

# Asthma and pregnancy

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### Activity Objectives

1. To realize that pregnant asthmatic patients have a higher risk of adverse perinatal outcomes.
2. To understand that because about two thirds of pregnant women have asthma symptoms that stay the same or increase during pregnancy, they need to be monitored closely during pregnancy.
3. To recognize that adherence to treatment, specifically inhaled corticosteroids, has been a problem for many pregnant asthmatic patients, and this is usually due to concerns regarding the safety of these medications during pregnancy.
4. To understand how spirometry provides objective longitudinal tracking of the patient's clinical course, especially because tests of airway obstruction (FEV<sub>1</sub>, FEV<sub>1</sub>/forced vital capacity ratio, peak expiratory flow rate, and forced expiratory flow at 25% to 75% of forced vital capacity) remain unchanged during pregnancy.
5. To recognize that symptoms and pulmonary function need to be monitored on a monthly basis in pregnant asthmatic women so that any change in course can be matched with an appropriate change in therapy.
6. To recognize that patient education is an important part of managing the pregnant asthmatic patient. This includes explaining the relationship between asthma and pregnancy, identifying asthma triggers, providing training on correct use of inhalers, and establishing an asthma action plan.

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### CLINICAL VIGNETTE

A 20-year-old woman (gravida 1 parity 0) with a history of asthma presents to the clinic. She found out recently that she is pregnant and currently is at an estimated 6 weeks' gestation. This is her first visit, and she is here to see you with complaints of dyspnea, wheezing, and nighttime awakenings caused by cough

and concerns about restarting her asthma medications. She is currently using an inhaled short-acting  $\beta$ -agonist 3 to 4 times a day. She was recently prescribed an inhaled corticosteroid but has been afraid to use the medication because of its possible effects on her unborn baby. She was given a diagnosis of asthma at the age of 2 years after she was hospitalized for pneumonia. In the last 2 years, she has received 2 courses of oral corticosteroids for acute attacks of asthma. One of these episodes occurred after she had visited a friend's house with 2 cats. She experienced shortness of breath and wheezing and went to the emergency department. She says that her asthma symptoms have been more frequent since that episode. Further questioning reveals that other triggers of asthma symptoms include cleaning her house, tobacco smoke exposure, and upper respiratory tract infections. She is a nonsmoker, has no pets at home, and has never been evaluated for allergies. She has a history of eczema.

The positive findings on physical examination are scattered end-expiratory wheeze and erythematous maculopapular plaques

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in the popliteal fossa bilaterally. Spirometry revealed an FEV<sub>1</sub> of 75% of predicted value, which increased to an FEV<sub>1</sub> of 88% of predicted value after administration of an inhaled bronchodilator. *In vitro* allergy testing was performed and demonstrated a specific IgE level of greater than 100 kU/L for dust mite and cat.

The relationship between asthma and pregnancy and the risk of untreated asthma was discussed with the patient. She was told that pregnant asthmatic patients have an increased risk of complications, including low birth weight, small for gestational age, preterm labor and delivery, and preeclampsia during pregnancy, and those women with uncontrolled asthma have an even greater risk. On the basis of the frequency of her

symptoms, she was told that her asthma was uncontrolled. She agreed to start inhaled budesonide (180 µg, 2 puffs twice a day) and was instructed on technique. The patient's reluctance to use asthma medications for fear of potential adverse effects on the fetus was acknowledged, but she was told that the risks of uncontrolled asthma for both the patient and her baby appear to be greater than the risks of using inhaled corticosteroids during pregnancy.

