

THE DIAGNOSIS AND MANAGEMENT OF ASTHMA DURING PREGNANCY

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Asthma is one of the most common illnesses that complicate pregnancy. It has been conservatively estimated that 1% to 4% of pregnancies are affected by bronchial asthma, but this figure may be much higher, as 10% or more of the general population appear to have nonspecific airway hyperreactivity, a hallmark of asthma.^{23, 35} If left untreated, asthma can lead to serious complications for both mother and fetus. Fortunately, when appropriately managed, mother and baby should have an outcome not significantly different from pregnancies unaffected by asthma.^{2, 11, 24, 55} Following the tragic experiences with thalidomide during the 1960s,⁵⁶ many women are reluctant to take, and some physicians to prescribe, medications during pregnancy. Although this reluctance to take medication can be very problematic, it may provide an opportunity to place emphasis on preventive measures, including smoking cessation and the avoidance of environmental triggers; however, medications will be necessary in many cases.

Because extensive controlled human safety data on the effects of exposure to most medications during pregnancy is lacking, it is generally recommended that the physician prescribe agents whose long track records have failed to demonstrate teratogenic or other adverse maternal or fetal effects. Prescribing any medication during pregnancy entails evaluating expected benefits and determining that these benefits outweigh the risks of adverse effects. When giving any treatment during

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pregnancy, one must obtain adequate informed consent, including an explanation of the consequences of failing to prescribe therapy that may alleviate the effects of potentially life-threatening asthma to mother, fetus, or both.²⁰

DIAGNOSIS OF ASTHMA DURING PREGNANCY

Fifty to 70% of pregnant women experience dyspnea, usually during their first or second trimesters, which cannot be explained by fetal growth.²³ It is vitally important to differentiate asthma from other causes of dyspnea, such as hormonally induced respiratory changes. In nonasthmatic physiologic dyspnea of pregnancy, there are no significant alterations in forced vital capacity (FVC) or forced expiratory volume in one second (FEV₁). In contrast, reduced values on spirometry or peak flow monitoring can usually be demonstrated if asthma is the cause of respiratory symptoms. If these objective measures are abnormal, they have clinical implications similar to those in nonpregnant persons and should be interpreted as evidence of abnormalities not explainable by the pregnancy.^{34, 31}

The single best measure of lung function in evaluating asthma is the FEV₁. If available, preconception baseline spirometry is helpful and is at least one reason for preconception communication and planning in known asthmatics. Pulmonary function tests (PFTs) should be performed on each visit during pregnancy to assess both severity and control of asthma. In moderate or severe cases, home peak flow meters should be provided, and any significant fluctuations reported to the physician at once. The symptoms of asthma can be insidious, and the uterus is not protected tissue. Thus, the pregnant woman may not feel markedly impaired yet could have pulmonary function abnormal enough to impair fetal oxygenation.²³

Other causes of gestational dyspnea (Table 1) include anemia, respiratory infections, such as bronchitis or pneumonia, cardiac disorders, physiologic dyspnea of pregnancy, and pulmonary embolism. If any of these conditions are suspected, chest radiographs (with proper shielding), echocardiography, or ventilation-perfusion scans can safely be obtained during pregnancy.¹⁰

PRINCIPLES FOR MANAGING ASTHMA DURING PREGNANCY

The principal goal of management of the pregnant asthmatic is to give birth to a healthy baby; other goals are similar to those for nonpregnant patients with asthma: to achieve normal, or near normal, pulmonary function with minimal or no adverse effects from therapy; to control symptoms without nocturnal awakening; to maintain normal activities without lost time from school or work; to actively participate

Table 1. CAUSES OF DYSPNEA IN PREGNANCY

Cause	Diagnostic Aids
Anemia	Hemoglobin/hematocrit
Anxiety-panic disorder	Spirometry, peak flow monitoring, pulse oximetry
Asthma	Spirometry, peak flow monitoring, pulse oximetry
Bronchitis or pneumonia	Chest radiograph to rule out pneumonia
Cardiac disease, including mitral stenosis; peripartum cardiomyopathy,* diastolic dysfunction associated with pre-eclampsia	Echocardiogram
Physiologic dyspnea of pregnancy	A diagnosis of exclusion; normal spirometry and peak flow
Pulmonary embolism	Ultrasonography or ventilation-perfusion scanning; pulmonary arteriography

*May occur after 20 weeks' gestation or up to 6 months postpartum.

Adapted from Carson MP, Rosene-Montella K: Common cardiac complications in pregnancy. *Women Health Primary Care* 2:533-544; 1999; with permission.

in exercise; and to avoid acute exacerbations and the need for emergency department visits or hospitalizations.²⁵ Undertreatment is the most common error in treating pregnant asthmatics.¹⁸ Although asthma experts stress the importance of asthma trigger avoidance, it is of great importance that aggressive medical treatment be administered, not only for acute symptoms, but for prevention of attacks. A crisis or emergency plan should be prepared for each patient in anticipation of an attack.

