# Continuing Education

# Caring for the Pregnant Patient

**Authors:**

Kaitlyn Bonds, Pharm.D.
Harrison School of Pharmacy, Auburn University

Megan Silvey, Pharm.D.
Harrison School of Pharmacy, Auburn University

Ryan Smith, Pharm.D.
Harrison School of Pharmacy, Auburn University

**Corresponding Author:**
Wesley T. Lindsey, Pharm.D.
Associate Clinical Professor
Drug Information and Learning Resource Center
Harrison School of Pharmacy, Auburn University

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## OBJECTIVES

Upon completion of this program, the pharmacist should be able to:

- Recognize the pharmacist's role in caring for the pregnant patient.
- Evaluate the risks associated with prescription and nonprescription medication use in the pregnant patient.
- Recommend common over the counter medications that are appropriate for the pregnant patient.
- Identify vaccines that are appropriate for the pregnant patient.

## INTRODUCTION

One of the most significant psychological and physical transitions a woman may undergo is during the period of time between conception and delivery.[1] During pregnancy, the role of the clinician is critical as they help guide the expectant mother.[1] Healthcare providers must always consider both the health and development of the fetus as well as the health and well-being of the mother. Pharmacists in particular play a vital role in the care of the pregnant patient.[2] Their expertise on drugs and accessibility to the public puts pharmacists in a role to have a positive impact on their pregnant patients.[2] Pharmacists are useful members of the healthcare team as they are often able to counsel their patients on potential fetal risk associated with various medications as well as reassure the patient that certain medications have shown little evidence of fetal toxicity.

Early intervention is key, and expectant mothers should be encouraged to begin prenatal care as soon as pregnancy is confirmed if not sooner.[1] During early prenatal care visits, comprehensive information should be gathered including a full past medical and surgical history, complete prescription and non-prescription medication use, lifestyle factors such as tobacco or alcohol use, immunization history, and prior reproductive history.[1] It is important to note that chemicals may affect fetal outcomes in any stage of pre or postnatal development.[3] Previously, focus was primarily on the first trimester of pregnancy; however, care should be exercised during every trimester.[3] Each stage of reproduction is represented by sensitivities to different agents and by various risks posed to the mother and fetus. Additionally, physiologic changes in the mother, such as a significant increase in total body water during pregnancy, allows for larger volume in which drugs may be distributed. While exposure to certain drugs poses a risk at any point throughout the pregnancy there is heightened concern during the periods of organogenesis.[2] Organogenesis is the period 20 to 55 days after conception.[2] This period is critical as many fetal structures are formed during this period of time.[2] For example, there is a risk of neural tube defects before 30 days, cleft palate before 10 weeks, and ventricular septal defect before 6 weeks.[2]

There is typically less reliable information regarding pharmacotherapy in pregnancy when compared to other patient populations.[3] This is in part due to ethical concerns surrounding randomized clinical trials.[3] Because there may not be human pregnancy data for the drug, clinical judgment may often be required. Additionally, manufacturers often provide a registry of patients who have taken the medication while pregnant and the associated outcomes. There are important questions that need to be considered when evaluating the safety of a drug for use in pregnancy. For example: has the drug actually been studied in human pregnant patients? Are other drugs within the same class known to cause toxicities? Can the drug cross the placenta? Has the drug been shown to cause toxicities in animal studies?[2] Table 1 provides a list of drugs and substances that are known to cause developmental toxicities.

