CLINICAL PRACTICE

Asthma in Pregnancy

Michael Schatz, M.D., and Mitchell P. Dombrowski, M.D.

This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

A 23-year-old nonsmoking woman (gravida 1, para 0) presents at 11 weeks' gestation with an 8-year history of asthma, which has worsened over the past year. She reports asthma symptoms requiring albuterol two or three times per day and interfering with sleep two or three nights per week. A corticosteroid inhaler was prescribed before pregnancy, but she has been afraid to use it. Cleaning her house triggers asthma, and she has had a cat at home for 1 year. Her forced expiratory volume in 1 second (FEV_1) is 75% of the predicted value; it increases to 88% of the predicted value after administration of albuterol. How should her case be managed?

THE CLINICAL PROBLEM

From the Department of Allergy, Kaiser Permanente Medical Center, San Diego, CA (M.S.); and the Department of Obstetrics and Gynecology, St. John Hospital, and Wayne State University Medical Center (M.P.D.) — both in Detroit. Address reprint requests to Dr. Schatz at the Department of Allergy, Kaiser Permanente Medical Center, 7060 Clairemont Mesa Blvd., San Diego, CA 92111, or at michael.x.schatz@kp.org.

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Asthma is probably the most common potentially serious medical problem that occurs during pregnancy, and approximately 8% of pregnant women reported current asthma in recent national surveys.[1] In several studies, even after adjustment for potential confounders, women with asthma have been reported to have higher risks of several complications of pregnancy, including preeclampsia,[2-7] preterm birth,[2-4,6] infants with low birth weight or intrauterine growth restriction,[2-4,6,7] infants with congenital malformations,[3,8,9] and perinatal death[2,4,10] than women without a history of asthma. Residual confounding[11] or common pathogenetic factors[12-14] may explain some of these associations. Nevertheless, observational data showing strong associations between poor asthma control during pregnancy (as evidenced by symptoms, impaired pulmonary function, or exacerbations) and these increased risks[15-19] suggest that better asthma control may improve pregnancy outcomes. Treatment also may reduce serious risks to the mother resulting from uncontrolled asthma, including death. However, the choice among medications must take into account their potential adverse effects on the fetus.

In addition to the effect of maternal asthma on pregnancy outcomes, pregnancy may affect the course of asthma. The severity of asthma may improve, worsen, or remain unchanged during pregnancy[20,21]; the mechanisms underlying changes in the severity of asthma during pregnancy remain undefined.

STRATEGIES AND EVIDENCE

DIAGNOSIS AND EVALUATION

The diagnosis of asthma is usually straightforward, since most patients have a known history of asthma antedating pregnancy. However, diagnostic testing is warranted in patients whose clinical picture or response to therapy is atypical or who present with respiratory symptoms during pregnancy in the absence of a history of asthma. The most common alternative diagnosis is dyspnea of pregnancy, which is not associated with cough, wheezing, chest tightness, or airway obstruction. Other po-

tential diagnoses include cough due to reflux or postnasal drip, bronchitis, laryngeal dysfunction, hyperventilation, pulmonary edema, and pulmonary embolism.[22,23] The demonstration of a reduced FEV_1 or ratio of FEV_1 to forced vital capacity with a 12% or greater improvement in FEV_1 after the administration of inhaled albuterol confirms a diagnosis of asthma in pregnancy.[23,24] Methacholine testing, which is used to confirm bronchial hyperreactivity in patients with normal pulmonary function, is contraindicated during pregnancy because of the lack of data on the safety of such testing in pregnant patients. Thus, women with a clinical picture that is consistent with new-onset asthma in whom the diagnosis is not confirmed on the basis of testing for reversibility of impairment in pulmonary function should be treated for asthma until methacholine testing can be performed post partum if indicated.[23] Exhaled nitric oxide has not been studied as a diagnostic measure of asthma in pregnant women.

Patients with persistent asthma who have not previously been tested for allergies should undergo blood testing for specific IgE antibodies to allergens such as dust mites, cockroaches, mold spores, and pets. Skin tests are not generally recommended during pregnancy because skin testing with potent antigens may be associated with systemic reactions.

Current asthma control should be assessed according to the frequency and severity of symptoms (including their interference with sleep and normal activity), the frequency of use of rescue therapy, the history of exacerbations requiring the use of systemic corticosteroids, and the results of pulmonary-function tests (Table 1). Spirometry is the preferred method of assessing pulmonary function, but peak flow measurement is an acceptable alternative. FEV_1 and peak flow rates do not change substantially as a result of pregnancy,[23] so these measures can be used for assessing asthma control in patients who are pregnant just as they are in patients who are not pregnant. Patients who have asthma that is well controlled and who are not receiving controller medications can be classified as having intermittent rather than persistent asthma.

