REVIEW ARTICLE

Allergy Medications During Pregnancy

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ABSTRACT

Allergic diseases are common in women of childbearing age. Both asthma and atopic conditions may worsen, improve or remain the same during pregnancy. Primary care physicians commonly encounter women receiving multiple medications for pre-existing atopic conditions, who then become pregnant and require medication changes to avoid potential fetal injury or congenital malformations. Each medication should be evaluated; intranasal and inhaled steroids are relatively safe to continue during pregnancy (budesonide is the drug of choice), second-generation antihistamines of choice are cetirizine and loratadine, leukotriene receptor antagonists are safe, sparing use of oral decongestants during the first trimester and omalizumab may be used for both uncontrolled asthma and for antihistamine-resistant urticaria. Medications to avoid during pregnancy include intranasal antihistamines, first-generation antihistamines, mycophenolate mofetil, methotrexate, cyclosporine, azathioprine and zilueton. Common allergic diseases may develop de novo during pregnancy, such as anaphylaxis.


INTRODUCTION

In the United States, more than 40% of women of childbearing age suffer from rhinitis and up to one-third of them experience worsening symptoms during pregnancy. Asthma affects up to 8% of pregnant women in the United States. The prevalence of anaphylaxis is approximately 2%, whereas chronic urticaria affects 0.5-1% of the general population. Hence, it is not at all uncommon for a woman with a pre-existing allergic condition to become pregnant. The most common concern is to identify effective medications that are safe for pregnant patients. This article reviews the most common medications used to treat, and to avoid, for pre-existing allergic conditions that continue during pregnancy. Additionally, allergic conditions that develop during pregnancy will be discussed.

ALLERGY MEDICATIONS FOR THE PREGNANT PATIENT

Pre-existing atopic conditions may worsen, remain the same or improve with pregnancy. As with non-pregnant patients, the initial management of allergic conditions during pregnancy is taking allergen avoidance measures. Pharmacotherapy is initiated when avoidance measures have failed to control symptoms. Selection of medications for allergic conditions during pregnancy should be based on Food and Drug Administration risk categories (Table 1). Category A and category B drugs are safe to use during pregnancy, whereas category D and category X drugs should be avoided. This leaves category C drugs (animal reproduction studies in humans) that should be considered on a case by case scenario. The most critical time that a potentially teratogenic drug could induce congenital malformations is during the first trimester. There are currently no category A medications used to treat allergic conditions during pregnancy; most medications belong to category B or category C. Table 2 summarizes allergy medications that should be completely avoided during pregnancy along with suitable alternatives presently believed to be safe. Ideally, these medications should be started before conception (to assure tolerance and efficacy) and women should be made aware of this advantage when planning to become pregnant.

Intranasal Steroids

Intranasal steroids (INS) (e.g., fluticasone, mometasone, budesonide, flunisolide and triamcinolone) are the drugs of choice for allergic rhinitis. It is not uncommon to see patients with established allergic conditions using these medications at the time of conception. These medications, virtually all category C drugs, are considered safe during pregnancy by current guidelines; if they were and remain effective, it is reasonable to continue them. However, most allergists would switch patients to budesonide, the only category B INS with extensive safety evidence for pregnant patients. Notably, rhinitis of pregnancy (discussed later) does not respond to INS. Furthermore, patients should be encouraged to continue avoidance measures of known allergens. Some effective measures include closing windows, using air conditioning, limiting exposure to the outdoors when pollen counts are high, wearing sunglasses, showering before bedtime, avoiding exposure to animal dander...
and using zippered casings for bedding (to minimize exposure to dust mites).8 Other approaches before starting INS include nasal saline irrigation methods via bulb syringe or various squeeze bottles (i.e., “sinus rinse”). Nonallergic rhinitis (e.g., vasomotor rhinitis) is diagnosed when patients with symptoms of sneezing, rhinorrhea, nasal congestion, or postnasal drainage (in any combination or all symptoms together) are present in the absence of a specific etiology. INS are also the drugs of choice for this condition during pregnancy.13

