CME CREDIT ***EDUCATIONAL OBJECTIVE:*** Readers will choose the safest possible drug treatments for pregnant patients consistent with the welfare of the mother and fetus

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Prescribing for the pregnant patient

ABSTRACT

Prescribing in pregnancy can be challenging for providers facing insufficient information about drug safety, overestimation of the risk of medications by both the patient and the care provider, and increasing litigation costs. This article provides key concepts to consider when prescribing for a pregnant patient and offers practical advice for choosing the safest possible drug treatments.

KEY POINTS

There is no protective physiologic barrier between the maternal and fetal environments.

The gestational stage may determine the effect of a medication on the fetus.

The physiologic changes of pregnancy affect the pharmacokinetics of medications.

Sole reliance on the US Food and Drug Administration's pregnancy safety category may be inadequate.

Key questions: Is the problem self-limited or amenable to nonpharmacologic management? How do the patient's (and provider's) presumptions affect decisions about this medication in pregnancy? How does pregnancy affect the problem, and how does the problem affect pregnancy?

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PRIMUM NON NOCERE: First, do no harm—a principle taught across the world to all medical students. It reminds the health care provider to consider the possible harm that any intervention might produce. Never is it more relevant in the mind of a clinician than when prescribing a medication for a pregnant woman. We are, after all, brought up in a society averse to medical risk.

When managing a pregnant patient, should the baby be the highest priority, whatever the mother may face? Or to take the extreme opposite position, should the mother be treated with the best possible options and the baby ignored?

And what about the views of the patient? There is a widespread cultural belief about the vulnerability of the mother and fetus during pregnancy. Therefore, when faced with the decision of whether to use a medication or not, what is the best recourse for the pregnant patient? Should she be the "good mother" and avoid all risk to the baby, or should she be the "responsible mother" who follows medical advice and takes treatment as recommended?

In truth, the path to safe management of a pregnant patient is rarely so dichotomous. In most cases, what is best for the mother is also best for the baby. However, caring for a pregnant or lactating woman can be challenging for clinicians facing insufficient information regarding medication safety, overestimation of the risk of medication by both the patient and the care provider, and increasing litigation costs.

This article provides key principles to guide clinicians caring for pregnant patients, as we find ourselves increasingly dependent on pharmacotherapy. It also includes sources of information clinicians can turn to when they need additional pregnancy safety data about a certain drug and when they want advice about conditions commonly seen in pregnancy and medications that can be justifiably used in those circumstances.

TABLE 1

US Food and Drug Administration pregnancy risk classification

Category A	Controlled studies show no risk, and the possibility of fetal harm appears remote
Category B	No evidence of risk in humans, based on animal studies alone or on both animal and human studies
Category C	Risk cannot be ruled out, either concerning animal data or no data for humans
Category D	Positive evidence of human fetal risk, but use may be justified in some circumstances
Category X	Contraindicated in pregnancy because of evidence of fetal risk based on animal or human studies or human experience; the drug's risks in pregnancy clearly outweigh any possible benefits

KEY CONCEPTS FOR PRESCRIBING IN PREGNANCY

The following concepts are key to prescribing for a pregnant patient:

In most cases, what is best for the mother is also best for the baby

No protective barrier exists between the maternal and fetal environments

The placenta contains a semipermeable membrane that selectively allows some substances to pass from the maternal to the fetal blood and excludes others. However, it is not really a "protective mechanism" when it comes to medications. Assume that the fetus will have exposure, at least to some degree.

In general, drugs that are lipophilic, of a low molecular weight, or not ionized at physiologic pH cross the placenta more efficiently than others. Heparin and insulin are notable exceptions to the rule that most drugs cross the placenta. They do not.

The gestational stage may determine the effect of a medication on the fetus

In animals and in humans, exposure of the embryo or fetus to a teratogen may produce a permanent abnormality of structure or function.

First-trimester exposures are most worrisome for structural malformations. However, fetal neurologic and behavioral development, fetal survival, and function of specific organs can be affected even after the first trimester. For example, while first-trimester exposure to angiotensin-converting enzyme inhibitors has been linked to a slight increase in congenital heart defects, exposure in the second or third trimester can result in fetal oligohydramnios, neonatal anuria, pulmonary hypoplasia, intrauterine growth restriction, and fetal death.

Physiologic changes of pregnancy affect the pharmacokinetics of medications

Pregnancy is associated with increased plasma volume, increased glomerular filtration rate, and dilutional hypoalbuminemia, which can all affect the bioavailability of medications. Absorption of oral agents also may be affected by slowed gastric motility in pregnancy.