**Table 1.[2,3] Drugs and Substances That Can Cause Developmental Toxicity**

| Drugs and Substances Known to Cause Developmental Toxicity | | |
|---|---|---|
| **Agent** | **Critical Period** | **Developmental Toxicity** |
| ACE inhibitors and Angiotensin II receptor antagonists | 2nd – 3rd trimesters | Fetal kidney toxicity/anuria, hypotension, pulmonary hypoplasia, limb contractures, neonatal renal failure, oligohydraminios |
| Alcohol | Throughout | Fetal alcohol syndrome |
| Androgens | 8 weeks – term | Masculinization of female fetus |
| Antineoplastics (busulfan, chlorambucil, cyclophosphamide, methotrexate) | 1st trimester | Cleft palate, pyloric stenosis, eye defects, cardiovascular defects, limb defects, genitourinary tract defects, neurobehavioral deficits |
| Atenolol | 2nd-3rd trimesters | Severe IUGR of placenta and fetus |
| Carbamazepine | 1st trimester<br><br>3rd trimester | Craniofacial defects, nail hypoplasia, developmental delay<br><br>Early hemorrhagic disease of the newborn |
| Cigarette smoking | Throughout | Abortion, stillbirths, intrauterine growth restriction, placenta abruption, preterm delivery, transient retinal abnormalities, long-term effects on cognitive performance, emotional development, and behavior |
| Cocaine | Throughout | CNS, intestinal, and kidney damage |
| Corticosteroids | 1st trimester<br><br>Throughout | Cleft lip and/or palate<br><br>Mild growth restriction (seen with higher doses of systemic corticosteroids) |
| Diethylstilbestrol | Up to 20 week | Multiple defects of the genital tract in female and male; vaginal-cervical cancer in adolescents |
| Fluconazole | 1st trimester | Craniofacial and skeletal defects, pulmonary artery hypoplasia |
| Iodine | 2nd-3rd trimesters | Goiter |
| Isotretinoin, Acitretin | 1st trimester | microtia, anotia, thymic aplasia, cardiovascular defects |
| Lithium | 1st trimester | Ebstein-anomaly |
| Methimazole | Up to 7 week from conception | aplasia cutis, choanal atresia, esophageal atresia, minor facial defects, hypoplastic or absent nipples, psychomotor delay |
| Methyl mercury | | Cerebral palsy, mental retardation |
| Methylene blue (intra-amniotic) | 2nd-3rd trimesters | Intestinal atresia and/or occlusion, newborn hemolytic anemia, hyperbilirubinemia |
| Misoprostol | 1st trimester | Defects secondary to attempted abortion, vascular disruption, limb defects |
| Mycophenolate | 1st trimester | Spontaneous abortion, external ear defects, facial anomalies, cleft lip/palate, defects of distal limbs, heart, esophagus, and kidneys |
| NSAIDs | After 32 weeks | Premature closure of the ductus arteriosus |
| Paramethadione | 1st trimester | Mental retardation, craniofacial defects, kidney/ureter defects, developmental delay |
| Penicillamine | Unknown | Cutis laxa, craniofacial defects |
| Phenobarbital/primidone | 1st trimester | Mental retardation, cardiovascular and urinary tract defects |
| Phenytoin | 1st trimester | Fetal hydantoin syndrome, facial defects, oral clefts, mental retardation |
| SSRIs, SNRIs | 2nd – 3rd trimester | Seizures, withdrawal, serotonin syndrome, low birth weights |
| Tamoxifen | 8 week – term | Ambiguous female genitalia |
| Tetracycline | 2nd – 3rd trimester | Discoloration of teeth |
| Thalidomide | 20-36 days after conception | Limb, skeletal, and craniofacial defects, brain, respiratory, gastrointestinal, cardiac and genitourinary defects |
| Trimethoprim | 1st trimester | Cardiovascular defects |
| Valproic acid | 1st trimester | Spina bifida, facial defects, retarded psychomotor development |
| Warfarin | 6th-9th week<br><br>2nd-3rd trimester | Fetal warfarin syndrome defects<br><br>Hemorrhage-induced brain damage, blindness, optic atrophy, microphthalmia |

Healthcare professionals who care for pregnant patients have a responsibility to use their knowledge and resources to provide conscientious care and recommendations for expectant mothers while also considering the care and well-being of her child.

## COUGH AND COLD

Cough and cold products are some of the most common recommendations made in the community pharmacy setting. These should be made based on a thorough patient history. Although OTC medications are generally regarded as safe when taken correctly for the typical patient population, pregnancy presents a unique situation. Many over the counter medications are available to treat the symptoms associated with various viral and bacterial infections. Although there are a multitude of over the counter products marketed, they only represent a few varied active ingredients. The remainder of this section will cover each class of these active ingredients.