Various groups, including the National Heart, Lung, and Blood Institute (NHLBI) at the National Institutes of Health (NIH),^{33, 35} World Health Organization (WHO),⁶ American Academy of Allergy, Asthma, and Immunology (AAAAI), and American College of Allergy, Asthma, and Immunology (ACAAI),^{41, 61} have established guidelines or practice parameters for the diagnosis and management of asthma. In 1993 an expert panel at the NHLBI, the Working Group on Asthma and Pregnancy, published the report *Management of Asthma During Pregnancy*.³⁵ In May 1997 an updated *Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma* was published by the NHLBI. Table 2 summarizes the pharmacologic step therapy of asthma during pregnancy and is based on the *Expert Panel Report 2* modified for pregnancy.⁴⁹

EMERGENCY TREATMENT FOR ACUTE ASTHMA

Aggressive treatment is essential for an acute asthma attack to assure adequate oxygen supply to the fetus. Oxygen is administered to maintain maternal and fetal PO_2 . Fetal heart rate must be monitored during an asthma attack, observing for decelerations or absent variability. A PCO_2 of more than 35 mm Hg indicates CO_2 retention during pregnancy and may signal impending respiratory failure. In the event

Table 2. RECOMMENDATIONS FOR THE PHARMACOLOGIC MANAGEMENT OF ASTHMA DURING PREGNANCY*

Category	Frequency/Severity of Symptoms (Sx)	Pulmonary Function (FEV ₁ or PEF _R)†	Step Therapy
Mild intermittent	Sx ≤2 times a week Nocturnal Sx ≤2/mo Exacerbations brief (few hours to few days) Asymptomatic between episodes	≥80% Normal between episodes	Inhaled β ₂ -agonists as needed (for all categories)
Mild persistent	Sx >2 times per week but not daily Nocturnal Sx >2/mo Exacerbations may affect activity	≥80%	Inhaled cromolyn Substitute low-dose inhaled beclomethasone or budesonide if not adequate‡
Moderate persistent	Daily Sx Nocturnal Sx >1/wk Exacerbations affect activity	60%–80%	Inhaled beclomethasone or budesonide‡ Add oral theophylline or inhaled salmeterol§
Severe persistent	Continual Sx Limited activity Frequent nocturnal Sx Frequent acute exacerbations	<60%	Above + oral corticosteroids (burst for active symptoms, alternate day or daily if necessary)

*Based on National Asthma Educational Program Guidelines,^{34, 35} modified by the Position Statement from the American College of Allergy, Asthma, and Immunology, endorsed by the American College of Obstetricians and Gynecologists.⁴⁹

†Based on norm for the patient, which may be standardized norms or personal best.

‡Or other inhaled corticosteroids, based on recommendations in the text of this article.

§Consider montelukast or zafirlukast under special circumstances and preferably after the first trimester, based on recommendations in the text of this article.

of respiratory failure, the mother must be intubated and mechanically ventilated urgently.¹¹

NONPHARMACOLOGIC THERAPIES

An obvious goal, whether or not the patient is pregnant, is to control the environment in order to lessen exposure to triggers. Environmental control measures may eliminate or lessen the need for pharmacologic therapies. The implications of medication use during pregnancy are sometimes sufficient to encourage environmental control measure compliance that is otherwise rejected by the patient before conception.³²

Smoking is certainly an important trigger for asthma. In the Third

National Health and Nutrition Examination Survey, 1988 to 1994, 23.8% of mothers smoked during pregnancy.²² During pregnancy, carbon monoxide, nicotine, and cyanide cross the placenta from a smoker's blood, entering the fetal circulation.⁴ Fetal levels of these toxic substances usually exceed those of the mother. Nonasthmatic smokers generally deliver babies weighing 200 g less than nonsmokers. Many other adverse effects are seen in pregnant asthmatic smokers with severe uncontrolled asthma, including spontaneous abortion, the placental abnormalities placenta previa and abruptio placentae, preterm birth, and perinatal death. In addition, smoking may lead to abnormal fetal lung development.³⁰ Exposure to passive smoking actually provides a greater exposure to carbon monoxide and potential carcinogens than mainstream smoke. Second-hand smoke is a trigger for asthma; it can only be conjectured if there are other adverse effects of passive smoking on the fetus.

Other environmental triggers include warm-blooded pets, household mites, cockroaches, pollens, and mold spores. Reasonably simple and relatively inexpensive measures to control dust-mite allergen exposures are worthwhile. Bedding encasements with adequate and frequent laundering and carpet removal, especially in humid climates, are very useful. The use of vacuum cleaners with double-thickness or high-efficiency particulate air (HEPA) bags, or electrostatic filtration systems on the exhaust air also may be helpful under some circumstances. Acaricides and denaturants are not only of minimal value, but are difficult and inefficient to use. In addition, pregnant patients may not feel comfortable being exposed to these agents. Currently there are inadequate data to recommend the use of ionizers or air-filtration devices to control dust mites.

Cat and dog removal from the home is the simplest answer to improve dander allergen control, but rarely is accomplished. Animal allergen particles are smaller than those of dust mites and remain airborne longer. Therefore, air filtration may be more effective. A combination of moving pets to nonliving areas of the home, washing cats weekly, and removing reservoirs of pet allergens, including carpets and upholstered furniture, may provide limited benefit.⁴⁴ Air-conditioning, dehumidifiers, and other mold removal measures should be employed. Preconception planning should include environmental control and, if insufficient to prevent symptoms, allergen immunotherapy should be considered (see this article's section on immunotherapy). Potential parents may be counseled that they will be raising children at high risk for developing asthma and that creating a low-dust-mite and pet-free home may reduce the risk that their offspring will develop asthma. This recommendation may assist in the creation of a more suitable environment for the mother.