Although these physiologic alterations do not routinely warrant a change in drug dosage, they may be important considerations when choosing an appropriate agent. For example, medications taken in multiple doses per day are more likely to have a sustained effect than once-daily medications, which would be rapidly cleared in a pregnant patient.

Sole reliance on the FDA pregnancy safety category may be inadequate

To help clinicians prescribe medications for pregnant women, the US Food and Drug Administration (FDA) assigns medications to one of five categories of risk (A, B, C, D, or X) (TABLE 1). Unfortunately, this classification system has several shortcomings:

- The categories are often seen as a grading system in which the risk increases from the lowest in category A to highest in category X, and the safety information in the accompanying narrative is not always appreciated by prescribers.
- Clinicians incorrectly assume that drugs in a particular category carry a similar risk. However, 65% to 70% of all medications are in category C. This category includes medications with adverse animal data or no animal data at all. In addition, adverse animal data may vary in severity from decreased fetal weight to major structural malformation and fetal loss, indicating a difference in expected risk.
- Most of the data on medication safety in pregnancy comes from animal studies, case re-

ports, case series, case-control studies, or pregnancy registries, and each of these sources has significant limitations.

- The categories do not distinguish between supporting data from animal studies and human studies. For instance, a category-B drug may have animal studies that show no risk but no adequate human studies, or may have animal studies showing risk but human studies that do not.

Looking at the pregnancy risk classifications used in the United States (ie, the FDA system), Australia, and Sweden, researchers compared the classification of 236 drugs between the three systems and found that only one in four drugs was similarly classified into the same risk category. This discrepancy further brings into question the usefulness and reliability of these classifications.[1]

Finally, none of the classification systems tells us the potential harm from withholding a medication in pregnancy.

RESOURCES TO ASSESS MEDICATION SAFETY IN PREGNANCY

The FDA has proposed changes in the labeling of medications related to pregnancy and lactation.[2] The proposed changes would eliminate the current categories and instead require a summary of the risks, the effects of the drug on the fetus, and clinical considerations for use during pregnancy. In addition, labeling would include a description of the medication's effects on milk production, the amount of drug present in milk, and possible effects on the infant.

Until such changes are in place, what other resources can a busy clinician turn to for support?

The official drug labeling (or the package insert), also published in the *Physicians' Desk Reference*, is one source of information, but it rarely provides up-to-date information about teratogenic risks in human pregnancies.

Several online databases review, summarize, and periodically update information from the peer-reviewed medical literature.[3–7] The REPRORISK system[4–7] maintained by Micromedex (Greenwood Village, CO) provides access to several databases that contain information about a wide range of individual medications: REPROTEXT, REPROTOX,[5] Shepard's Catalog of Teratogenic Agents,[7] and the Teratogen Information System (TERIS).[4] Online access and a smartphone "app" for these databases are available for a subscription fee. Summaries for individual medications can be ordered directly from TERIS, also for a fee. Several other resources are available in textbook format.[8–10]

In addition, health care providers can obtain information from or can refer pregnant and breastfeeding patients to a teratology information service for information and counseling about medication exposures. MotherToBaby,[11] a service of the nonprofit Organization of Teratology Information Specialists, provides fact sheets, free phone consultation, risk assessment, and counseling by trained teratogen information specialists about environmental exposures, including prescription and over-the-counter medications and dietary and herbal supplements. Counselors from these services gather and synthesize information about exposures from the databases mentioned above, from the peer-reviewed medical

TABLE 2

Known and suspected teratogens

Alcohol
Angiotensin-converting enzyme inhibitors
Antidepressants (eg, paroxetine)
Antiepileptics (eg, phenytoin, carbamazepine, phenobarbital, valproic acid)
Antineoplastics (eg, cyclophosphamide, methotrexate)
Androgens
Anxiolytics
Carbimazole
Cocaine
Estrogens (eg, diethylstilbestrol)
Fluconazole
Lithium
Methimazole
Misoprostol
Penicillamine
Radioactive iodine (sodium iodide-128)
Retinoids (eg, isotretinoin)
Statins
Tetracyclines
Thalidomide
Vaccines (live)
Warfarin

INFORMATION FROM REFERENCES 12 AND 13

TABLE 3

Selected drugs for conditions often seen in pregnancy

Acne
Drugs of choice: topical erythromycin, topical benzoyl peroxide, topical clindamycin
Alternatives: oral erythromycin, topical tretinoin[14]
Comments: isotretinoin is contraindicated