### Nasal Decongestants

Nasal decongestants are a common go-to product for many patients seeking relief for symptoms of several infectious processes. Although there are numerous products marketed as decongestants there are only two main over the counter oral decongestants: pseudoephedrine and phenylephrine. Pseudoephedrine and phenylephrine have similar mechanisms of action in regards to their decongestant effects with one exception: pseudoephedrine acts as a sympathomimetic that directly stimulates alpha and beta-adrenergic receptors, whereas phenylephrine is a potent alpha-adrenergic agonist with no beta activity.[2,4,5,6] This is a small but important distinction in pregnancy since alpha stimulation promotes uterine contractions and beta stimulation has the opposite effect. This generally leads to the conclusion that pseudoephedrine is preferred for nasal decongestion in pregnancy over phenylephrine.[5] Even so, both compounds should be avoided during the first trimester of pregnancy since there have been case reports and surveillance studies showing a possible connection between their use and intestinal abnormalities and obstructions. The two decongestants should also be used with caution in patients with hypertension, preeclampsia, diabetes, premature labor, preterm premature rupture of membranes, and incompetent cervix.[2] There are also several over the counter decongestant nasal sprays. These nasal sprays contain alpha adrenergic medications that are generally regarded as safe as long as they are used intermittently. They are administered for local effect but do have some systemic absorption and should therefore be used sparingly.

### Antihistamines

There are a wide number of antihistamines available in multiple formulations. As a general rule, first generation antihistamines are preferred during pregnancy.[4] These include diphenhydramine, chlorpheniramine, and clemastine; diphenhydramine has the most data to support its use.[5,6] One exception to the support of diphenhydramine use was a case report from 1971 in which authors concluded that there may be an association between 1st trimester exposure and cleft palate.[4] Second generation antihistamines are acceptable to use during pregnancy after the 1st trimester if a first generation cannot be utilized. The second generation antihistamines include loratadine, cetirizine, and fexofenadine. Loratadine and cetirizine have more data to support their use compared to fexofenadine and the non-racemic isomers levocetirizine and desloratadine.[2] In general, antihistamines do not have any direct action on the heart, affect blood glucose, or have action with the uterus or its vasculature.

### Fever and/or Anti-inflammatory

There are two main OTC classes of medications used for the treatment of fever: acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs). When used for fever reduction, acetaminophen is preferred since it is a weaker inhibitor of prostaglandins and cyclooxygenase.[2,6] Therefore, it has less risk associated with bleeding and uterine contractions. NSAIDs are potent inhibitors of prostaglandins and cyclooxygenase and have been known to cause complications in pregnancy such as prolonged gestation, dysfunctional labor, increase hemorrhage, and premature constriction of the ductus arteriosus. NSAIDs could be used during the 1st and 2nd

trimester as a single dose if it is the only option since it is unlikely to cause serious fetal harm with a single dose. However, use in the 3rd trimester should always be avoided.

## Expectorants

There is currently only one expectorant available: guaifenesin. The mechanism of action of guaifenesin is not well understood but it is thought to act as an expectorant by hydration of the respiratory tract.[6] Guaifenesin also acts by inhibiting cough reflex sensitivity in patients with upper respiratory tract infections possibly by increasing sputum volume that may cover the cough receptors within the respiratory tract. Since guaifenesin has minimal actions systemically and few side effects it is generally regarded as safe to use during pregnancy.[2,4]

## Cough suppressant

There is currently only one active ingredient used as an antitussive that is available over the counter: dextromethorphan. There is a low risk of congenital defects within the normal dose range.[2,4,6] Patients should be counseled that there are formulations that contain ethanol which should be avoided during pregnancy. Dextromethorphan is generally regarded as safe for use during pregnancy within the normal dosage range, and caution should be used when selecting the appropriate formulation.