**TABLE 1.** FDA pregnancy risk categories.

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Adequate studies in pregnant women have not demonstrated a risk to the fetus in the first trimester of pregnancy, and there is no evidence of risk in later trimesters.</td>
</tr>
<tr>
<td>B</td>
<td>Animal studies have not demonstrated a risk to the fetus, but there are no adequate studies in pregnant women. Or Animal studies have shown an adverse effect, but adequate studies in pregnant women have not demonstrated a risk to the fetus in the first trimester of pregnancy and there is no evidence of risk in later trimesters.</td>
</tr>
<tr>
<td>C</td>
<td>Animal studies have shown an adverse effect on the fetus, but there are no adequate studies in human beings/the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks. Or There are no animal reproduction studies and no adequate studies in human beings.</td>
</tr>
<tr>
<td>D</td>
<td>There is an evidence of human fetal risks, but the potential benefits from the use of the drug in pregnant women may be acceptable despite potential risks.</td>
</tr>
<tr>
<td>X</td>
<td>Studies in animals or human beings demonstrate fetal abnormalities, or adverse reaction reports indicate evidence of fetal risk. The risk of use in pregnant woman clearly outweighs any possible benefit.</td>
</tr>
</tbody>
</table>

**Intranasal Antihistamines**

Azelastine is a phthalazinone derivative with histamine-1 receptor binding approximately 10-fold greater than chlorpheniramine,10 which is available in 2 forms—intranasal azelastine hydrochloride and azelastine with sorbitol nasal spray.11 This common intranasal antihistamine used for allergic rhinitis and nonallergic rhinitis should be avoided during pregnancy. It has been associated with minor adverse effects on fetal animals and no safety data are available in humans. This medication is also costly12 and is associated with sedation.13

**Oral Antihistamines**

Antihistamines are commonly used to treat pruritus and rhinorrhea in the general population. First-generation antihistamines (e.g., brompheniramine and hydroxyzine) are not prescribed by allergists to pregnant patients. Diphenhydramine has been associated with fetal development of cleft palate14 if administered during the first trimester. There is recent evidence demonstrating the association of first-generation antihistamines use and increased risk of dementia.15

Second-generation antihistamines are preferred over first-generation agents in both pregnant and nonpregnant individuals. Patients should be started on cetirizine16,17 or on loratadine18,19 based on their excellent safety data and recommendation in multiple guidelines for other allergic conditions (e.g., asthma20 and chronic urticaria21) during pregnancy. As an added benefit, cetirizine may also relieve nausea and vomiting during pregnancy.22 Both fexofenadine and desloratadine have been associated with low—birth-weight offspring in animal models and are currently classified as category C drugs. The use of high-dose antihistamines

**TABLE 2.** Drugs to avoid during pregnancy and alternatives.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Avoid</th>
<th>Alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic rhinitis</td>
<td>Oral/intranasal decongestants, intranasal antihistamines</td>
<td>Intranasal steroids, budesonide is preferred8</td>
</tr>
<tr>
<td>First-generation systemic antihistamines</td>
<td>Cetirizine,16,17 loratadine18,19</td>
<td></td>
</tr>
<tr>
<td>Most second-generation systemic antihistamines</td>
<td>Cetirizine,16,17 loratadine18,19</td>
<td></td>
</tr>
<tr>
<td>Rhinitis of pregnancy</td>
<td>Intranasal antihistamines</td>
<td>Avoidance measures, intranasal steroid trial, ipratropium bromide, limited use of phenylpropanolamine26</td>
</tr>
<tr>
<td>Asthma</td>
<td>Systemic corticosteroids</td>
<td>Inhaled corticosteroids, budesonide is preferred,28 omalizumab41</td>
</tr>
<tr>
<td>Most inhaled long-acting beta agonists</td>
<td>Salmeterol,26 omalizumab41</td>
<td></td>
</tr>
<tr>
<td>Zileuton</td>
<td>Montelukast or zafirlukast23,24</td>
<td></td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>Ultraviolet therapy, topical calcineurin inhibitors and high-potency steroids</td>
<td>Low-to-mid potency topical steroids36</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>Skin testing, challenges</td>
<td>Serum-specific IgE testing, epinephrine</td>
</tr>
<tr>
<td>Chronic urticaria/angioedema</td>
<td>Metycloprenol maleate, methylxenate, cyclosporine, azathiophine</td>
<td>Cetirizine, loratadine, omalizumab16-19,41</td>
</tr>
<tr>
<td>Drug allergy</td>
<td>Skin testing, challenges</td>
<td>Serum-specific IgE testing</td>
</tr>
</tbody>
</table>
in patients with chronic urticaria patients (who may require up to 4 times the Food and Drug Administration-approved dose), has not been studied in pregnancy. Risk and benefits should be considered along with the expertise of a board-certified allergist before using these medications.21 Medications commonly used in the general population for antihistamine-resistant chronic urticaria, including mycophenolate mofetil, methotrexate, cyclosporine and azathioprine, are contraindicated during pregnancy.

