Medications in Pregnancy

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KEY POINTS

1. All medications should be viewed with caution in pregnancy.
2. Management of medication use in pregnancy ideally begins with adequate preconception counseling and pre-pregnancy planning.
3. Medications used in pregnancy require clear identification of indication for use, duration of treatment, expected outcome, and signs or symptoms requiring early termination of their use.
4. When in doubt consultation with an expert in maternal–fetal medicine is strongly recommended.

BACKGROUND

With the exception of prenatal vitamins and possibly iron supplementation, all medications should be used with caution during pregnancy. Although clinical experience with many medications in pregnancy is quite extensive and the safety and efficacy is reasonably established, pregnancy represents a unique challenge in medication assessment. It would not be ethical, under most circumstances, to randomize pregnant patients to receive increasing doses of medications to assess safety and efficacy of a medication known to produce or suspected of producing harm in pregnancy. This limits the degree to which safety can be categorically stated for the use of any medication in pregnancy. Many medications once thought to be safe in pregnancy have subsequently been shown to be harmful. Other medications originally thought to be harmful have...
been shown to have beneficial effects when used for specific medically indicated purposes.

Many medications can and should be used in pregnancy for a variety of legitimate medical indications. Although it is beyond the scope of this chapter to discuss in detail the use of all medications in pregnancy, a few general guidelines can be offered. Texts exist that detail the risks and benefits of many available medications. Such a text should be a routine part of every obstetrical provider’s library. When doubt exists concerning the indications for or the safety or efficacy of any medication, consultation with an expert in maternal fetal medicine is strongly recommended.

GENERAL PRINCIPLES OF MEDICATION USE IN PREGNANCY

The three general principles are as follows:

1. Chronic medications should be reviewed to assess safety and efficacy.
2. The risk of not treating (or treating less effectively) an identified disease (acute or chronic) should be weighed against the risks of the proposed treatment.
3. All medications used in pregnancy require clear identification of indication for use, duration of treatment, expected outcomes, and signs or symptoms that require early termination of use.

Chronic Medical Conditions

Some patients have chronic medical conditions that predate pregnancy. The management of many of these conditions will include the use of medication. Although it is always important to consider safety and efficacy when using medications, with the onset of pregnancy these considerations become considerably more complex. Ideally, a consideration of the impact of pregnancy on the medical condition as well as the impact of the medical condition on pregnancy would occur prior to pregnancy. For some patients, this leads to a recommendation to delay pregnancy until the medical condition can be more adequately controlled. In other circumstances, it may lead to a recommendation to avoid pregnancy altogether.

Under many circumstances (both planned and unplanned), however, management of pregnancy will overlap with management of chronic medical conditions and their associated medications. The first consideration should be for the safety of the mother. Disease processes that are life-threatening to the mother may require continuation of treatment even if the pregnancy is continued. The provider should explore treatment alternatives with equal efficacy and better established safety profiles when possible. When safer alternatives are not available, providers should discuss with patients the potential risks of continuing the pregnancy while simultaneously continuing the use of the
required medication versus the potential risks of terminating medication use for the duration of pregnancy. Patients must be given sufficient information to make an informed decision concerning their health and the health of their developing fetus, especially during the critical period of organogenesis early in pregnancy. In all circumstances providers and patients must make individualized treatment decisions based on the medical conditions of the specific patient.

**Acute Medical Conditions**

Pregnant patients are vulnerable to all the acute medical conditions of non-pregnant patients. Medical decisions concerning the treatment of acute medical conditions that arise during pregnancy must follow the same general guidelines as those for chronic conditions. Will the medical condition adversely affect the pregnancy? Will treatment of the condition ameliorate or eliminate these potential effects? Will the proposed treatment adversely affect the pregnancy? Are there safer or more well-established alternative treatment options? What are the likely consequences of not treating the medical condition? What are the potential consequences of not treating the medical condition?

As with the treatment of chronic medical conditions it is critical that both providers and patients have sufficient information concerning the risks and benefits of treatment options to make informed, individualized decisions. When providers cannot adequately answer these questions, patients should be referred to a provider with sufficient expertise to provide more complete information.

**Acute Obstetrical Conditions**

Pregnancy may be accompanied by a variety of complications that require consideration of medication use. The same general principles apply and the same questions must be answered. When these complications are relatively common, much established data may exist to guide providers and patients in their decision-making process. When the complications are less common, consultation may be required.