Asthma
Drugs of choice: inhaled beta agonists (both long- and short-acting), inhaled corticosteroids, inhaled ipratropium, inhaled cromolyn, systemic steroids
Alternatives: leukotriene inhibitors, omalizumab
Comments: see national recommendations for the management of asthma in pregnancy at www.nhlbi.nih.gov/guidelines/asthma/astpreg.htm

Constipation
Drugs of choice: bisacodyl, docusate, glycerin, psyllium, magnesium hydroxide, mineral oil

Cough
Drugs of choice: guaifenesin, codeine, dextromethorphan

Depression
Drugs of choice: sertraline, amitriptyline, nortryptiline
Alternatives: fluoxetine, fluvoxamine, escitalopram, citalopram, venlafaxine
Comments: small increased risk of teratogenicity and neonatal syndromes with paroxetine; best avoided

Diabetes
Drug of choice: insulin
Comments: glyburide and metformin may have a developing role in the management of gestational diabetes; most studies of insulin glargine in pregnancy are small, retrospective, and include women with preexisting diabetes and gestational diabetes; there appear to be no major safety concerns, so it seems reasonable to continue insulin glargine if required to achieve excellent glycemic control[15]

Dyspepsia
Drugs of choice: ranitidine, famotidine, cimetidine, sucralfate, antacids
Alternatives: omeprazole, lansoprazole, esomeprazole

Headache, pain
Drugs of choice: acetaminophen, codeine, meperidine, morphine, metoclopramide, caffeine
Comments: occasional intermittent use of a nonsteroidal anti-inflammatory drug (NSAID) until 20 weeks of gestation may be justifiable in some cases; some, but not all, epidemiologic studies have suggested that use of NSAIDs, including ibuprofen, during pregnancy may increase the risk of cardiac defects and gastroschisis; use during late pregnancy is avoided because of concern about premature ductal closure[6]

literature, from drug manufacturers, and from other sources.

With the advent of electronic medical records and computerized provider order entry, clinical decision support systems hold promise as an additional resource for safe prescribing in pregnancy.

Fortunately, the list of teratogenic medications that are absolutely contraindicated in pregnancy remains small (TABLE 2).[12,13]

THE FOUR-QUESTION APPROACH TO CARING FOR THE PREGNANT PATIENT

Is the symptom self-limited or amenable to nonpharmacologic management?

It has been said that we live in a culture where every symptom warrants a pill. If this is true, there can be no better time for re-evaluating this practice than during pregnancy.

Many of the medications most commonly used in pregnancy are for upper-respiratory-tract infections, headache, or psychological distress. Pregnancy is the ideal time to educate patients about the limited effectiveness of most cough-and-cold remedies and the inappropriateness of antibiotics for colds and viral bronchitis. It is also an ideal time for a trial of lifestyle modifications, relaxation, and biofeedback for a chronic headache problem. For cases of mild to moderate depression, it may be worth considering treatment with psychotherapy rather than medications.

Offering patients the option of no treatment or nonpharmacologic treatment for self-limited symptoms is an option worth considering.

How do the patient's (and your) values and understanding affect the decision?

Is the patient willing to take medication? What are her beliefs with regard to her problem and how it should be managed in pregnancy?

Women and clinicians bring many worries and prejudices to the use of medications

Hypertension
Drugs of choice: labetalol, nifedipine, methyldopa, hydralazine
Alternatives: other beta-blockers except atenolol (because of a possible association with intrauterine growth restriction)
Comments: angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are contraindicated

Hyperthyroidism
Drugs of choice: propylthiouracil in first trimester, methimazole after the first trimester
Alternatives: beta-blockers for symptoms
Comments: surgery may be possible in the second trimester; radioactive iodine is contraindicated in pregnancy

Infection
Drugs of choice: penicillins, cephalosporins, azithromycin, nitrofurantoin, vancomycin, isoniazid, acyclovir, zidovudine, other antiretrovirals
Alternatives: aminoglycosides, trimethoprim, sulfonamides, metronidazole
Comments: clarithromycin and fluoroquinolones are best avoided

Nasal congestion
Drugs of choice: oxymetazoline, nasal steroids, nasal cromolyn, nasal ipratropium
Comments: pseudoephedrine and phenylephrine are avoided during pregnancy because of possible vasoconstrictive activity and findings in some case-control studies suggesting a small increase in unusual birth defects such as gastroschisis and hemifacial microsomia[5]