PHARMACOTHERAPY

Avoidance of environmental triggers rarely prevents asthma symptoms totally during pregnancy. Therefore, medication usually is necessary to control asthma in the mother. Therapy must allow adequate

oxygenation and growth of the fetus. The use of newer, more effective therapeutic options with no or inadequate human pregnancy data may be weighed against the use of older, less efficacious medications. When choosing drugs, the prescriber must look at the effects on both the mother and the fetus. Maternal considerations may include adverse effects such as drowsiness, tremors, or nausea. Fetal effects that should be contemplated include teratogenicity, growth retardation, and toxicity. Effects may vary during different stages of pregnancy (see article by Polifka and Jones elsewhere in this issue).

Many clinicians rely predominantly on the Food and Drug Administration (FDA) pregnancy risk categories to guide them on the selection of medications during pregnancy (Table 3). Based principally on animal studies, FDA risk categories offer only little comfort for prescriber or patient.³⁵ Recently, the FDA has recognized that these categories are inadequate and may be misleading and confusing. Public hearings are being held to consider an alternative to the current system of labeling.¹⁹ Older category C drugs, such as prednisone, inhaled corticosteroids, or theophylline, are effective therapies and have been used for many years with little or no apparent major problems; however, using only FDA risk categories as a guide, less efficacious category B products with only limited clinical experience, such as the leukotriene receptor antagonists, may be chosen.

Antihistamines

Approximately 20% of pregnancies are complicated by allergic rhinitis and other allergic disorders. Another 10% have nonallergic causes of

Table 3. FDA PREGNANCY RISK CATEGORIES

Category A	Controlled studies in women fail to demonstrate a risk to the fetus during the first trimester (and there is no evidence of a risk in later trimesters), and the possibility of fetal harm appears to be remote.
Category B	Either animal-reproductive studies have not demonstrated a fetal risk, but there are no controlled studies in pregnant women, or animal reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies during the first trimester (and there is no evidence of a risk in later trimesters).
Category C	Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women, or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.
Category D	There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).
Category X	Studies in animals or humans have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience or both, and the risk of use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.

rhinitis.⁵² Though allergic rhinitis, eczema, or urticaria may not be life threatening, these conditions can cause considerable discomfort to pregnant women. Additionally, uncontrolled rhinitis may lead to sinusitis or exacerbate asthma. Therefore, antihistamines often are used during pregnancy.⁵¹ In the past, it has been believed inappropriate to use antihistamines in asthmatics because of the potential for drying bronchial mucus.³⁶ Many antihistamines, both prescription and over-the-counter, have a mandatory labeling warning against their use in asthma⁴³; however, antihistamines are now frequently given to patients with asthma and have been shown to reduce asthma symptoms,³⁶ improve pulmonary function tests, and enhance quality of life.⁶⁰ Before resorting to oral antihistamines, it would seem reasonable to institute a trial of intranasal cromolyn or more potent intranasal therapy, such as beclomethasone or budesonide, for uncontrolled symptoms of allergic rhinitis.⁴⁹ In addition, the use of hypertonic nasal solution has been shown to increase mucociliary clearance and ciliary beat frequency. The use of saline also removes allergens and other debris from the nasal passages.^{59, 66}

Tripelemnamine and chlorpheniramine have been the recommended histamine blockers of choice by most experts, including the Working Group on Asthma and Pregnancy, because of their long availability and the existence of reassuring animal and human data^{35, 51}; however, identifying the antihistamine of choice is more complex now that non-sedating antihistamines such as loratadine and fexofenadine are available. There are also the mildly sedating antihistamines, cetirizine and intranasal azelastine. For women who must be alert when driving or in other situations where cognitive and psychomotor skills are essential, the nonsedating antihistamines may be desirable. Most states now consider driving under the influence of sedating medications as being impaired. Sedating antihistamines taken during the evening have been shown to increase daytime sleepiness and decrease alertness.²⁸ Despite the paucity of human data in pregnancy for loratadine, animal studies are negative (FDA risk classification B). A recent abstract reviews the outcomes of 49 women (51 fetuses) exposed to loratadine during pregnancy with no unexpected differences in birth weight, head circumference, length, and Apgar scores from a control group.⁸ Cetirizine also has reassuring animal studies but very limited ($n = 33$) human pregnancy data.¹⁷ These small sample size studies do not exclude as much as a sevenfold increased risk of congenital malformations with 95% certainty.⁵¹ Animal studies have not been reassuring, and there are no published data in human pregnancy for fexofenadine. There are no reports of human pregnancy studies for the ophthalmic agents ketorolac and levocabastine and only limited preliminary reassuring data for pheniramine.³⁷

Among the older sedating antihistamines there are some reports of major and minor birth defects that approach clinical significance in a few older studies, but more recent data are reassuring. In a surveillance study of 229,101 completed pregnancies in Michigan Medicaid recipients from 1985 to 1992,⁷ 1461 mothers were exposed to diphenhydramine (Benadryl, Schering Pharmaceuticals, NJ) during the first trimester.

Eighty (5.5%) of these infants had major birth defects; 62 were expected. The even older Collaborative Perinatal Project reported 595 first trimester exposures in 50,282 pregnancies with no firm evidence of increased risk. In this same project, there were 10 major birth defects, a statistically significant association, in the 65 first trimester exposures to brompheniramine.⁷ The following caveats summarize recommendations for antihistamine use during pregnancy:

- (1) Use topical nasal cromolyn or corticosteroids and normal or hypertonic saline nasal washes first line
- (2) Use chlorpheniramine or tripeleminamine, with loratadine or cetirizine being reserved for those patients in whom sedation must be avoided or minimized
- (3) Try to avoid oral antihistamines during the first trimester unless there is medical justification, such as substantial quality-of-life issues. In the event that alternative antihistamines without reassuring data are begun before conception, reassure the mother that there is little likelihood of major congenital defects occurring from these drugs³⁷
- (4) Only very limited data are available on newer antihistamines, and therefore risk-benefit analysis generally reserves these agents for special circumstances.