## Throat lozenges

Various types of throat lozenges and cough drops are available over the counter with a wide variety of ingredients. Camphor, menthol, and benzocaine are some of the more common ingredients but others may include dyclonine, phenol, resorcinol, boric acid, and cetylpyridinium.[2] The majority of the lozenges and cough drops have agents that include a local anesthetic and/or antiseptic/disinfectant that act locally. Since the majority of use is as needed, little systemic absorption occurs; however, with prolonged or excessive use systemic absorption can occur. The majority of the ingredients cross the placenta but little data exists as to the effects. Benzocaine has been reported to cause methemoglobinemia very rarely so should be avoided if prolonged use is necessary.

# CONSTIPATION AND DIARRHEA IN PREGNANCY

## Constipation

Constipation is described as infrequent bowel movements or difficulty of evacuation, and an estimated 11-38% of pregnant women experience constipation. This is likely because pregnancy predisposes women to developing constipation due to hormonal changes. Increased progesterone levels and decreased motilin levels during pregnancy account for a prolonged bowel transit time. In addition to this, the intestines increase their water absorption, promoting stool to dry out. Increased vitamin (iron and calcium) intake and decreased maternal activity can also contribute to constipation. As pregnancy progresses, a larger uterus slows the progression of feces. If left untreated constipation can lead to fecal impaction. It is second only to nausea as the most common gastrointestinal complaint in pregnancy.[7]

Treatment of constipation is often relieved by increasing dietary fiber and fluid intake, probiotics, as well as exercise. These should always be used as first-line therapy before progressing to laxatives. In general, there is limited evidence on the use of laxatives in pregnancy, but in general they appear to not be systemically absorbed well. Table 2 provides a list of laxatives.[7]

**Table 2. Laxatives**

| Treatment | Mechanism of Action | Examples |
|---|---|---|
| Bulk-forming agents | Binding of water increases stool's bulk making it easier to pass | Psyllium, bran |
| Stool softeners | Stimulates secretion of water, sodium, chloride, and potassium, and inhibits absorption of glucose and bicarbonate | Docusate sodium or calcium |
| Lubricant laxatives | Decreases surface tension of bowel's liquid contents | Mineral oil |

| Treatment | Mechanism of Action | Examples |
|---|---|---|
| Osmotic laxatives | Increases osmolar tension leading to increased water collection | Salts, magnesium sulfate, lactulose, sorbitol PEG |
| Stimulant laxatives | Stimulates colonic motility | Bisacodyl, senna |

Bulk forming agents are not absorbed in the intestines and are not associated with fetal malformations. They are safe to use long-term, although some side effects may include gas, bloating, and cramping. Regarding stool softeners, docusate sodium has not been associated with adverse effects and is considered safe for use in pregnancy. Of note, there is one case report of maternal chronic use with docusate sodium throughout pregnancy and led to symptomatic hypomagnesemia in the neonate. Mineral oil is also poorly absorbed and safe for use in pregnancy. Osmotic laxatives lactulose and PEG are not absorbed systemically and their use has not been associated with adverse effects. Stimulant laxatives bisocodyl and senna have poor bioavailability and are therefore not well absorbed. In general, the osmotic and stimulant laxatives are considered safe to use, though prolonged use could lead to electrolyte imbalances. In general, it is not recommended that the stronger laxatives (cascara, senna, castor oil, and magnesium products at laxative doses) be used without the knowledge of the patient's provider.[2,7]

## Diarrhea

While diarrhea is not as common as constipation, it is still a complication that pregnant women may experience. Diarrhea often is relieved after a couple of days without any medication. Loperimide is a potential treatment option. Diphenoxylate is not recommended for use as it often contains atropine which crosses the placenta and can increase fetal heart rate.[2,7]

## NAUSEA AND VOMITING IN PREGNANCY

Nausea and vomiting of pregnancy (NVP) occurs in 70-85% of all pregnant women.[2] It is thought that estradiol and human chorionic gonadotropin (hCG) are responsible for NVP. Although NVP is a troublesome problem, there has been substantial evidence showing that women who experience it have fewer pregnancy losses.[2] Although there are several treatment options, many women forgo treatment either due to ineffective therapy or fear of harm to the fetus. The primary goal of therapy is prevention. In the case of NVP occurring, the secondary goal of therapy is to treat the symptoms to a tolerable level. The most severe form of NVP is hyperemesis gravidarum. There have been several risk factors for NVP and hyperemesis gravidarum identified, including increased placental mass, family or personal history of hyperemesis gravidarum, and a history of motion sickness or migraine headaches.[2]