**Therapeutic Categories and Considerations**

Any drug used during pregnancy should be checked for safety prior to use. Keeping in mind the general considerations just given, the following recommendations may be considered:

1. When antibiotics are indicated consider penicillin, cephalosporins (except cefotetan), clindamycin, and macrolides. Avoid sulfa drugs (contraindicated in first and third trimester), quinolones, tetracyclines, and aminoglycosides (oto-toxic; may be indicated for severe Gram-negative infections).
2. When analgesics are indicated consider acetaminophen and narcotic analgesia (consult reference for specific agents). Narcotic analgesics do cross the placenta and may affect the fetus transiently. Long-term narcotic analgesia use (or abuse) during pregnancy can be associated with withdrawal symptoms in the newborn. Narcotic analgesia at or near delivery has been associated with respiratory depression in newborns, which can be reversed, if necessary, with naloxone. Avoid aspirin (in analgesic doses) and nonsteroidal anti-inflammatory drugs (NSAIDs; contraindicated in late pregnancy).

3. For treatment of hypertension, consider labetalol (individual β-blockers should be reviewed prior to use as some β-blockers have been associated with adverse effects on uteroplacental and fetal hemodynamics and fetal growth), methyldopa, and hydralazine. Avoid angiotensin-converting enzymes (and angiotensin receptor blockade agents).

4. For patients with diabetes, consider insulin, regular and intermediate acting agents; but avoid oral hypoglycemics (recent data suggests that some oral hypoglycemics may be safely used in pregnancy but experience is limited and individual agents should be reviewed prior to use).

5. For patients suffering from nausea, consider using diclectin (doxylamine/pyridoxine) or chlorpromazine.

6. In cases of gastritis/peptic ulcer disease, consider magnesium hydroxide, aluminum hydroxide, calcium carbonate, and bismuth subsalicylate.

**PROVEN HUMAN TERATOGENS**

Some agents have proven teratogenic potential. These agents are summarized in Table 2. Although the effects of such agents are potentially variable and predictable, their use should be very limited or avoided during pregnancy. Category D agents have proven teratogenic potential but may, under certain circumstances, be indicated. Prior to using any category D agent, providers should perform a careful review of indications, duration of therapy, all potential
effects, and all potential alternatives to the proposed therapy. In addition, patients should be informed of these considerations, allowing for informed consent to the proposed therapy. Category X medications have proven teratogenic potential and use should be avoided in pregnancy.

SPECIAL CONSIDERATIONS

In addition to the use of medications in pregnancy, a variety of other exposures may occur with possible effects on pregnancy. These might include occupational exposures, legal and illegal drugs or nonpharmacological items such as exercising, lifting, or other activities. As previously noted, most such exposures will be subject to limited data concerning possible pregnancy effects. For this reason, the same general principles should apply that apply to medication use:

1. Is there any data available to guide the decision?
2. Is there a specific and compelling reason for the exposure?
3. Do safer alternatives exist?
4. Can potential adverse effects be monitored?
5. Can exposure be limited or modified in such a way as to minimize potential risks?

Although a full discussion of all such exposures is the work of an entire text in its own right, three common and frequently encountered exposures deserve attention.

Table 2
Proven Human Teratogens

<table>
<thead>
<tr>
<th>Category D</th>
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<tbody>
<tr>
<td>Cyclophosphamide</td>
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<td>Lithium</td>
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<td>Paramethadione</td>
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<td>Phenytoin</td>
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<td>Barbiturates</td>
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<td>Benzodiazepines</td>
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<td>Systemic retinoids</td>
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<td>Tetracycline</td>
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<tr>
<td>Trimethadione</td>
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<td>Valproic acid</td>
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<tr>
<td>Warfarin</td>
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<tr>
<td>Category X</td>
<td></td>
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<tr>
<td>Thalidomide</td>
<td></td>
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<tr>
<td>Danazol</td>
<td></td>
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<tr>
<td>Misoprostil</td>
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<td>Diethylstilbestrol</td>
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**Tobacco**

Tobacco is associated with a variety of adverse outcomes including low birthweight, increased risk of fetal demise, abruptio placentae, and placenta previa. Although the absolute risk associated with tobacco use is not clearly defined, the outcomes are potentially quite severe. As tobacco has no known benefits in pregnancy, every effort should be made to reduce or eliminate tobacco exposure during pregnancy.

**Alcohol**

Fetal alcohol syndrome (FAS) is a constellation of developmental and physical findings in neonates born to mothers who consumed large quantities of alcohol during pregnancy. FAS is associated with growth retardation, microcephaly, microphthalmia, and central nervous system deficiencies. The use of alcohol is quite prevalent and a significant number of pregnant mothers will have consumed alcohol prior to becoming pregnant. The question frequently arises whether alcohol can be safely used in any quantity during pregnancy. Although data is limited, there is no established safe level of alcohol use in pregnancy. For this reason, patients should be encouraged to eliminate or significantly limit alcohol use during pregnancy.