Decongestants

Decongestants frequently are prescribed alone or combined with antihistamines, as the latter agents fail to relieve nasal blockage common in rhinitis patients.³⁹ The topical drug oxymetazoline (Afrin, Schering Pharmaceuticals, NJ) is the preferred decongestant³⁵ during early pregnancy because of its limited systemic absorption at recommended doses; however, topical decongestants have long been implicated as a cause of rhinitis medicamentosa, or rebound nasal congestion, and their continuous use should not exceed 2 to 3 days.¹⁶

The oral decongestant pseudoephedrine, long considered safe during any stage of pregnancy,³⁵ has been implicated along with phenylpropanolamine as a cause of the rare birth defect gastroschisis.^{67, 70} In the Collaborative Perinatal Project, 50,282 mother-child pairs were monitored, with 1249 first trimester exposures to phenylephrine, 2489 to phenylpropanolamine, and 9719 to pseudoephedrine. An association was found between sympathomimetic drugs as a class and major and minor birth defects; however, these agents are rarely used alone, and it is unclear if these drugs alone or other factors were responsible for the defects.⁷ It is now suggested that all oral decongestants be avoided during the first trimester. Pseudoephedrine remains the oral decongestant drug of choice after the first trimester.⁴⁹

β Agonists

Short-acting β agonists have been a mainstay of asthma therapy for many years and are used across the entire spectrum of asthma from

mild intermittent to severe symptoms. This use is no different during pregnancy. Because data are more available for terbutaline, metaproterenol, and albuterol, they are the usual recommended choices. The use of epinephrine for status asthmaticus has been questioned for at least two reasons: (1) the drug is teratogenic in some animal species, although birth defects in humans exposed to epinephrine are probably related to other factors, including the severe disease for which it is prescribed⁷; (2) epinephrine has largely been replaced by nebulized drugs of this class.³⁴ Terbutaline is preferable in the rare instance where a subcutaneous product is needed for acute asthma⁵³; however, epinephrine is still the drug of choice for treating acute anaphylaxis.³⁵

There are no reports of significant adverse pregnancy outcomes from the other β_2 -agonists drugs in this class, such as bitolterol or pirbuterol; however, data are limited, at best. An older drug, isoproterenol, an analogue of epinephrine, is rarely used today, and human pregnancy exposure data also are limited.^{49, 56} High doses of β agonists may cause side effects, including tachycardia, hyperglycemia, hypokalemia, nervousness, and tremor in the mother and exposed newborn, but their benefits far outweigh these relatively minor reactions. In the acute setting, where high-dose therapy is indicated, serum electrolyte monitoring is indicated. Cardiac monitoring and supplemental oxygen reduce the chance of an untoward event. The inhaled route of administration is preferred, but there may be instances when oral forms of the medications are useful. In this case, terbutaline would be recommended based on reassuring animal studies.³⁵ It should be noted that β_2 -agonists also are used intravenously for their tocolytic benefits, delaying delivery in premature labor, or countering fetal bradycardia during childbirth.⁵⁶

Ipratropium

The anticholinergic agent ipratropium occasionally is useful in patients who cannot tolerate β_2 -agonists. Although human pregnancy data are lacking, animal studies are reassuring.⁴³ Nebulized ipratropium may provide additional bronchodilation when added to inhaled β -agonist therapy for status asthmaticus.³⁴ It is recommended that ipratropium be considered when initial inhaled β -agonist treatment for acute asthma does not elicit an adequate response.⁴⁹

Theophylline

Formerly a mainstay of asthma management, the methylxanthine theophylline¹⁴ has assumed a lesser role in asthma management since the acceptance of inhaled corticosteroids, long-acting β agonists, and other newer therapies. Nevertheless, this agent has a long track record of use in pregnancy. Physicians and patients may feel more comfortable with this agent rather than with some of the newer drugs.

Theophylline generally is used for its mild-to-moderate bronchodilatory effects. Weinberger and Hendeles⁶⁸ and other investigators⁶⁴ report immunomodulatory, anti-inflammatory, and bronchoprotective properties that may better explain its efficacy in the treatment of asthma. Theophylline, in its sustained release form, is an option when therapy in addition to inhaled corticosteroids is required for night-time awakening or frequent need for β_2 -agonists during the day.

Toxic effects of theophylline range from mild-to-severe gastrointestinal symptoms to cardiac arrhythmias and seizures. Blood levels should be monitored to achieve and maintain serum theophylline levels of between 5 and 12 $\mu\text{g/mL}$ during pregnancy.¹⁸ With the widespread pressure to prescribe generic drugs, it is advisable to request branded theophylline to decrease pharmacokinetic variability so that blood levels are more consistent.