As stated previously, prevention is the primary goal of NVP. The recommended options are in Table 3. [2]

**Table 3. Recommended Options for Prevention of NVP**

| | |
|---|---|
| **Diet** | Avoiding spicy foods, eating frequent small meals, high protein snacks in the morning, and a dry low-fat bland diet. |
| **Multivitamins** | Begin taking multivitamins at time of conception. |
| **Rest** | Not directly studied, but may alleviate initial symptoms of NVP. |
| **Avoidance of Emetogenic Odors** | Triggering odors include foods, body odors, cigarette smoke, and perfumed soap. |
| **Avoidance of Iron Tablets** | Iron tablets often cause gastric upset. Iron supplementation is important, but if nausea/vomiting is present, women should stop taking the iron until nausea/vomiting has ceased. |

If prevention is inadequate, then treatment should be warranted. For women with nausea alone and none or infrequent vomiting, treatment should follow the same as prevention recommendations (avoiding triggers, rest, diet modification etc.), as well as vitamin B6 (pyridoxine) and pyridoxine/doxylamine (Diclegis). Vitamin B6 is the only vitamin to show an antiemetic effect and is a safe option for any pregnant woman suffering from NVP. Nausea that involves vomiting should be treated with doxylamine (a preferred antihistamine) and the combination of pyridoxine/doxylamine (Diclegis).

Other approved first-line and add-on pharmacologic options include:

- diphenhydramine 25-50mg every 4-6 hours
- meclizine 25mg every 4-6 hours
- dimenhydrinate (Dramamine) 25-50mg every 4-6 hours

Second line appropriate options include:

- metoclopramide (Reglan) 10mg every 6-8 hours
- promethazine 12.5-25mg every 4 hours
- perchlorperazine 5-10mg every 6 hours

A third-line option for patients with severe nausea/vomiting or have a history of hospitalizations due to NVP is ondansetron 4mg every 8 hours. Ondansetron should not be given during the first trimester due to a risk of fetal cardiovascular malformations. If NVP is refractory, then corticosteroids may be used. These should be a last-line option and are not to be given in the first trimester. Adjunctive agents for acid suppression may also be a beneficial choice. Aluminum or calcium containing, not bismuth or bicarbonate containing, antacids may be used. The greatest experience with acid suppression therapy in pregnant women is with the H2 receptor antagonists ranitidine and cimetidine.[8] A common non-pharmacologic treatment for women who have been dehydrated secondary to NVP include intravenous hydration. Typically, 1-2 liters of isotonic fluids are infused over several hours. [2,8]

A community pharmacist may be helpful in this area as many of the above drugs are available over the counter. Dimenhydrinate, meclizine, cyclizine, doxylamine, diphenhydramine, and H2 receptor antagonists are all options to recommend a pregnant patient who presents with nausea and/or vomiting. [2,8]

In summary, the combination of doxylamine and vitamin B6 should be first line treatment. If NVP persists, diphenhydramine or meclizine should be added. If symptoms do not improve, a dopamine antagonist such as metoclopramide should be added to therapy. For patients who become hospitalized due to dehydration from vomiting, ondansetron is recommended outside of the first trimester. If refractory NVP persists, corticosteroids can be used outside of the first trimester. [2,8]

## MANAGING PAIN AND HEADACHE IN THE PREGNANT PATIENT

As stated earlier, in the case of over the counter medications and conditions that are commonplace such as headache, pharmacists are in a position to offer their expertise to the expectant mother. While many pregnant patients will opt to refrain from taking any medications during pregnancy out of precaution, inadequately treated pain can lead to more serious complications such as hypertension, anxiety, or depression.[9] Analgesics can be broadly divided into two separate categories; namely, nonopioid analgesics and opioid analgesics.[9]