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## DISCUSSION

### Overview

Asthma is one of the most common potentially serious medical problems to complicate pregnancy, and asthma can adversely affect both maternal quality of life and perinatal outcomes. A recent meta-analysis derived from a substantial body of literature spanning several decades and including very large numbers of pregnant women (>1,000,000 for low birth weight and >250,000 for preterm labor) indicates that pregnant women with asthma are at a significantly increased risk of a range of adverse perinatal outcomes, including low birth weight, small for gestational age, preterm labor and delivery, and preeclampsia.<sup>E1</sup>

Mechanisms postulated to explain the possible increased perinatal risks in pregnant asthmatic women demonstrated in previous studies have included (1) hypoxia and other physiologic consequences of poorly controlled asthma, (2) medications used to treat asthma, and (3) pathogenic or demographic factors (eg, race, ethnicity, smoking, and obesity) associated with asthma but not actually caused by the disease or its treatment, such as abnormal placental function.

Several recent prospective studies have shown that the pregnant asthmatic patient with disease of mild-to-moderate severity can have excellent maternal and fetal outcomes.<sup>E2-E5</sup> In contrast, suboptimal control of asthma or more severe asthma during pregnancy might be associated with increased maternal or fetal risk.<sup>E6,E7</sup>

Asthma course can worsen, improve, or remain unchanged during pregnancy, and the overall data suggest that these various courses occur with approximately equal frequency. Patients with more severe asthma before pregnancy are more likely to further worsen during pregnancy.

Proposed mechanisms responsible for the altered asthma course during pregnancy include fetal antigens, sex hormones, and emotional stress.

In addition, infections during pregnancy can certainly affect the course of gestational asthma. Sinusitis, a known asthma trigger, has been shown to be 6 times more common in pregnant compared with nonpregnant women.<sup>E8</sup> In addition, pneumonia has been reported to be greater than 5 times more common in asthmatic than nonasthmatic women during pregnancy.<sup>E9</sup> Adherence to therapy can change during pregnancy, with a corresponding change in asthma control. Most commonly observed is decreased adherence as a result of a mother's concerns about the safety of medications for the fetus.

### Diagnosis and evaluation

Many patients with asthma during pregnancy will already have a physician's diagnosis of asthma. A new diagnosis of asthma is usually suspected on the basis of typical symptoms, which include wheezing, chest tightness, cough, and associated shortness of breath. These symptoms tend to be episodic or at least fluctuating in intensity and are typically worse at night. Ideally, the diagnosis of asthma would be confirmed by demonstrating airway obstruction on spirometry that is at least partially reversible (>12% increase in FEV<sub>1</sub> after bronchodilator). The most common differential diagnosis is dyspnea of pregnancy, which can occur in early pregnancy in approximately 70% of women. This dyspnea is differentiated from asthma by its lack of association with cough, wheezing, or airway obstruction.

Clinical evaluation includes subjective assessments and pulmonary function tests. In patients who are not taking controller

therapy, it is useful to assess severity classification. In those patients who are taking controller therapy, it is useful to assess control. Assessing severity or control involves determining the frequency of daytime symptoms, nighttime symptoms, activity limitation, frequency of rescue therapy, and FEV<sub>1</sub>. Women with asthma must be followed particularly closely during pregnancy so that any change in course can be matched with an appropriate change in therapy.

### Management

Identifying and avoiding asthma triggers can lead to improved maternal well-being with less need for medications. In previously untested patients, *in vitro* (RAST or ELISA) or skin testing should be performed to identify relevant allergens, such as mite, animal dander, mold, and cockroach, for which specific environmental control instructions can be given. Smokers must be encouraged to discontinue smoking, and all patients should try to avoid exposure to environmental tobacco smoke and other potential irritants as much as possible.

Patients with intermittent asthma can use short-acting  $\beta$ -agonists, preferably in the form of albuterol, for quick relief of bronchospasm. Two recent studies found the use of short-acting  $\beta$ -agonists was associated with an increased risk of congenital malformations, including gastroschisis and cardiac defects. It remains to be determined, however, whether these associations are confounded by indication (use for exacerbations) because asthma exacerbations during the first trimester have been associated with an increased risk of congenital malformations.<sup>E10,E11</sup>

In patients with persistent asthma, controller therapy should be initiated and progressed in steps until adequate control is achieved.