Women who have previously received prescriptions for asthma medications should be asked about their use in order to classify their current level of therapy (according to a stepped-care approach, with step 1 indicating no treatment and step 6 indicating the most aggressive treatment) (Table 2) and to assess potential problems with and barriers to adherence. Adherence to treatment with inhaled corticosteroids has been reported to be poor in many studies. For example, the reported adherence rate was approximately 50% in one study involving adults with asthma; decreased adherence was associated with an increased frequency of asthma exacerbations.[26] Women with asthma have been reported to decrease their use of inhaled corticosteroids during early pregnancy, as compared with their use of these agents in the 20 weeks before their last menstrual period[27]; this may be due to their reported concern regarding the safety of inhaled corticosteroids during pregnancy.[28] Moreover, a substantial proportion of asthmatic exacerbations during pregnancy have been associated with nonadherence to treatment with inhaled corticosteroids.[29] In addition to assessing adherence, asking about past medications and their effectiveness and any side effects can help to guide subsequent management decisions.

MANAGEMENT OF ASTHMA

All patients should be educated regarding the relationship between asthma and pregnancy, and they should be taught about self-treatment, including inhaler techniques, adherence to medication, and control of potential environmental triggers (Table 3). The appropriate management of common coexisting conditions that can aggravate asthma, such as rhinitis, sinusitis, and gastroesophageal reflux, can improve asthma control. Women who smoke must be informed of the potential adverse effects of smoking on the fetus, which may add to the fetal effects of uncontrolled asthma,[15] and should be strongly encouraged to quit. Advice on environmental control measures for reducing exposure to allergens can be provided on the basis of the results of allergy testing (Table 4).

Medications for asthma are divided into long-term controller medications that prevent the manifestations of asthma (inhaled corticosteroids, long-acting β-agonists, leukotriene modifiers, cromolyn, and theophylline) (Table 5) and rescue therapy that provides quick relief of symptoms (primarily short-acting inhaled β-agonists). In studies involving patients who were not pregnant, inhaled corticosteroids were the most effective controller medications in terms of reducing symptoms and exacerbations and improving pulmonary function, and all controller medications have been

Table 1. Assessment of Asthma Control in Pregnant Women.*

Variable	Well-Controlled Asthma	Asthma Not Well Controlled	Very Poorly Controlled Asthma
Frequency of symptoms	≤2 days/wk	>2 days/wk	Throughout the day
Frequency of nighttime awakening	≤2 times/mo	1–3 times/wk	≥4 times/wk
Interference with normal activity	None	Some	Extreme
Use of short-acting β-agonist for symptom control	≤2 days/wk	>2 days/wk	Several times/day
FEV_1 or peak flow (% of the predicted or personal best value)	>80	60–80	<60
Exacerbations requiring use of systemic corticosteroid (no.)	0–1 in past 12 mo	≥2 in past 12 mo	

* Data are from the National Asthma Education and Prevention Program.[24] The level of control is based on the most severe category. The frequency and effect of symptoms should be assessed according to the patient's recall of the previous 2 to 4 weeks. FEV_1 denotes forced expiratory volume in 1 second.

shown to improve these outcomes better than placebo.[24] Long-acting β-agonists have been shown to be more effective than leukotriene-receptor antagonists or theophylline as add-on therapy to inhaled corticosteroids.[24] Evidence of the efficacy of these drugs during pregnancy is largely extrapolated from studies involving patients who were not pregnant. To our knowledge, only two randomized, controlled trials specifically involving pregnant patients with asthma have been conducted. These studies showed that inhaled beclomethasone is more effective than theophylline in improving pulmonary function[30] and that prescribing inhaled beclomethasone in addition to oral corticosteroids and inhaled β-agonists at the time of discharge after hospitalization for asthma results in fewer subsequent readmissions for asthma as compared with oral corticosteroids and inhaled β-agonists alone.[31]

Although data on adverse effects of asthma medications in pregnancy are of necessity largely observational, most of the findings are reassuring. Many studies have shown no increased perinatal risks (including preeclampsia, preterm birth, low birth weight, and congenital malformations) associated with the use of inhaled β-agonists or inhaled corticosteroids[32-38] in women who were exposed to these agents; one study involved 2968 women.[38] Among the drugs for which reassuring data on use in pregnancy are available, albuterol is the inhaled β-agonist that has been studied most extensively,[33] and budesonide is the most extensively studied inhaled corticosteroid.[37,38]