### Nonopioid analgesics

"Nonopioid analgesics" is sometimes used to refer to medications such as aspirin, acetaminophen, and NSAIDs.[9] This category of medications in particular warrants discussion as often times pregnant women may "self-treat" by obtaining these medications over the counter. Often times, over the counter medications are marketed using brand or trade names.[2] It is important to note that sometimes companies will change the active ingredient in these medications but keep the trade name the same. Therefore, it is incumbent upon pharmacists and other healthcare providers to always pay attention to the active ingredients in over the counter medications.[9]

### Acetaminophen

Acetaminophen has been studied in pregnancy and is the first-line choice for nonopioid analgesics in pregnancy.[2] Unlike aspirin or NSAIDs, acetaminophen does not affect bleeding time.[2] As is the case with pregnant patients and non-pregnant patients, acetaminophen overdose is a concern and patients should be counseled about the appropriate dosage of acetaminophen. Barring overdose, acetaminophen is the analgesic of choice in pregnancy.[2] Of note, recent findings have suggested a risk of abnormal neurodevelopment associated with maternal acetaminophen use during pregnancy. Thus far, these findings are varied. One study published in *JAMA Pediatrics* found that maternal acetaminophen use in the 2nd and 3rd trimester is associated with higher incidence of multiple behavioral problems in children.[11] This study aimed to account for potential non-medical confounders that could explain the association. No obvious confounders were found; and, further research is needed to confirm these proposed risks.[11]

### Nonsteroidal Anti-inflammatory Drugs

There have been no conclusive studies that show that NSAIDs are teratogenic.[2] Similar to aspirin, NSAIDs exert action on the enzyme prostaglandin, and thus have the potential to cause similar adverse events when used chronically. Examples of this include prolonged gestation or dysfunctional labor.[2] However, a single dose of NSAID is unlikely to cause any significant problems.[2] Generally, NSAIDs are not a first-line option but can be considered in the 1st and 2nd trimester.[3] Use in the 3rd trimester is relatively contraindicated.[3] If it must be used in the 3rd trimester, close monitoring of the mother and fetus is warranted.[3]

### Aspirin

Aspirin is commonly used over the counter in pregnany.[2] Studies have shown that evidence for aspirin causing birth defects is inconclusive.[2] The use of aspirin to treat a short-term pain such as headache would likely pose little risk to the mother or fetus.[2] If used chronically more risk may be present. Aspirin inhibits prostaglandin synthetase, which is an enzyme that has a role in parturition.[2] Because inhibiting this enzyme may affect labor, one potential adverse effect of long-term use in pregnancy could be prolonged gestation.[2] Additionally, aspirin inhibits cycloxygenase, which could theoretically lead to prolonged bleeding time.[2] Due to these and other potential risks, the manufacturer recommends avoiding aspirin during pregnancy especially during the third trimester.[10] Despite these manufacturer recommendations, aspirin is commonly used and even occasionally recommended by physicians to prevent high blood pressure.[3] Studies have observed that low-dose aspirin (75-300 mg) may be useful in preventing high blood pressure in pregnancy.[3] Overall, aspirin may be a second-choice option for analgesic treatment in pregnancy (second to acetaminophen).[3] Individual doses do not appear to have negative effects, but regular use during pregnancy, especially during the third trimester, is not recommended due to potential fetal adverse outcomes.[3]

## Opioid analgesics

Opioids can be subdivided into pure agonists, partial agonists/antagonists, and pure antagonists.[3] This class of medication should be reserved for instances where other nonopioid pain medications are insufficient and the benefit to the mother outweighs the risk to the infant. With all opioid analgesics, there is a risk of respiratory depression and withdrawal symptoms in the infant, especially when used long term.[3] Preference should always be given to nonopioid analgesics if possible.[3] Even so, if indicated, options such as codeine or fentanyl may be used during pregnancy. Data suggests that withdrawal symptoms may be less severe with codeine as opposed to morphine.[3] Fentanyl is commonly used intravenously or via epidural during labor. When administered transdermally long-term during pregnancy, fentanyl has been shown to cause a mild withdrawal syndrome without long term effects. Caution should be exercised if these are used close to term due to the risk of respiratory depression and withdrawal.[3,4]