Multiple controlled studies, including one during pregnancy by Wendel et al,⁶⁹ have determined that there is no advantage to including intravenous aminophylline for the treatment of status asthmaticus. There may be an indication for aminophylline during hospitalization in a pregnant patient with impending or acute respiratory failure. A 6 mg/kg loading dose, followed by initial maintenance dosage of 0.5 mg/kg/h and adjustments to keep a serum theophylline level at 8 to 12 g/mL is recommended.⁶¹

Mast Cell Inhibitors

Cromolyn sodium and nedocromil sodium are noncorticosteroid medications with modest anti-inflammatory properties. Both agents are devoid of significant side effects, and cromolyn has an especially long safety record. Unfortunately, there is a significant delay in onset of benefit with these medications, and they are of no use during acute attacks of asthma.¹⁴ They may play a role in mild persistent asthma, especially if the prospective mother is reluctant to use inhaled corticosteroids. Good response to either of these agents before pregnancy favors their continued use during gestation.⁴⁹

Corticosteroids

Inhaled corticosteroids are accepted as the most effective medication for the long-term control of patients with persistent asthma.^{27, 33-35, 49, 61} The most human pregnancy data are available for beclomethasone and budesonide. In one European study, 257 pregnant asthmatic women were treated with beclomethasone or budesonide from conception, with only 4% experiencing acute asthma, compared with 17% in another group not initially treated with these drugs.⁶³ In a randomized American study, Wendel et al⁶⁹ found that only 12% of hospitalized patients discharged on inhaled beclomethasone, albuterol, and oral steroid taper

required readmission, compared with 33% of those not on an inhaled corticosteroid. A Swedish Birth Registry documents 2014 infants exposed to inhaled budesonide in early pregnancy. There was no significant difference in the incidence of congenital malformations in the treated group (3.8%, 95% confidence interval 2.9%–4.6%) when compared with the general population (3.5%).²⁶ Similarly, preliminary data from the ACAAI Registry for Asthmatic and Allergic Pregnant Patients (RAAPP) described the first 182 completed pregnancies. All subjects received inhaled corticosteroids, and 73 (39.9%) required oral corticosteroids. There was no significant variation from the expected birth weight for gestational age distribution or incidence of birth defects in this population.⁵⁰

Oral corticosteroids are essential in managing acute and severe asthma during pregnancy.^{35, 49, 61} Several trials involving more than 500 patients have demonstrated the safety of short-term, high-dose systemic corticosteroids and lack of increased perinatal mortality.¹² Rosa,⁴⁶ an epidemiologist at the FDA, reviewed surveillance data from Michigan involving 333,000 completed pregnancies, which included 458 women on oral corticosteroids, 222 patients on methylprednisolone, and 236 on prednisone. There were a total of 25 malformations, with 19 expected.⁴⁶ Also, in a literature review of 457 infants exposed to systemic corticosteroids, Fraser and Sajoo²¹ reported a 3.5% incidence of congenital malformations. In a case-control study of 20,830 infants with congenital malformations, 322 mothers of malformed infants received systemic corticosteroids. This incidence of exposure (1.55%) was not significantly different from that in mothers of normal infants (1.41%).¹³ In one less reassuring case-control study, there was a significant increase in oral clefts with first trimester systemic corticosteroid exposure.^{45, 54} Several studies also have suggested an increased risk of pre-eclampsia with oral corticosteroid use (see article by Schatz and Dombrowski elsewhere in this issue); however, there are insufficient data to differentiate a medication effect from an effect of severe asthma.^{47, 48}

Long-term use of systemic corticosteroids also carries the risk of significant hyperglycemia and its associated risks. There are reports of fetal distress from severely elevated glucose levels in previously undiagnosed or well-controlled gestational or type-I diabetics within 24 to 48 hours of the administration of high-dose oral or parenteral corticosteroids.¹² Gestational or pre-existing diabetes mellitus may be exacerbated by the use of systemic corticosteroids, and glucose monitoring is required in that situation.¹¹ Considering the high risk of status asthmaticus, however, it is still generally accepted that the benefits of appropriate use of systemic corticosteroids for severe asthma far outweigh any presumed risks of direct adverse effects to mother or baby.^{48, 49}

Leukotriene Modifiers

Three leukotriene modifier drugs are currently available in the United States. A number of well-controlled long-term studies have dem-

onstrated their effectiveness to control asthma symptoms. They are useful as monotherapy in mild asthma³⁴ or as add-on therapy in more severe asthma.⁶⁵

Data for human pregnancy exposures are extremely limited. Merck³⁸ reports 25 exposures to montelukast in the first year of a pregnancy registry, and no human pregnancy data are available for zafirlukast (Kris Shields, MSN, MPH, personal communication). Animal studies have been reassuring for both of these selective leukotriene receptor antagonists. There are no available human data, and animal studies have demonstrated adverse effects for zileuton, a lipoxygenase inhibitor.⁴³ In a position statement, the ACAAI recommends using zafirlukast or montelukast only in patients with recalcitrant asthma who have shown a uniquely favorable response prior to pregnancy.⁴⁹

IMMUNOTHERAPY

Allergen immunotherapy, or *allergy shots*, lessens the effect of chronic allergen stimulation on the hyperresponsive airways of asthma patients.⁴¹ Studies have demonstrated the long-term benefit of immunotherapy¹⁵ in reducing the symptoms of allergic rhinitis and asthma. Although medications provide symptomatic relief, allergen avoidance and immunotherapy are the only therapeutic measures that have the potential to modify the natural course of these diseases.⁶