In one recent case–control study, the use of bronchodilators during pregnancy was associated with an increased risk of gastroschisis among infants (odds ratio, 2.1; 95% confidence interval [CI], 1.2 to 3.6).[39] Also, in a recent cohort study involving 4558 women, exposure to bronchodilators during pregnancy was associated with an increased risk of cardiac defects among infants (odds ratio, 1.4; 95% CI, 1.1 to 1.7).[9] However, the reported increased risk of congenital malformations among infants whose mothers had asthma with exacerbations as compared with those who did not have exacerbations[40] suggests that these associations with bronchodilators may be confounded by indication (i.e., underlying exacerbations may lead to the need for bronchodilators) or other factors, such as obesity or lower household socioeconomic status, that may be associated with both more severe asthma and congenital malformations.[41,42]

The use of oral corticosteroids among pregnant women with asthma has been associated with increased risks of preeclampsia and prematurity among their offspring, as compared with the use of other asthma medications. Although these associations have remained significant after adjustment for several potential confounders,[32,33] residual confounding by greater disease severity and poorer asthma control in these studies cannot be ruled out.

Reassuring data on the use of cromolyn and theophylline in pregnant women have been published.[25] Data on the use of leukotriene-receptor antagonists during pregnancy are more limited; we are aware of only one published study, involving 96 patients, that supports their safety during pregnancy.[43] Data are lacking regarding the safety

of long-acting β-agonists during pregnancy, although the inhalational route and the generally reassuring data on short-acting β-agonists suggest that these agents are probably safe.[25] A possible association between long-acting β-agonists and an increased risk of severe and even fatal asthma exacerbations has been observed in patients who were not pregnant. Although the data are sparse, expert panels suggest that the benefits of the use of long-acting β-agonists appear to outweigh the risks as long as they are used concurrently with inhaled corticosteroids.[44,45] Overall, the risks associated with asthma medications in current use are considered to be definitely lower than the risks associated with uncontrolled asthma.

It is appropriate for pregnant patients with well-controlled asthma to continue taking their medications. In patients who are not pregnant and who have asthma that has been controlled for at least 3 months with the use of controller medications, guidelines recommend consideration of a step down in therapy[24]; however, it may be prudent to maintain the current level of therapy during pregnancy in order to reduce the risk of a loss of control. For patients at step 5 or 6 (Table 2), a careful reduction in therapy may be considered if the previous course of asthma and the course during pregnancy suggest that a reduction is likely to be tolerated without a loss of control.

Therapy should be increased by one step (Table 2) in patients with asthma that is not well controlled despite consideration of the nonpharmacologic strategies described above. A two-step increase, a course of oral corticosteroids, or both should be recommended for women with asthma that is very poorly controlled.

Monthly visits to assess asthma control are recommended for women who require controller therapy during pregnancy. This assessment may be performed as part of routine obstetrical visits or by the primary care physician or asthma specialist who is managing the patient's asthma. Patients with very poorly controlled asthma should be seen every 1 to 2 weeks until control is achieved.

Table 2. Steps of Asthma Therapy during Pregnancy.*

Step	Preferred Controller Medication	Alternative Controller Medication
1	None	—
2	Low-dose inhaled corticosteroid	LTRA, theophylline, or cromolyn
3	Medium-dose inhaled corticosteroid	Low-dose inhaled corticosteroid plus LABA, LTRA, or theophylline
4	Medium-dose inhaled corticosteroid plus LABA	Medium-dose inhaled corticosteroid plus either LTRA or theophylline
5	High-dose inhaled corticosteroid plus LABA	—
6	High-dose inhaled corticosteroid plus LABA plus oral prednisone	—

* Data are from the National Asthma Education and Prevention Program.[24,25] We have modified step 3 to reflect the choice of a medium-dose inhaled corticosteroid over a low-dose inhaled corticosteroid plus a long-acting β-agonist (LABA) because of the lack of safety data on the use of LABA during pregnancy. LTRA denotes leukotriene-receptor antagonist.

Table 3. Patient Education for Self-Treatment of Asthma during Pregnancy.