Nausea and vomiting
Drugs of choice: metoclopramide, prochlorperazine, dimenhydrinate, promethazine, doxylamine plus pyridoxine, ondansetron

Thrombosis
Drugs of choice: heparin (low-molecular-weight and unfractionated)
Comments: warfarin, a known teratogen, is believed by some to have a role in management of prosthetic heart valves after the first trimester, as it may have lower risk of prosthetic valve thrombosis[16]; there are no adequate studies evaluating the newer anticoagulants in pregnancy; however, fondaparinux has been successfully used in pregnancy in the setting of heparin-induced thrombocytopenia[17]

INFORMATION FROM KWEDER SL, POWRIE RO. PRESCRIBING IN PREGNANCY: A PRACTICAL APPROACH. IN: POWRIE RO, GREENE M, CAMANN W, EDITORS. DE SWIET'S MEDICAL DISORDERS IN OBSTETRIC PRACTICE. 5TH ED. HOBOKEN, NJ: WILEY-BLACKWELL; 2010:633–640.

in pregnancy. The experiences of the patient and her family and friends may present huge obstacles to needed medication use in pregnancy. Misinformation in the media and from family members, friends, and other health care providers are other obstacles. The only way to deal with this issue is to ask your patient directly about her fears and concerns regarding each prescription written.

Clinicians also need to address fears or prejudices they themselves may have about medication safety in pregnancy. These may arise from a single bad experience in caring for a pregnant woman, discomfort with uncertainty, or a belief that pregnant women should avoid any and all risks of exposures, even when the mother's condition warrants pharmacologic treatment.

Being informed, both scientifically and about one's own biases or tendencies, is an essential foundation for rational prescribing in pregnancy.

Is the problem affected by pregnancy, and how?

Pregnancy can affect many medical conditions, and in different ways. Conditions such as asthma, migraine headache, and cardiac arrhythmia are exacerbated in pregnancy, placing the mother and fetus at increased risk of morbidity. Conditions such as Graves disease and hypertension may improve as pregnancy progresses, and medications often can be withdrawn as the patient progresses further along in gestation.

Understanding the effect of pregnancy on a particular problem may help the clinician to make an informed decision about medication use in pregnancy.

How does the problem affect pregnancy?

Considering the risk of untreated disease to the pregnancy may help in decision-making.

Many medical conditions can negatively affect the development of the fetus. A glaring example is diabetes mellitus, with poor

glycemic control being linked to congenital malformations, spontaneous abortion, and fetal demise. Chronic conditions with periodic exacerbations such as asthma or epilepsy place the fetus at increased risk during a flare-up.

Therefore, for chronic conditions, continuing maintenance therapy is best. Preconception counseling in such cases is crucial, so that a drug with adequate safety data can be substituted before pregnancy. In this way, any risk to the mother or the embryo from exacerbation of disease as such adjustments are made is avoided.

For conditions arising de novo in pregnancy, the underlying principle remains the same. Is the risk of pharmacotherapy more than the risk of untreated disease? Invariably, the answer to this question supports medication use, and an educated provider will be able to choose a treatment that is justifiable in most circumstances.

CHOOSING A MEDICATION

Fetal well-being depends on maternal well-being. It therefore helps to think of medication use in pregnancy as "justified or not" rather than "safe or not." **TABLE 3** lists some conditions commonly seen in pregnancy, selected drugs of choice that can be safely used for treating those conditions, and alternates that may be justified in some circumstances.[5,6,14–18]

GOOD PRACTICES WHEN PRESCRIBING IN PREGNANCY

Prescribing in pregnancy will be most successful when both the patient and the prescribing physician consider the fetal benefit gained from optimizing maternal health. Good prescribing practices to ensure optimum therapeutic benefit when caring for a pregnant patient are to:

- Involve the patient in decision-making. Recognize her concerns, worries, and preferences regarding her illness and its treatment.
- Inform the patient of the risk of an untreated medical condition, weighed against the risk of medication.
- Choose medications with the most available safety data. Let the patient know what resources you have referred to in choosing the medication.
- It is advisable to perform a search each time a prescription is written for a pregnant or lactating woman.
- When possible, have the discussion in the preconception period.
- Consider the dynamic physiology of gestation. Choose the right drug for the right trimester.
- Discuss the plan with the patient and other providers.
- Define clear criteria for when to discontinue the treatment.

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