Inhaled corticosteroids are the mainstay of controller therapy during pregnancy. Because it has the most published reassuring human gestational safety data, budesonide is considered the inhaled corticosteroid of choice for asthma during pregnancy. It is important to note that no data indicate that other inhaled corticosteroid preparations are unsafe. Therefore inhaled corticosteroids other than budesonide can be continued in patients whose symptoms were well controlled by these agents before pregnancy, especially if it is thought that changing formulations might jeopardize asthma control. The following drugs are considered by the National Asthma Education and Prevention Program to be alternative but not preferred treatments for persistent asthma during pregnancy: cromolyn because of decreased efficacy compared with inhaled corticosteroids; theophylline, primarily because of increased side effects compared with the alternatives; and leukotriene receptor antagonists because of the availability of fewer published human gestational safety data for these drugs. Although oral corticosteroids have been associated with possible increased risks during pregnancy (oral clefts, prematurity, and lower birth weight),<sup>E12,E13</sup> they should be used if needed because these risks are less than the potential risks of severe uncontrolled asthma. The use of long-acting  $\beta$ -agonists is the preferred add-on controller therapy for asthma during pregnancy. This therapy should be added on when patients' symptoms are not controlled with the use of medium-dose inhaled corticosteroids. Because long-acting and short-acting inhaled  $\beta$ -agonists have similar pharmacology and toxicology, long-acting  $\beta$ -agonists are expected to have a safety profile similar to that of albuterol. Two long-acting  $\beta$ -agonists are available: salmeterol and formoterol. Limited observational data exist on their use

during pregnancy. A possible association between long-acting  $\beta$ -agonists and an increased risk of severe and even fatal asthma exacerbations has been observed in nonpregnant patients. As a result, long-acting  $\beta$ -agonists are no longer recommended as monotherapy for the treatment of asthma and are available in fixed combination preparations with inhaled corticosteroids. Expert panels suggest that the benefits of the use of long-acting  $\beta$ -agonists appear to outweigh the risks as long as they are used concurrently with inhaled corticosteroids.<sup>E14</sup>

Education is an important part of the management of the pregnant asthmatic patient. Each patient should be provided basic information about asthma and the relationship between asthma and pregnancy. Monthly visits to assess asthma control and adherence are recommended for women who require controller therapy during pregnancy. Each patient should also receive a self-treatment action plan that includes how to recognize a severe exacerbation and when to seek urgent or emergency care.

## THE CASE REVISITED

This is a pregnant asthmatic patient with poorly controlled persistent asthma according to National Asthma Education and Prevention Program guidelines, as evidenced by her daily symptoms, daily use of rescue therapy, interference with sleep more than once a week, and an FEV<sub>1</sub> of less than 80% of the predicted value. She was initially prescribed an inhaled corticosteroid by another physician but is currently receiving rescue therapy alone. It is not uncommon to find decreased adherence as a result of a mother's concerns about the safety of medications for the fetus. One study found that women with asthma significantly decreased their asthma medication use from 5 to 13 weeks of pregnancy. During the first trimester, there was a 23% decrease in inhaled corticosteroid prescriptions, a 13% decrease in short-acting  $\beta$ -agonist prescriptions, and a 54% decrease in rescue corticosteroid prescriptions.<sup>E15</sup> After being educated regarding the potential risks of uncontrolled asthma for herself and her pregnancy, she should be instructed regarding environmental control for her clinically relevant dust mite allergy. Inhaled budesonide (180  $\mu$ g per puff, 2 puffs twice a day) was chosen 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 optimal inhaler technique and 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. It was recommended that she return for follow-up every 1 to 2 weeks initially to ensure

that asthma control is improving and then, once control has been achieved, monthly for review of her symptoms and adherence to treatment, as well as pulmonary function testing. If her asthma symptoms remain uncontrolled, her therapy should be stepped up by adding a long-acting  $\beta$ -agonist. In addition to the above, she should be considered for serial ultrasound examinations and antenatal fetal testing to monitor fetal growth and activity, which is typically indicated for women with moderate-to-severe or poorly controlled asthma.

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