Subject	Recommendation
General information	Provide basic information about asthma and relationship between asthma and pregnancy
Use of inhaler device	Demonstrate proper technique for specific device and ask patient to perform the technique; demonstrate use of spacer device for metered-dose inhaler if patient's inhaler technique is suboptimal
Adherence to treatment	Discuss self-reported adherence to treatment with controller medication and, if needed, address barriers to optimal adherence (e.g., cost, convenience, concern about side effects)
Self-treatment action plan	Provide schedule for maintenance medication and doses of rescue therapy for increased symptoms; explain when and how to increase controller medication and when and how to use prednisone (for patients with previous prednisone use or poorly controlled asthma); explain how to recognize a severe exacerbation and when and how to seek urgent or emergency care

ASTHMA EXACERBATIONS

An asthma exacerbation in a pregnant patient, as in any adult, should be managed with inhaled β-agonists, inhaled anticholinergic drugs, and systemic corticosteroids.[23,24] Maintenance of an arterial oxygen saturation of at least 95%, measured by means of pulse oximetry, is recommended to ensure sufficient oxygenation in both the mother and the fetus.[22] Assessment of the fetus during an acute asthma episode depends on the stage of the pregnancy, but continuous electronic fetal monitoring, a biophysical profile, or both should be considered if the fetus has reached the stage of viability.[23] A biophysical profile includes a nonstress test for a reactive fetal heart rate, ul-

Table 4. Environmental Control Measures to Reduce Exposure to Allergens.*

Allergen	Instructions	Level of Evidence
Animal dander	Remove pet from house; if removal not acceptable, keep pet out of bedroom	Consensus judgment
Dust mites	Encase pillow and mattress with impermeable covers; wash sheets and blankets weekly in hot water	Data from several randomized, controlled trials
Cockroaches	Do not leave food or garbage exposed; use poison baits or traps rather than chemical agents, which can aggravate asthma	Few randomized, controlled trials

* Data are from the National Asthma Education and Prevention Program.[24] These data are not specific to pregnancy.

trasonographic measurement of amniotic-fluid volume, observation of the presence or absence of fetal breathing movements, and observation of gross body movements and fetal tone. If oxygen saturation remains below a level of at least 95% (as measured by means of pulse oximetry) while the patient is breathing ambient air, if FEV_1 or peak expiratory flow remains below 70% of the predicted value, or if there is evidence of fetal compromise, the patient should be hospitalized, with careful medical and obstetrical surveillance.[22,23] This pulmonary-function criterion, which is based on general recommendations for asthmatic exacerbations, is supported by some observational data,[24] although we are aware of no specific data in pregnant women with asthma.

OBSTETRICAL CARE

In general, data are lacking on the optimal obstetrical care of patients with asthma, and recommendations are based on extrapolation of data from other clinical settings and expert opinion. Women with asthma that is not well controlled may benefit from increased fetal surveillance. Ultrasonographic examinations can be helpful to establish accurate pregnancy dating and monitor fetal growth, which (as described above) can be affected by uncontrolled asthma. Assessment of fetal well-being, usually by means of nonstress testing, should be considered, starting at 32 weeks' gestation.[23]

Adequate hydration and analgesia should be maintained during labor and delivery; analgesia should not compromise the patient's respiratory status, and insufficient pain control could trigger bronchospasm. Use of asthma medications should be continued during labor and delivery. It is commonly recommended that women who are currently taking systemic corticosteroids or who have received several short courses of systemic corticosteroids during pregnancy receive intravenous corticosteroids (e.g., hydrocortisone at a dose of 100 mg every 8 hours) during labor and for 24 hours after delivery in order to prevent adrenal crisis.[22] Prostaglandin E_1 or E_2 can be used for cervical ripening, management of spontaneous or induced abortions, or postpartum hemorrhage, although the patient's respiratory status should be monitored for bronchospasm.[46] In contrast, carboprost (15-methyl prostaglandin $F_2\alpha$) and ergonovine may trigger bronchospasm and should be avoided, if possible.[22] If tocolysis is required, magnesium sulfate and terbutaline are preferable because they are bronchodilators; in contrast, indomethacin can induce bronchospasm in a patient with aspirin-sensitive asthma.[22]

Cesarean delivery is rarely required in patients with an acute asthmatic exacerbation; maternal and fetal compromise usually responds to aggressive medical management. Lumbar anesthesia can reduce oxygen consumption and minute ventilation during labor.[47] The obstetrician, anesthesiologist, and pediatrician should coordinate intrapartum and postpartum care. In general, only small amounts of the asthma medications listed in Table 5 enter breast milk; none are a contraindication to breast-feeding.[23,25]

AREAS OF UNCERTAINTY

The mechanisms linking poorly controlled asthma to adverse perinatal outcomes remain unclear. It is not possible in observational studies to definitely distinguish the potential contributions of increased asthma severity and poor asthma control from the potential effects of medications used in more severe cases. Because of the ethical issues raised, controlled trials cannot be performed to determine the effects of asthma control, as compared with lack of control, on perinatal outcomes. Controlled trials are unlikely to be large enough to determine the absolute safety of various asthma medications during pregnancy, especially with regard to uncommon outcomes such as specific congenital malformations.

