

Current Guidelines for the Management of Asthma During Pregnancy

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Asthma is the most common, potentially serious medical problem to complicate pregnancy. Studies have shown that pregnant asthmatic women have an increased risk of adverse perinatal outcomes [1,2], whereas controlled asthma is associated with reduced risks [3]. Managing asthma during pregnancy is unique because the effect of the illness and the treatment on the developing fetus as well as the patient must be considered.

The two main goals of asthma management during pregnancy are to optimize maternal and fetal health. This article summarizes specific studies and recently published guidelines regarding the optimal management of asthma during pregnancy.

Prevalence of asthma during pregnancy

Previous estimates of asthma prevalence during pregnancy were between 4% and 7% [1–5]. Many of these reports were from retrospective data, rather than being based on a nationally representative sample. Recently, Kwon and colleagues [6] reviewed U.S. national health surveys spanning 1997 to 2001. The aim was to determine more definitively the prevalence of asthma in pregnant women ages 18 to 44. Time trends also were examined using health surveys from 1976 to 1980 and 1988 to 1994. They found that asthma affected between 3.7% and 8.4% of pregnant women in the United States between 1997 and 2001. There

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was a twofold increase in the prevalence of asthma (from 2.9% to 5.8%) between 1976 and 1980 and 1988 and 1994. This study supports initial prevalence estimates, but also suggests that they may have been conservative. More importantly, this study supports the observation that asthma affects more pregnant women each year.

Effects of uncontrolled asthma on pregnancy

The potential effects of asthma on the course of pregnancy are reviewed elsewhere in this issue. Observations that support the hypothesis that uncontrolled asthma increases perinatal risks, whereas controlled asthma reduces these risks form an important basis for the management recommendations in this article. For example, studies have shown that better controlled asthma (defined by lack of acute episodes or higher maternal pulmonary function) leads to improved intrauterine growth (measured by birth weight or ponderal indices [7–10]). In contrast, patients who have daily asthma symptoms are at increased risk for intrauterine growth retardation and preeclampsia [11,12].

Asthma management during pregnancy: nonpharmacologic

The general principles of asthma management during pregnancy do not differ substantially from the management of nonpregnant asthmatics. The ultimate goal for the pregnant asthmatic is to have no limitation of activity, minimal chronic symptoms, no exacerbations, normal pulmonary function, and minimal adverse effects of medications. It is the clinician's job to provide optimal therapy to maintain asthma control that improves maternal quality of life and allows for normal fetal maturation.

Assessment and monitoring

Objective assessments and monitoring should be performed on a monthly basis. Such assessments should include pulmonary function testing (ideally spirometry), detailed symptom history (symptom frequency, nocturnal asthma, interference with activities, exacerbations, and medication use), and physical examination with specific attention paid to auscultation of the lungs. Schatz and colleagues [13] observed that 30% of subjects whose asthma was classified as mild at entry "switched" categories during pregnancy to the moderate or severe groups. Thus, pregnant asthmatic patients, even those who have mild or well-controlled disease, need to be monitored closely during pregnancy [13]. It also was observed that patients with a forced expiratory volume in 1 second (FEV₁) of less than 80% of predicted are at increased risk of asthma morbidity [13] and

pregnancy complications [14]. Home peak flow monitoring may be a valuable tool in managing the pregnant asthmatic who has moderate to severe disease.

Because asthma has been associated with intrauterine growth retardation and preterm birth, it is useful to establish pregnancy dating accurately by a first trimester ultrasound. Patients should be instructed to be attentive to fetal activity. Some women may benefit from additional evaluation of fetal activity and growth by serial ultrasound examinations. According to current guidelines, women who have moderate to severe asthma or suboptimally controlled asthma, or who are recovering from a severe exacerbation are candidates for antenatal surveillance [15].

There should be open lines of communication with the patient's obstetrician. Obstetricians should be involved in asthma care and should obtain information on asthma status during prenatal visits.