**Illicit Drugs**

A variety of illicit drugs are associated with adverse pregnancy outcomes. Each drug should be reviewed individually for specific concerns. In addition to the medical considerations, all such drugs are, by definition, illegal and carry with them significant social risk. All pregnant patients should be screened by history for illicit drug use and when present, counseled concerning the desirability of reduction or elimination. This screening and counseling should be approached in a nonjudgmental and nonthreatening manner. A threatening or legalistic approach to patients is likely to reduce patient reporting and therefore limit providers’ ability to effectively intervene.

**OVER-THE-COUNTER MEDICATIONS**

Questions concerning the use of over-the-counter (OTC) medications arise frequently during the course of pregnancy. The general considerations for use are the same as for prescription medications. The ease of access combined with the frequency with which OTC medications are used makes recommendations in pregnancy particularly challenging. It is estimated that more than half of all medication use in the United States is OTC. Approximately 75% of all pregnant patients will use one or more OTC medication during the course of pregnancy.

Although providers can control access to prescription medications, OTC medications are, by definition, available to patients without the necessity of a
prescription. In addition, the safety of OTC medications may vary with the time in pregnancy when they are used. For example, OTC NSAIDs that may be safely used early in pregnancy are generally contraindicated in the third trimester. For this reason, providers must be able to discuss in detail the appropriate uses and precautions that patients must keep in mind when deciding whether to use OTC medications during pregnancy.

Food and Drug Administration (FDA) pregnancy safety ratings are available for all OTC medications and should be reviewed prior to their use. It should be noted that supplements such as herbal and/or natural preparations are not subject. FDA oversight and information concerning safety in pregnancy may be very limited. The breadth of OTC medications available make a comprehensive review beyond the scope of this text; however, two common categories of medications warrant consideration: pain medications and cough/cold/allergy medications.

**OTC Pain Medications**

Pain is among the most common of medical complaints and although the frequency of pain in pregnancy may not be higher than in the non-pregnant state, it is certainly not any less common. For this reason, patients will often seek advice from their providers on OTC pain medication options.

**ACETAMINOPHEN**

Acetaminophen is widely used in pregnancy and early childhood. Although randomized, controlled trials concerning the safety of acetaminophen in pregnancy are lacking, the extensive experience combined with few reports of complications makes the use of acetaminophen a safe choice in pregnancy. Acetaminophen is a category B drug in all stages of pregnancy.

**ASPIRIN**

Use of aspirin has been associated with a variety of potential pregnancy complications, including prolonged gestation and decreased birthweight. In addition, aspirin has potent antiplatelet activity that may predispose patients to bleeding. The use of aspirin in pregnancy has been associated with neonatal hemorrhage. Aspirin is a category D drug in all stages of pregnancy and its use as an OTC medication should be discouraged during pregnancy.

**NONSTEROIDAL ANTI-INFLAMMATORY DRUGS**

Although NSAIDs are often combined as a single class, significant differences may exist in their use during pregnancy. Indomethacin (a prescription NSAID) has been used in pregnancy for preterm labor (see Chapter 7) but has been associated with significant complications and should only be used with caution and for specific indications. OTC NSAIDs, including ibuprofen and naproxen, are category B drugs in early pregnancy but category D drugs in the
third trimester. In the absence of a compelling indication for the use of NSAIDs in pregnancy, their use as an OTC medication should probably be limited.

**OTC Cough/Cold/Allergy Medications**

Given the duration of pregnancy, the likelihood of experiencing symptoms of allergies or viral respiratory infections is quite high. A wide variety of OTC medications are available to treat the various symptoms of viral respiratory infections and allergies and their use is quite common in pregnancy.

**Antihistamines**

Chlorpheniramine is a commonly used antihistamine in a variety of allergy and cold formulations. Chlorpheniramine is a category B drug and is probably safe for use during pregnancy. Diphenhydramine is the second commonly used antihistamine and is also a category B medication. It should, however, be used with caution as it has been shown to cross the placenta, may have oxytocin-like effects at high doses, and may interact with other drugs in pregnancy.

**Decongestants**

Pseudoephedrine has been the subject of animal studies and has had widespread human use in pregnancy. Pseudoephedrine is a category B medication and its use in pregnancy is probably safe. Because it has been associated with a possible increase in the risk of gastroschisis, its use in the first trimester of pregnancy should probably be avoided when possible.

**Cough Medications**

Cough medications fall into two broad categories: antitussive medications and expectorants. Both categories of medication are available in a wide variety of OTC formulations. Guaifenesin, a common expectorant, is a category C drug. Its use in the first trimester of pregnancy has been associated with a possible increased risk of neural tube defects but data is limited. It is probably safest to avoid the use of guaifenesin in the first trimester of pregnancy when possible. Dextromethorphan is also a category C drug. Animal studies have shown an association between dextromethorphan exposure and birth defects. Human data has not found a similar association.

**Sources**