## INSOMNIA IN PREGNANCY

Pregnancy creates many different hormonal imbalances, which can affect sleep. Approximately 66-94% of women report sleep disturbances while pregnant with the primary change being insomnia. Insomnia is defined as one or more of the following: waking from sleep too early, difficulty initiating or maintaining sleep, and complaints of nonrestorative sleep. As evidenced by surveys, sleep increases during the first trimester and decreases during the third. The rate of sleep disturbances also increases among trimesters: 13% in first, 19% in second, and 66% in third. In pregnancy, it is hypothesized that sleep loss leads to negative pregnancy outcomes both for the mother and fetus. It has been shown that women who sleep less than 6 hours a night are at risk for longer labors, more Cesarean sections, and more spontaneous preterm deliveries.[12]

It is always recommended for pregnant women to attempt non-pharmacologic treatment before progressing to medication. Improving sleep hygiene, stimulus control, managing physical discomfort, exercise, meditation, and cognitive behavioral therapy may help insomnia. Most of the research being done is on the effects of *pharmacologic* therapy in pregnant women for insomnia, particularly with the newer hypnotic medications (zolpidem, zaleplon etc.) Evidence is lacking on the effectiveness of the *nonpharmacological* recommendations specifically in pregnant women.[12] Therefore, the first-line recommendation of nonpharmacological treatment stems from the concept of minimizing risk to the fetus.[12]

Pharmacologic treatment options for insomnia include benzodiazepines, hypnotics, and antihistamines. Benzodiazepines enhance the effect of the neurotransmitter GABA at the $GABA_A$ receptor. This results in sedative, hypnotic, anxiolytic, anticonvulsant, and muscle relaxant properties. Benzodiazepines do cross the placenta, and therefore have the potential to cause adverse events. Of all studies done, no statistically significant malformations were found in a control group vs. a benzodiazepine group. It remains uncertain as to if they increase the risk of low birth weight and preterm birth. All benzodiazepines are pregnancy category D, except temazepam, which is category X, due to their ability to cross the placenta. Benzodiazepines may be used in pregnant patients under the supervision of a physician and given in the lowest possible dose for the minimum amount of time.

The hypnotics, (zolpidem, zaleplon, eszopiclone) have effects like benzodiazepines but are structurally different. While these are the more popular agents in pregnancy, there remains minimal literature on their safety profiles. As stated above, much of the research being performed is currently aimed to this class. All three of these medications are pregnancy class C. Most studies that have been performed found no adverse events in the fetus of mother's who took zolpidem; although one study in Taiwan found an increase in low birth weight. There are no human studies for use of eszopiclone in pregnancy, but animal studies showed no teratogenicity. Studies evaluating zaleplon have shown no teratogenicity.[12,13]

Pregnant patients will often try to self-treat their insomnia with nonprescription antihistamines. While these are primarily used for allergy symptoms, they also have a sedating effect. Diphenhydramine is the only antihistamine, which has outcomes data for use in insomnia. Data has shown no increased risk of cardiac effects, birth defects or major malformations. Again, it is always advised to counsel on non-pharmacologic treatments before recommending medications.[13]

## VACCINES IN PREGNANCY

The administration of vaccines during pregnancy is of concern for many physicians and patients that are either pregnant or wish to become pregnant. Although the majority of the vaccines are safe and even recommended during pregnancy, there are still misconceptions about what can and cannot be administered. There has been no evidence of risk vaccinating pregnant women with inactivated virus or bacterial vaccines or toxoids.[2] Furthermore, the risk of fetal harm is theoretical with live vaccines, but does warrant contraindication. An example of this can be shown with measles, mumps, and rubella (MMR). The risk of possible transmission of disease from mother to fetus

could potentially lead to an increased risk of spontaneous abortion for all three diseases and measles has been linked to malformations in the fetus.[3]