Avoidance of asthma triggering factors

Avoidance of asthma triggers, such as animal dander, tobacco smoke, and pollutants, is important because exposure may lead to increased asthma symptoms and the potential need for more medication. Often, allergen immunotherapy is effective for those patients in whom symptoms persist, despite optimal environmental control and proper drug therapy. Allergen immunotherapy can be continued carefully during pregnancy in patients who are deriving benefit, who are not experiencing systemic reactions, and who are receiving maintenance doses. Benefit-risk considerations do not generally favor beginning immunotherapy during pregnancy for most patients because of (1) the undefined propensity for systemic reactions, (2) the increased likelihood of systemic reactions during initiation of immunotherapy, (3) the latency of immunotherapy effect, and (4) the frequent difficulty in predicting which asthmatic patients will benefit from immunotherapy [15].

Smoking should be discouraged strongly, and all patients should try to avoid environmental tobacco smoke exposure as much as possible. Morbidity during pregnancy that is due to smoking may be independent of, and additive to, morbidity that is due to asthma [8].

Patient education

Patient education is more important than ever during pregnancy. The patient must understand the potential adverse effects of uncontrolled asthma on the well-being of the fetus, and that treating asthma with medications is safer than increased asthma symptoms that may lead to maternal and fetal hypoxia. Above all, she should be able to recognize symptoms of worsening asthma and be able to treat them appropriately. This requires an individualized action plan that is based on a joint agreement between the patient and the clinician. Correct inhaler technique should be assured, and the patient also should understand how she can reduce her exposure to, or control those, factors that exacerbate her asthma.

Updated guidelines for the pharmacologic management of asthma during pregnancy

General information regarding the safety of medications during pregnancy and gestational data for specific asthma and allergy medications are summarized elsewhere in this issue. In 1993, the National Asthma Education and Prevention Program Expert Panel Report (NAEPP) published the *Report of the Working Group on Asthma and Pregnancy* [16], which reviewed the data from available studies, and presented recommendations for the pharmacologic management of asthma during pregnancy. Since then there have been new developments, including the introduction of new medications, the availability of additional safety data, and revisions to severity classification and treatment guidelines in the general management of asthma [17,18]. All of these developments led to an update of the 1993 report which was published recently: *NAEPP Working Group Report on Managing Asthma During Pregnancy: Recommendations for Pharmacologic Treatment—Update 2004* [15]. The focus of this update was to review new data regarding the safety and effectiveness of asthma medications taken during pregnancy and lactation. Although this report presents an extensive review of the current literature with specific recommendations, the working group members stress that these guidelines are meant to assist clinical decision-making and should be used adjunctively when designing a treatment plan that is tailored specifically to the needs of a pregnant patient.

There are several differences between the recommendations that were made in the 1993 report, the 2002 EPR-2 update [18], and the recent update in 2004. The 1993 report recommended that controller therapy for moderate asthma (which included what was later defined as mild or moderate persistent asthma) be initiated with cromolyn because of its safety profile. Since then, strong evidence demonstrates that cromolyn is not as effective as inhaled corticosteroids for the treatment of persistent asthma, and new information regarding the safety of inhaled corticosteroids has been published [18]. Therefore, inhaled steroids are recommended as the preferred controller therapy for all levels of persistent asthma. Compared with the EPR-Update in 2002, the most important difference is that two equal treatment options are recommended for moderate persistent asthma: a combination of low-dose inhaled corticosteroids plus a long-acting β -2 agonist, or medium-dose inhaled corticosteroids.

Effectiveness of inhaled corticosteroids during pregnancy

Inhaled corticosteroids are well documented to prevent asthma exacerbations in nonpregnant women. This also is true in the pregnant population as reported by Stenius-Aarniala and colleagues [19]. They found a higher incidence of asthma exacerbations in those who were not treated initially with inhaled corticosteroid in comparison with patients who had been on an inhaled corticosteroid from the

beginning of pregnancy. In addition, two randomized controlled trials during pregnancy support the efficacy of inhaled steroids during pregnancy [20,21].

First, a prospective randomized controlled trial studied 72 pregnant asthmatics who presented to an emergency department or prenatal clinic with an asthma exacerbation. There was a 55% reduction in exacerbations and readmissions in women who were given inhaled beclomethasone dipropionate with oral corticosteroids and β -2 agonists compared with women who were treated with oral corticosteroids and β -2 agonists alone [20].