**Antileukotriene Agents**

Montelukast and zafirlukast are leukotriene receptor antagonists believed to be safe to use for both asthma and allergic rhinitis during pregnancy.23,24 These medications are suitable alternatives as sole therapy in mild persistent asthma (step 2) or as an alternative to long-acting beta agonists in moderate persistent asthma (step 3 or 4). Antileukotriene agents are not an alternative treatment in severe persistent asthma (step 5 or 6).20 Zileuton, a 5-lipoxygenase inhibitor, is contraindicated during pregnancy.

**Oral Decongestants**

Oral decongestants should be avoided during the first trimester owing to a risk of developing gastroschisis (an abdominal wall birth defect) and small intestinal atresia in the offspring.7 After the first trimester, these should be used sparingly (<3-day course).25 There is some limited evidence of the therapeutic value of phenylpropanolamine after the first trimester26 for pregnancy rhinitis (discussed below).

**Inhaled Corticosteroids and Bronchodilators**

Pregnancy affects asthmatics in different ways—one-third of patients will worsen, one-third will improve and one-third will remain unchanged.5,27 Severe acute asthma attacks can result in hypoxia, adversely affecting both mother and fetus. Thus, national guidelines28 recommend having maternal asthma under control on medications rather than allowing the mother to suffer with uncontrolled asthma to avoid medications. The approach to asthma during pregnancy is very similar to the paradigm in nonpregnant asthmatics—prevention of severe exacerbations, improvement of quality of life and maintenance of normal lung function. Methacholine challenge tests are not recommended during pregnancy, though simple spirometry is safe to perform. Close follow-up with, and coordination between, the patient’s obstetrician and asthma care provider is imperative for all pregnant women with asthma.

A recent Cochrane review29 failed to identify an optimal (safe and effective) combination of medications to control asthma during pregnancy. Albuterol is the preferred short-acting β2-agonist and budesonide is the preferred inhaled corticosteroid. This is based on multiple studies demonstrating their safety in pregnant women with asthma.28 A systematic review of 16 studies concluded that there was no association between the use of bronchodilators or inhaled corticosteroids or both with congenital malformation risk.30 The safety of long-acting bronchodilators (salmeterol and formoterol) during pregnancy is comparable to that of inhaled corticosteroids.31 The preferred long-acting bronchodilator for pregnant patients is salmeterol.28,32 Salmeterol should not be used as a single controlling agent, as it has been associated with serious asthma episodes or asthma-related deaths.23 Long-acting bronchodilators should only be used in combination with inhaled corticosteroids.

**Oral Corticosteroids**

Systemic steroids are commonly used to treat acute asthma exacerbations. These may increase the risk of low birth weight, intrauterine growth restriction,33 preterm birth34 and preeclampsia.35 However, the benefits of systemic steroids in controlling asthmatic attacks outweigh the risks during pregnancy, as adequate asthma control on medications is superior to no control off medications. Prednisone may also be indicated for acute exacerbations of urticaria or anaphylaxis.

**Topical Steroids**

Topical steroids are commonly used for atopic dermatitis. The treatment of atopic dermatitis during pregnancy should focus on avoidance measures and use of emollients. Topical glucocorticoids have been shown to be safe during pregnancy.36 However, these should be limited to low-level and mid-level potency steroids, as higher potency agents have been implicated in fetal growth restriction.37 Topical calcineurin inhibitors should be avoided during pregnancy.

**Omalizumab**

Omalizumab is a humanized monoclonal antibody approved for uncontrolled allergic asthma and antihistamine-resistant chronic idiopathic urticaria. In an observational study of 188 pregnant women on omalizumab for uncontrolled asthma, there was no apparent increase in the incidence of birth anomalies compared to pregnant patients not receiving omalizumab in the general population.38 There are only observational studies on the use of omalizumab for chronic idiopathic urticaria.39,40 Many allergists recommend not starting omalizumab during pregnancy because of the black box warning risk of anaphylaxis, which may jeopardize the lives of both mother and fetus.