The Working Group on Asthma and Pregnancy,³⁵ the ACAAI, the AAAAI,⁴¹ and others recognize the benefits of immunotherapy during pregnancy. Effective immunotherapy may lessen symptoms, thus reducing the need for systemic medications. To reduce the risk of anaphylaxis, it is recommended that immunotherapy be initiated electively in anticipation of a planned pregnancy so that maintenance levels can be reached before conception. Initiation of and increasing doses of immunotherapy and skin testing is generally avoided during pregnancy.^{35, 41} Unfortunately, allergen immunotherapy received by mothers during pregnancy does not appear to lessen the chances of the development of allergies or asthma in the offspring of these mothers.⁵⁷

IMMUNIZATIONS

Influenza vaccine, an inactivated viral product, is recommended for pregnant asthmatic women, as influenza may trigger exacerbations of asthma in many individuals. Theophylline levels should be closely monitored following administration of the vaccine.⁶¹ Pneumococcal vaccine is not recommended in pregnant patients.⁴³

Nonimmune women exposed to chicken pox or herpes zoster should be given varicella immune globulin as soon as possible. This is especially important if oral corticosteroids are needed. Preferably the immune status of all adults should be determined before pregnancy and

varicella vaccine administered. A number of fatalities in children^{34, 61} have been documented when patients on high-dose oral corticosteroids have developed varicella infections. Acyclovir also should be started immediately.¹

GASTROESOPHAGEAL REFLUX

Gastroesophageal reflux (GER) is common in both asthma and pregnancy. GER is now recognized as an important comorbid and exacerbating factor when treating asthma. Bronchoconstriction is believed to occur by complex neurogenic mechanisms when gastric acid is present in the esophagus.⁹

Dietary restrictions of caffeine, smoking, chocolate, and other substances known to adversely affect the gastroesophageal sphincter have varying rates of success, and drug therapy is often indicated. Based on animal reproductive studies and some human data, all histamine type-2 receptor antagonists except nizatadine appear to be safe during pregnancy.^{7a}

In a recent report^{46a} of 134 pregnant women exposed to omeprazole, a proton pump inhibitor, compared with 1547 controls, there were no significant differences in the incidence of major malformations. Based on the number of exposures but still limited data, ranitidine is the drug of choice at this time. Omeprazole can be considered if symptoms are not controlled by an H₂-blocker. The potential for drug interactions makes cimetidine a less favorable choice.²⁹

ALTERNATIVE THERAPIES

Chiropractic, acupuncture, herbals, homeopathic or Ayurvedic medicine, reflexology, yoga, meditation, and massage are among the alternative or complementary treatments used by millions of Americans and patients around the world. Whether they are used for reasons of philosophy or economics, these methods must be held to the same scrutiny that medications approved by the FDA are subjected to before they can be recommended. It would seem that those therapies such as chiropractic and acupuncture, which do not expose the fetus to ingested substances from the mother, would be the ideal solution; however, although many of these therapies may seem harmless in themselves, they may be mistakenly used in place of needed medication, or in the case of some herbs, may be toxic.^{3, 40, 42}

SUMMARY

Successful management of pregnant women with asthma can be a challenge for both physicians and patients. The situation demands that informed consent for all management decisions be obtained and docu-

mented. Realizing that many factors in addition to asthma may complicate pregnancy, the preponderance of evidence indicates that, if the asthma is appropriately managed, the outcome will result in the birth of a healthy baby.³⁵

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References

1. American College of Obstetrics and Gynecology: Immunization during pregnancy: ACOG Technical Bulletin Number 160, October 1991. *Int J Gynaecol Obstet.* 43:67-74, 1993
2. Bailey B, Addis A: Motherisk Update: Asthma during pregnancy. *Canadian Family Physician* 43:1711-1718, 1997
3. Balon J, Aker PD, Crowther ER, et al: A comparison of active and simulated chiropractic manipulation as adjunctive treatment for childhood asthma. *N Engl J Med* 339:1013-1020, 1998
4. Baruca ER: Modulatory effect of maternal serum on xenobiotic metabolizing activity of placental explants: Modification by cigarette smoking. *Hum Reprod* 9:1017-1021, 1994
5. Bonati M, Tognoni G: Drug use in pregnancy: A preliminary report of the International Co-operative Drug Utilization Study. *Pharmacy World Science* 12:75-78, 1990
6. Bousquet J, Lockey RF, Malling HJ: WHO Position Paper Allergen Immunotherapy: Therapeutic vaccines for allergic diseases. *Allergy, European Journal of Allergy and Clinical Immunology.* 44:12, 1998
7. Briggs GG, Freeman RK, Yaffe SJ: *Drugs in Pregnancy and Lactation.* Baltimore, Williams and Wilkins, 1994
- 7a. Broussard CN, Richter JE: Treating gastro-esophageal reflux disease during pregnancy and lactation: What are the safest therapeutic options? *Drug Safety* 19:325-337, 1998
8. Brown JE, Stern H, Leeds T: Loratadine and pregnancy: Outcomes in 49 pregnancies. *Research Abstracts from the 37th Annual Scientific Session of the Western Society of Allergy, Asthma, and Immunology in Allergy and Asthma Proceedings* 20:199, 1999
9. Bruno G, Graf U, Andreozzi P: Gastric asthma: An unrecognized disease with an unsuspected frequency. *J Asthma* 36:315-325, 1999
10. Carson MP, Rosene-Montella K: Common cardiac complications in pregnancy. *Women Health Primary Care* 2:533-544, 1999
11. Chazotte C: Asthma in pregnancy: A review. *Journal of the Association for Academic Minority Physicians* 5:107-110, 1994
12. Clark SL, Iffy L, Ganesh V, et al: Asthma in pregnancy [letter]. *Obstet Gynecol* 83:638-639, 1994
13. Czeizel AE, Rockenbauer M: Population-based case control study of teratogenic potential of corticosteroids. *Teratology* 56:335-340, 1997
14. Dombrowski MP: Pharmacologic therapy of asthma during pregnancy. *Obstet Gynecol Clin North Am* 24:559-574, 1997
15. Durham SR, Walker SM, Varga E-M, et al: Long-term clinical efficacy of grass-pollen immunotherapy. *N Engl J Med* 341:468-475, 1999
16. Dykewicz MS, Fineman S, Skoner DP: Joint Task Force Summary Statements on Diagnosis and Management of Rhinitis. *Ann Allergy Asthma Immunol* 81:469-518, 1998