Second a prospective, double-blind, double placebo-controlled randomized clinical trial that was published recently by Dombrowski and colleagues [21] compared the efficacy of inhaled beclomethasone dipropionate with oral theophylline for the prevention of asthma exacerbations during pregnancy. There was no significant difference in the proportion of asthma exacerbations among the 194 women who used beclomethasone dipropionate versus the 191 women who took theophylline. There were fewer reported side effects, less discontinuation of medication, and a lower proportion of women with FEV₁ less than 80% in the group that used beclomethasone dipropionate. This study supports previous guidelines that inhaled corticosteroids are the therapy of choice for persistent asthma during pregnancy.

Choice of specific medications during pregnancy

Inhaled corticosteroids

In 1993, the Working Group on Asthma and Pregnancy stated that corticosteroids are the most effective anti-inflammatory drugs for the treatment of asthma. At that time, beclomethasone dipropionate, triamcinolone, and flunisolide were recognized as treatment options; there was the most experience during pregnancy with beclomethasone dipropionate. Therefore, it was recommended as the inhaled corticosteroid of choice at that time [16]. Publications since then have supported the overall safety of inhaled corticosteroid use in pregnancy; the most safety data are available for inhaled budesonide. Thus, in the current guidelines, budesonide is the preferred inhaled corticosteroid during pregnancy.

The recent guidelines emphasize that there are no data to suggest that other inhaled corticosteroids are less safe during pregnancy. Thus, if a pregnant asthmatic woman is using an alternative inhaled corticosteroid before pregnancy and her asthma is well controlled, it would not be unreasonable to continue it through the pregnancy.

Oral corticosteroids

Data regarding the use of systemic corticosteroids during pregnancy have not been totally reassuring. Recent available human studies include a meta-analysis of 6 cohort studies by Park-Wyllie and colleagues evaluating the relationship

between corticosteroid use during pregnancy and congenital malformations, and four case-control studies evaluating the potential relationship between systemic corticosteroid use during pregnancy and oral clefts [22]. They found that while there was no definite increased risk of total congenital malformations, there was a statistically significant increased risk of oral clefts in infants of mothers treated with corticosteroids during the first trimester (summary odds ratio [OR], 3.35; 95% confidence interval, 1.97–5.69).

Other adverse outcomes that recently were associated with systemic corticosteroid use during pregnancy include preeclampsia, low birth weight, and preterm delivery [9,23–25]. The available data make it difficult to separate the effects of the corticosteroids on these outcomes from the effects of severe or uncontrolled asthma. It must be stressed that the potential risks of oral corticosteroid use during pregnancy must be balanced against the risks to the mother and infant of poorly managed severe disease, which include maternal mortality, fetal mortality, or both [15]. The current recommendations support the use of oral corticosteroids when indicated for the long-term management of severe asthma or for severe exacerbations during pregnancy [15].

Short-acting bronchodilators

The 1993 guidelines did not make a recommendation regarding a specific short-acting inhaled β -agonist for use during pregnancy [16]. Based on the data that have been published since then, albuterol is recommended as the inhaled, short-acting β -agonist of choice during pregnancy [15].

Long-acting β -agonists

Since 1993, two long-acting inhaled bronchodilators have become available—salmeterol and formoterol. There are few published data regarding the safety of these drugs during pregnancy. The new guidelines recommend salmeterol as the long-acting β -agonist of choice during pregnancy because it has been available for a longer period of time in this country [15].

Other medications

The 1993 report recognized the use of nebulized ipratropium in women who presented with acute asthma who do not improve substantially with the first inhaled β -agonist treatment. Since then, there have been no further published data on anticholinergics in pregnancy, but this recommendation is maintained in the updated guidelines [15]. Other medications are recommended only as alternative, but not preferred, choices during pregnancy. These include cromolyn (for mild persistent asthma), theophylline (for mild persistent asthma or as

add-on therapy to inhaled corticosteroids), and zafirlukast or montelukast (for mild persistent asthma or as add-on therapy to inhaled corticosteroids). The serum concentrations of theophylline need to be monitored closely, and low-dose therapy is recommended with maintenance serum levels targeted at 5 to 12 $\mu\text{g/mL}$.