**Allergen Immunotherapy**

Allergen immunotherapy, either subcutaneous or sublingual, should never be initiated during pregnancy because of the risk of anaphylaxis. However, if a patient who becomes pregnant is already receiving
allergen immunotherapy, it should be continued (but without increasing the dose) throughout her pregnancy.41,42

ALLERGIC CONDITIONS FIRST PRESENTING DURING PREGNANCY

Rhinitis of Pregnancy

Rhinitis of pregnancy is diagnosed after 6 weeks of significant nasal congestion and rhinorrhea without evidence of respiratory infection or history of rhinitis. Symptoms usually start after the second month of pregnancy and resolve within 2 weeks after delivery. It has been estimated to occur in 20-30% of pregnancies.43 The pathophysiology is unknown. Management should be focused on nonpharmacologic therapies such as saline sprays or irrigation,44 nasal alar dilators45 and regular physical exercise.46 Pregnancy rhinitis generally does not respond to pharmacotherapy, including INS.9 However, INS should be used on a trial basis as some patients may respond to this therapy. There is some anecdotal evidence that ipratropium bromide nasal spray (0.03%), category B rating in pregnancy, may be of some benefit. There is limited evidence that phenylpropanolamine (an oral decongestant) may be beneficial during pregnancy but should be limited to a 3-day course and avoided completely during the third trimester.26 Patients with rhinitis of pregnancy may benefit from an allergy evaluation. A suggested approach to pregnancy rhinitis is presented in the Figure.

Anaphylaxis

Anaphylaxis may occur at any stage of pregnancy and place both mother and fetus in jeopardy.3 The prevalence is approximately 3 cases per 100,000 deliveries.47 Etiologies during pregnancy are the same as in the general population. During the peripartum period, the most common identifiable trigger is prophylactic beta-lactam antibiotics administered to prevent neonatal group B streptococcal infection.57

The evaluation of anaphylaxis during pregnancy should be limited to measurement of serum allergen-specific immunoglobulin E (IgE). However, serum allergen-specific IgE has a lower sensitivity yield compared to skin prick testing. Skin testing, antigen challenges, desensitization and immunotherapy initiation should be deferred until after delivery because of a small risk of anaphylaxis associated with these procedures. However, in some cases the benefits may outweigh the risk (i.e., venom immunotherapy initiation during pregnancy41 or penicillin desensitization in maternal syphilis). The management of anaphylaxis during pregnancy is the same as for nonpregnant patients (i.e., epinephrine and advanced cardiac life support).

Drug, Food and Stinging Insect Allergy

Penicillin skin testing, performed by a board-certified allergist, can be performed safely in pregnant women with a history of mild cutaneous reactions to penicillin.48 This is particularly useful to prevent group B streptococcal disease during pregnancy.49 There have been no studies evaluating stinging insect allergies during pregnancy. However, there are limited data suggesting a 20% prevalence of food allergies in a study of almost 1,000 pregnant women in the United Kingdom.50 As previously discussed, skin testing and desensitization should be deferred until after pregnancy in these conditions. There are some exceptions—anaphylaxis due to

![FIGURE. A suggested approach to pregnancy rhinitis. INS, intranasal steroid.](https://www.amjmedsci.com/C15)
insect stings and syphilis during pregnancy in a penicillin-allergic patient. Management is limited to avoidance measures and blood testing for serum-specific IgE.

Contact Dermatitis

There are no data on the prevalence of contact dermatitis during pregnancy. Patients who are pregnant or who are breastfeeding should not be patch tested.33

CONCLUSIONS

Allergic conditions are common in the pregnant patient. Medications for pre-existing allergic conditions during pregnancy should be evaluated and changed according to both safety and efficacy data. Allergen avoidance measures to known allergens, as previously discussed, remain the best first-line approach during pregnancy.

The most commonly applied principle for INS during pregnancy is to maintain administration of the drug (i.e., fluticasone) that has controlled the patient’s symptoms in the past. If the pregnant patient has not initiated an INS, budesonide should be the INS of choice. The same concept applies for inhaled corticosteroids during pregnancy. As the drug also relieves nausea, cetirizine should be used sparingly and only after the first trimester.

There are also de novo conditions during pregnancy such as anaphylaxis. The approach to anaphylaxis is similar to that in the nonpregnant patient; for acute anaphylaxis, epinephrine and advanced cardiac life support should be provided. However, skin testing or challenges or both as part of a diagnostic evaluation should be avoided in almost all conditions.

Patients should be invited to participate in the decision-making process with a discussion of the risks and benefits of each medication. Ideally, patients planning on becoming pregnant should have this discussion with their primary care providers before conception.

REFERENCES