17. Einarson A, Bailey B, Jung G, et al: A prospective controlled study of hydroxyzine and cetirizine during pregnancy. *Ann Allergy* 78:183-186, 1997
18. Esplin MS, Clark SL: Outpatient management of asthma during pregnancy. *Clin Obstet Gynecol* 41:555-563, 1998
19. FDA Notice of Public Hearing, Request for Comments: Content and format of labeling for human prescription drugs; pregnancy labeling; public hearing. *Fed Regist* 62:41061-41063, 1997
20. Fern FH, Brushwood DB: Medical—Legal aspects of prescribing during pregnancy. In Schatz M, Zeiger RS, Claman HN (eds): *Asthma and Allergy in Pregnancy and Early Infancy*. New York, Marcel Dekker, 1993, pp 187-209
21. Fraser FC, Sajoo A: Teratogenic potential of corticosteroids in humans. *Teratology* 51:45-46, 1995
22. Gergen PJ, Fowler JA, Maurer KR, et al: The burden of environmental tobacco smoke exposure on the respiratory health of children 2 months through 5 years of age in the United States: Third National Health and Nutrition Examination Survey, 1988 to 1994. *Pediatrics* 101:E8, 1998
23. Gluck JC, Gluck PA, Bahna SL: The effect of asthma on pregnancy and labor. In Schatz M, Zeiger RS, Claman HN (eds): *Asthma and Allergy in Pregnancy and Early Infancy*. New York, Marcel Dekker, 1993, p 213
24. Greenberger P, Patterson R: The outcome of pregnancy complicated by severe asthma. *Allergy Proc* 9:540-543, 1988
25. Kaliner MA: Asthma in Allergy Essentials. American College of Allergy, Asthma, and Immunology, 1997
26. Kallen B, Rydhstroem H, Aberg A: Congenital malformations after the use of inhaled budesonide in early pregnancy. *Obstet Gynecol* 93:392-395, 1999
27. Karpel J, et al: The pharmacokinetic/pharmacodynamic properties of inhaled corticosteroids. *Dialogues in Asthma* 1:1-10, 1999
28. Kay G, Berman B, Mackowiak SH, et al: Initial and steady-state effects of diphenhydramine and loratadine on sedation, cognition, mood, and psychomotor performance. *Arch Intern Med* 157:2350-2356, 1997
29. Lalkin A, Magee L, Addis A, et al: Acid-suppressing drugs during pregnancy. *Motherisk Update* 8/23/99. Available at: <http://www.motherisk.org/publi/>
30. Lipkowitz MA, Navarra T: *Allergies A to Z*. New York, Facts on File, 1994, pp 241-242
31. Luskin A: Diagnosis and differential diagnosis of bronchial asthma in pregnancy. In Schatz M, Zeiger RS, Claman HN (eds): *Asthma and Allergy in Pregnancy and Early Infancy*. New York, Marcel Dekker, 1993
32. Luskin A: Shared decision making between patient and physician: An opportunity to improve patient adherence and self-management of asthma. ACAAI Annual Meeting, Chicago, November 6, 1999
33. National Asthma Education Program Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma, Publication Number 91-3042, Bethesda, MD, 1991
34. National Asthma Education Program Highlights of the Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma, Publication Number 97-4051, Bethesda, MD, 1997
35. National Asthma Education Program Report of the Working Group on Asthma and Pregnancy: Management of asthma during pregnancy. NIH Publication #93-3279, September 1993
36. Mathison DA: Asthma in adults. In Middleton E Jr, Reed CE, Ellis EF, et al (eds): *Allergy: Principles and Practice*, ed 5. St. Louis, Mosby, 1998, p 910
37. Mazzotta P, Loebstein R, Koren G: Treating allergic rhinitis in pregnancy: Safety considerations. *Drug Safety* 20:361-375, 1999
38. Merck Pregnancy Registries: First annual report on exposure during pregnancy from the Merck Pregnancy Registry for Singulair (montelukast sodium). Covering the period from approval through June 1999, Whitehouse Station, PA, Merck Co.
39. Naclerio R, Solomon W: Rhinitis and inhalant allergens. *JAMA* 278:1842-1848, 1997
40. Navarra T, Lipkowitz MA: *Encyclopedia of Vitamin, Minerals, and Supplements*. New York, Facts on File, 1996
41. Nicklas RA, Bernstein IL, Blessing-Moore J, et al: Joint Task Force Practice Parameters

