish oil, and botanical products. It is critical that all health care professionals ask their patients what vitamins, minerals, herbs, traditional remedies, and other dietary supplements they are using.

Recommendations by other groups

Health Canada has reported that at this time there is not enough scientific information about the safety of various herbs and herbal products to recommend their general use during pregnancy and lactation. Women should use these products cautiously, and critically examine any information about their proposed benefits.[41]

Recommendation. Health care providers should educate women of reproductive age about the need to discuss the use of dietary supplements before pregnancy, including herbs, weight loss products, and sport supplements, and should caution women about the unknown safety profile of many supplements. High-quality and prescription-quality dietary supplements should be encouraged. *Strength of recommendation:* A; *quality of evidence:* II-C.

Conclusion

Given the widespread use of prescription and OTC medications and dietary supplements—including herbs, weight loss products, and sport supplements—among women of reproductive age, the growing prevalence of women with chronic conditions during their reproductive years, and the unknown safety profile or known risk of teratogenicity of many medications and supplements, health care providers should educate women of reproductive age about the

TABLE 3
FDA classification of common over-the-counter medications

Drug name	FDA Class by Trimester	Drug Class	Use in Pregnancy
Analgesics			
Acetominophen	B/B/B	Nonnarcotic	Pain reliever of choice.
Aspirin	D/D/D	Salicylate	Not recommended except for specific indications; associated with increased perinatal mortality, neonatal hemorrhage, decreased birth weight, prolonged gestation and labor, and possible teratogenicity.
Ibuprofen Ketoprofen Naproxen	B/B/D B/B/D B/B/D	NSAID NSAID NSAID	Avoid in 3rd trimester; associated with oligohydramnios, premature closure of the fetal ductus arteriosus with subsequent persistent pulmonary hypertension of the newborn infant, fetal nephrotoxicity, and periventricular hemorrhage.
Cough and cold remedies			
Chlorpheniramine	B	Antihistamine	Antihistamine of choice.
Pseudoephedrine	B	Decongestant	Oral decongestant of choice; possible association with gastroschisis.[33]
Guaifenesin	C	Expectorant	Possible increased risk of neural tube defects.
Dextromethorphan	C	Antitussive	Appears to be safe in pregnancy.
Diphenhydramine	B	Antihistamine	Possible oxytocin-like effects at high dosages.
Clemastine	B	Antihistamine	Unknown safety profile.
Gastrointestinal remedies			
Aluminum hydroxide/ Magnesium hydroxide	B	Antacid	Appears to be safe in pregnancy.
Calcium carbonate	C	Antacid	Appears to be safe in pregnancy.
Simethicone	C	Antiflatulant	Appears to be safe in pregnancy.
Cimetadine	B	Antihistamine	Preferred after antacids; generally regarded as safe.
Ranitidine	B	Antihistamine	Preferred after antacids; generally regarded as safe.
Nizatidine	C	Antihistamine	Not recommended because of adverse animal studies.
Famotidine	B	Antihistamine	Probably safe; data needed.

FDA, Food and Drug Administration.
Adapted with permission from "Over the Counter Medications in Pregnancy," June 15, 2003, American Family Physician.[43]

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need to discuss the use of all medications and supplements with their health care provider, particularly if they are planning a pregnancy or could become pregnant. Numerous resources exist to aid health care providers in selecting appropriate medications that balance the risk and benefit (for both the woman and any offspring she may conceive) of using particular medications while planning a pregnancy or during pregnancy.

In medically managing the chronic and acute health conditions women may face while planning a pregnancy, it is useful to classify medications as either "essential" or "nonessential." Essential medications are those necessary to treat diseases with serious morbidity for the women and/or her fetus. Nonessential medications are those used to treat conditions without serious morbidity. In general, the goals of preconception medical management include the following[42]:

1. Identify the pattern of medication and supplement use before conception.
2. Counsel women with chronic conditions about the potential impact of the condition and its various treatments on the health of the woman and the fetus. Provide preconception counseling of women for whom drugs are essential to allow them to make informed decisions regarding the avoidance or timing of pregnancy.
3. Establish effective treatment for chronic conditions before conception.
4. Manage all chronic conditions and acute illnesses throughout pregnancy.
5. Counsel women to avoid the use of nonessential medications, including prescription (eg, isotretinoin for acne) and OTC medications and dietary or herbal supplements.
6. Avoid the use of medications with high teratogenic risk when equally effective treatments with lower risks are available, for example, warfarin (an

anticoagulant), and valproic acid (an anticonvulsant).
7. Limit the use of essential medications to the smallest number of drugs possible that will effectively treat maternal disease without compromising the health of the woman or her fetus.
8. Limit each essential medication to the smallest dose that can be used to effectively treat maternal disease without compromising the health of the woman or her fetus. ■

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