Pharmacologic step therapy during pregnancy

Many pregnant asthmatic women require medications to control their asthma. Current guidelines recommend a generalized stepwise approach (Table 1) in achieving and maintaining asthma control. The number and dose of medications used are increased as necessary and decreased when possible. Decreasing doses should be done carefully because this may lead to an exacerbation of symptoms. Current guidelines suggest that it may be prudent to postpone attempts at reducing therapy that is controlling the patient's asthma until after the infant's birth.

The classification of asthma severity as outlined in the current guidelines also may help to predict asthma morbidity during pregnancy. Schatz and colleagues [13] reported that asthma morbidity (hospitalizations, office visits, oral corticosteroid use) correlated closely with asthma classification applied to the

Table 1
Stepwise approach for the management of chronic asthma during pregnancy

Category	Step therapy
Mild intermittent	Inhaled β -agonist as needed ^a
Mild persistent	Low-dose inhaled corticosteroid ^b Alternative: cromolyn, leukotriene receptor antagonist, or theophylline ^c
Moderate persistent	Low-dose inhaled corticosteroid and long-acting β -agonist ^d or medium-dose inhaled corticosteroid or (if needed) medium-dose inhaled corticosteroid and long-acting β -agonist Alternative: low-dose or (if needed) medium-dose inhaled corticosteroid and either theophylline or leukotriene receptor antagonist
Severe persistent	High-dose inhaled corticosteroid and long-acting β -agonist and, if needed, oral corticosteroids Alternative: High-dose inhaled corticosteroid and theophylline

Based on the recommendations of the National Asthma Education Program Report of the Working Group on Asthma During Pregnancy Update 2004 [15].

^a More published human data on using albuterol during pregnancy than on using other short-acting β -agonists.

^b More data on using budesonide than on using other inhaled corticosteroids.

^c Maintain to serum concentration of 5–12 $\mu\text{g/mL}$.

^d Salmeterol is considered the long-acting β -agonist of choice during pregnancy because of its longer availability in this country.

subjects at entry (ie, subjects who had mild asthma experienced fewer hospitalizations, unscheduled visits, oral corticosteroid courses, and total exacerbations than those who had moderate asthma; subjects who had severe asthma at entry experienced the greatest risk of asthma morbidity during pregnancy).

Management of acute exacerbations of asthma during pregnancy

A recent large multicenter study reported that 20% of women who have persistent asthma experienced an unscheduled (emergency department or physician) visit for asthma during pregnancy, and 8% required hospitalization [13]. Such exacerbations can compromise fetal well-being; therefore, aggressive home management of acute symptoms needs to be reviewed with pregnant asthmatic patients. Above all, pregnant asthmatic patients should be taught to recognize the early signs and symptoms of exacerbations. The current recommendations for home and emergency department management of asthma exacerbations in pregnant asthmatic women are not different from the EPR-2 [17] recommendations in nonpregnant asthmatic women that were published previously. These guidelines are reviewed in detail elsewhere in this issue.

Management of asthma during labor and delivery

Only approximately 10% to 20% of women develop an exacerbation of asthma during labor and delivery [13,26]. Nonetheless, asthma medications should be continued during labor and delivery. If a systemic steroid has been used in the previous month, then stress-dose steroid should be administered during labor to prevent maternal adrenal crisis. Practitioners should be aware of the potential side effects that labor medications that are used commonly may have on asthma. For instance, prostaglandin F₂ alpha and methylergonovine, which are used for postpartum hemorrhage, can induce bronchospasm. Prostaglandin E₂ and magnesium sulfate may be used safely in asthmatic patients. Maternal and fetal hypoxia that is due to asthma during labor and delivery can be managed medically. It is rarely necessary to perform an emergent caesarean section.

Summary

Over the past few years, much has been learned that is relevant to the management of asthma in pregnancy. Although the studies that were reviewed herein provide more insight into the mechanisms that are involved and the treatment of asthma during pregnancy, there are more questions to be answered. It is hoped

that the updated guidelines, which address the safety of contemporary asthma medications during pregnancy, will be a helpful resource in the treatment of our pregnant asthmatic patients.

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