- of American College of Allergy, Asthma, and Immunology, American Academy of Allergy, Asthma, and Immunology: Practice parameters for allergen immunotherapy. *J Allergy Clin Immunol* 98:1002, 1996
42. O'Mathuna DP: Acupuncture for quick relief of asthmatic exacerbation. *Alternative Medicine Alert*, October 1998
 43. Physicians Desk Reference. Oradell, NJ: Medical Economics, 1999
 44. Platts-Mills TAE, Vervloet D, Thomas, WR, et al: Indoor allergens and asthma: Report of the third international workshop. *J Allergy Clin Immunol* 100:S1-S24, 1997
 45. Rodriguez-Pinella E, Martinez-Frias ML: Corticosteroids during pregnancy and oral clefts: A case control study. *Teratology* 58:2-5, 1998
 46. Rosa F: Databases in the assessment of the effects of drugs during pregnancy. *J Allergy Clin Immunol* 103:S360-361, 1991
 - 46a. Ruigomez A, Rodriguez LAG, Cattaruzzi C, et al: Use of cimetidine, omeprazole and ranitidine in pregnant women and pregnancy outcomes. *Am J Epidemiol* 150:476-481, 1999
 47. Schatz M: Commentary: Asthma and pregnancy. *Lancet* 353:1202-1204, 1999
 48. Schatz M: Interrelationships between asthma and pregnancy: A literature review. *J Allergy Clin Immunol* 103:S330-S336, 1999
 49. Schatz M, Lipkowitz MA, Huff R, et al: Position statement: The use of newer asthma and allergy medications during pregnancy. *Ann Allergy Asthma Immunol* 84:475-480, 2000
 50. Schatz M, Lipkowitz M, Chilingar S, et al: A Progress Report. Abstract presented at the ACAAI Meeting, Chicago, November 1999
 51. Schatz M, Pettiti D: Antihistamines and pregnancy [editorial]. *Ann Allergy Asthma Immunol* 78:157-159, 1997
 52. Schatz M, Zeiger RS: Asthma and allergy in pregnancy: Perinatal care for chronic maternal conditions. *Clin Perinatol* 24:407-432, 1997
 53. Schatz M, Zeiger RS: Asthma during pregnancy: What to do. *J Respir Dis* 19:731-738, 1998
 54. Schatz M, Zeiger RS, Harden K, et al: The safety of asthma and allergy medications during pregnancy. *J Allergy Clin Immunol* 100:301-306, 1997
 55. Schatz M, Zeiger RS, Hoffman CP, et al: Perinatal outcomes in the pregnancies of asthmatic women: A prospective controlled analysis. *Am J Respir Crit Care Med* 151:1170-1174, 1995
 56. Scialli AR, Lione A: The reproductive effects of specific medications for asthma and allergy. In Schatz M, Zeiger RS, Claman HN (eds): *Asthma and Allergy in Pregnancy and Early Infancy*. New York, Marcel Dekker, 1993 pp 140-141
 57. Settupane RA, Chafee FH, Settupane GA: Pollen immunotherapy during pregnancy: Long-term follow-up of offsprings. *Allergy Proc* 9:555-561, 1988
 58. Seto E, Einarson T, Koren G: Pregnancy outcome following first trimester exposure to antihistamines: A Meta-analysis. *Am J Perinatol* 14:119-124, 1997
 59. Shoseyov D, Bibi H, Shai P, et al: Treatment with hypertonic saline versus normal saline nasal wash of pediatric chronic sinusitis. *J Allergy Clin Immunol* 101:602-605, 1998
 60. Spector S: Clinical challenges in the management of allergic asthma. Syllabus of Scientific Papers, 1998 Annual Meeting American College of Allergy, Asthma & Immunology, p 27
 61. Spector S, Nicklas RA, Joint Task Force Practice Parameters of American College of Allergy, Asthma, and Immunology, American Academy of Allergy, Asthma, and Immunology: Practice parameters for the diagnosis and treatment of asthma. *J Allergy Clin Immunol* 96:809, 1996
 62. Stenius-Aarniala B: Pulmonary function during pregnancy in health and in asthma. In Schatz M, Zeiger RS, Claman HN (eds): *Asthma and Allergy in Pregnancy and Early Infancy*. New York, Marcel Dekker, 1993, p 53
 63. Stenius-Aarniala BSM, Hedman J, Teramo KA: Acute asthma during pregnancy. *Thorax* 51:411-414, 1996
 64. Sullivan P, Bekir S, Jaffear Z, et al: Anti-inflammatory effects of low-dose oral theophylline in atopic asthma. *Lancet* 343:1006-1008, 1994

65. Szeffler S: Leukotriene modifiers: What is their position in asthma therapy. *J Allergy Clin Immunol* 102:170-172, 1998
66. Tabot AR, Herr TM, Parsons DS: Mucociliary clearance and buffered hypertonic saline solution. *Laryngoscope* 107:500-503, 1997
67. Torfs CP, Katz EA, Bateson TF: Maternal medications and environmental exposures as risk factors for gastroschisis. *Teratology* 54:84-92, 1996
68. Weinberger M, Hendeles L: Theophylline in asthma: Review article. *N Engl J Med* 334:1380-1388, 1996
69. Wendel PJ, Ramin SM, Barnett-Hamm C, et al: Asthma treatment in pregnancy: A randomized controlled study. *Am J Obstet Gynecol* 175:150-154, 1996
70. Werler MM, Mitchell AA, Shapiro S: First trimester maternal medication use in relation to gastroschisis. *Teratology* 45:361-367, 1992

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