Table 5. Controller Medications for the Management of Asthma during Pregnancy.*

Drug	Usual Dose	Potential Adverse Effects	FDA Pregnancy Class†	Recommended Use‡
Inhaled corticosteroids				Preferred controller therapy
Budesonide	Low: 180–600 μg/day; medium: >600–1200 μg/day; high: >1200 μg/day	Cough, dysphonia, thrush; potential systemic effects at high doses; local side effects decreased with valved holding chamber (spacer) for metered-dose inhalers that are not breath-actuated and with mouth washing and spitting after inhalation	B§	Preferred inhaled corticosteroid because of more reassuring data in humans
Beclomethasone	Low: 80–240 μg/day; medium: >240–480 μg/day; high: >480 μg/day		C¶	
Fluticasone	Low: 100–300 μg/day; medium: >300–500 μg/day; high: >500 μg/day		C¶	
Long-acting β-agonists		Tachycardia, skeletal-muscle tremor, hypokalemia; possible increase in risk of severe, life-threatening, or fatal exacerbation		Preferred add-on therapy to medium- or high-dose inhaled corticosteroids
Salmeterol	1 blister twice daily		C¶	
Formoterol	1 capsule twice daily		C¶	
Leukotriene- receptor antagonists				Alternative for mild asthma or as add-on therapy to inhaled corticosteroids, especially in patients with good response before pregnancy
Montelukast	10 mg daily	No major adverse effects identified	B‖	
Zafirlukast	20 mg twice daily	Cases of hepatitis reported	B‖	
Cromolyn	2 puffs four times daily	Cough	B‖	Alternative for mild asthma
Theophylline	400–600 mg/day (based on theophylline level)	Insomnia, gastric upset, aggravation of gastroesophageal reflux	C¶	Alternative for mild asthma or as add-on therapy to inhaled corticosteroids

* Data are from the National Asthma Education and Prevention Program.[24,25] FDA denotes Food and Drug Administration.
† A pregnancy rating of B indicates that reassuring data from studies in animals or humans have been submitted to the FDA, and a rating of C that a risk to the fetus cannot be ruled out on the basis of submitted data.
‡ Data are based on relative efficacy in all patients with asthma and safety data in pregnant women.
§ Data are based on nonreassuring studies of systemic administration in animals, but reassuring data in humans have been submitted to the FDA.
¶ Data are based on nonreassuring studies of systemic administration in animals, and no data in humans have been submitted to the FDA.
‖ Data are based on reassuring studies in animals, but no data in humans have been submitted to the FDA.

GUIDELINES

National guidelines for the management of asthma during pregnancy were most recently updated in 2004,[25] and general guidelines for the management of asthma in all patients were updated in 2007.[24] The American College of Obstetricians and Gynecologists published guidelines on the clinical management of asthma during pregnancy in 2008.[23] The recommendations in this article are consistent with these guidelines.

CONCLUSIONS AND RECOMMENDATIONS

Although uncontrolled asthma may increase the risk of adverse perinatal outcomes, women with well-controlled asthma in pregnancy generally have good pregnancy outcomes.[48-50] The patient described in the vignette has poorly controlled asthma, as evidenced by daily symptoms and daily use of rescue therapy, asthma that interferes with sleep more than once a week, and an FEV_1 of less than

80% of the predicted value. This patient should be educated regarding the potential risks of uncontrolled asthma for herself and her pregnancy. We would recommend testing for sensitivity to mites, cat dander, and cockroach allergens and initiate medium-dose inhaled corticosteroids (a two-step therapy increase). We would choose inhaled budesonide (180 μg per puff, two puffs twice a day) over other inhaled corticosteroids because more safety data are available on the use of this drug during the gestational period. The patient should also be instructed in the use of an optimal inhaler technique, and she should be given a personalized self-treatment action plan for asthma that includes instructions regarding the maintenance medication schedule, doses of rescue therapy for increased symptoms, and when and how to seek urgent or emergency care. We would recommend follow-up every 1 to 2 weeks initially to ensure that asthma control is achieved and then, once the patient's condition is stable, at least monthly throughout the pregnancy.

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