Due to these theoretical risks the vaccination adverse events reporting system (VAERS) was utilized to search for adverse events in pregnant women for the past 20 years; including females ages 18 to 59 years. The reporting system produced two incidences of complications in a pregnant woman. The two incidences occurred with women that were ages 30 to 39 years. The first woman passed away due to cardiac arrest of unknown cause two days after receiving two different inactivated influenza vaccines. The second female had a stillbirth six days after receiving tetanus and diphtheria toxoids and acellular pertussis vaccine (Tdap). In both cases vaccines were administered, but both patient outcomes were deemed due to unknown cause.[14]

Since there is limited evidence to suggest harm in vaccination during pregnancy, and the benefits of vaccination outweigh the risk, it is important to understand the current Center for Disease Control's (CDC) recommendations. The recommendations for vaccinations during pregnancy have not changed drastically in recent years. The current recommendations are summarized in Table 4.

**Table 4. [3,14,15,16] Vaccine Recommendations for the Pregnant Patient**

| Vaccine | Recommended | Comments |
|---|---|---|
| Influenza | Yes | All inactivated vaccines are recommended for all patients during flu season.<br>Live vaccines (ex. FluMist) are contraindicated. |
| Tdap | Yes | Recommended for every pregnancy regardless of time elapsed.<br>Recommended during weeks 27 to 36 gestation. |
| Td | Possible | Tdap is preferred, though Td may be given if Tdap will be unavailable during pregnancy. |
| HepA | Possible | Risk of infection and harm from infection is low for mother and baby. If patient is at high risk then vaccination may be recommended.[A] |
| HepB | Possible | Only recommended for pregnant women who are at risk for hepatitis B infection.[B] |
| Meningococcal | Possible | Recommended if other conditions warrant vaccination. |
| Pneumococcal | Possible | Recommended if other conditions warrant vaccination. |
| HPV | Not recommended | If patient is found to be pregnant after initiation of series, then delay the remaining doses until after the pregnancy. |
| HZV | Contraindicated during pregnancy | May consider if other conditions warrant vaccination. |
| MMR | Contraindicated during pregnancy | Pregnant women who do not have evidence of immunity to rubella should receive 1 dose of MMR upon completion or termination before discharge. |
| VAR | Contraindicated during pregnancy | Pregnant women who do not have evidence of immunity should receive 1st dose of VAR upon completion or termination of pregnancy before discharge, followed by 2nd dose 4 to 8 weeks later. |

[A] *Risk for hepatitis A infection: chronic liver disease, receive clotting factor concentrates, use of injection or non-injection drugs, work with infected primates or research laboratory, or travel to countries with high or intermediate levels of endemic hepatitis A infection.*

[B] *Risk for hepatitis B infection: more than one sex partner during the previous six months, being evaluated or treated for a sexually transmitted infection, recent or current injection drug use, or had an HBsAG-positive sex partner.*

Although no vaccine is currently available for Zika virus the National Institute for Allergy and Infectious Diseases is actively working on a vaccine in animal models.[17] The Zika virus is a member of the flavivirus family, which includes such diseases as dengue, yellow fever, and West Nile fever. Infected individuals are usually unaware, and of the 20% of individuals that do have symptoms, they are typically mild. Symptoms of the virus typically include fever,

rash, and joint pain. Though symptoms of the virus are usually mild in the infected patient, Zika virus can be transmitted from mother to fetus and lead to serious birth defects. Therefore, the National Institute for Allergy and Infectious Diseases has made the discovery of a vaccine of upmost importance. Current guidance from the CDC and HAN advisory are for pregnant women to not travel to areas with active Zika virus, if partner travels to areas with Zika virus; then use condom to prevent transmission, and if possible exposure to the virus then get tested 2 to 12 weeks after possible exposure.[18,19]

## CONCLUSION

In summary, pharmacists play a key role in the care of the pregnant patient. They are uniquely equipped and positioned to make recommendations to their patients regarding common ailments and complaints. For some of these common complaints, such as cough and cold, headache, constipation, etc. pharmacists can make educated recommendations to the pregnant patient for appropriate over the counter medications. Under any circumstance, whether over the counter or prescription medications, it is always imperative for the pharmacist to consider the well-being of both the mother and her child to provide the best possible care.

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