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Asthma and Pregnancy

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Asthma complicates 4–8% of pregnancies. Mild and well-controlled moderate asthma can be associated with excellent maternal and perinatal pregnancy outcomes. Severe and poorly controlled asthma may be associated with increased prematurity, need for cesarean delivery, preeclampsia, growth restriction, other perinatal complications, as well as maternal morbidity and mortality. Optimal management of asthma during pregnancy includes objective monitoring of lung function, avoiding or controlling asthma triggers, patient education, and individualized pharmacologic therapy. Those with persistent asthma should be monitored by peak expiratory flow rate, spirometry to measure the forced expiratory volume in 1 second, or both. Step-care therapeutic approach uses the least amount of drug intervention necessary to control a patient's severity of asthma. Inhaled corticosteroids are the preferred treatment for the management of all levels of persistent asthma during pregnancy. It is safer for pregnant women with asthma to be treated with asthma medications than it is for them to have asthma symptoms and exacerbations. The ultimate goal of asthma therapy is maintaining adequate oxygenation of the fetus by prevention of hypoxic episodes in the mother. Asthma exacerbations should be aggressively managed, with a goal of alleviating asthma symptoms and attaining peak expiratory flow rate or forced expiratory volume in 1 second of 70% predicted or more. Pregnancies complicated by moderate or severe asthma may benefit from ultrasound for fetal growth and accurate dating and antenatal assessment of fetal well-being. Asthma medications should be continued during labor, and parturients should be encouraged to breastfeed.

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Asthma may be the most common potentially serious medical condition to complicate pregnancy.¹ Asthma is characterized by chronic airway inflammation with increased airway responsiveness to a variety of stimuli and airway obstruction that is partially or completely reversible.¹ Insight into the pathogenesis of asthma has changed with the recognition that airway inflammation is present in nearly all cases. Current medical management for asthma emphasizes treatment of airway inflammation to decrease airway

responsiveness and prevent asthma symptoms. Approximately 4–8% of pregnancies are complicated by asthma.^{2,3} In general, the prevalence, morbidity, and mortality from asthma are increasing.

DIAGNOSIS

The enlarging uterus elevates the diaphragm about 4 cm, with a reduction of the functional residual capacity (Fig. 1). However, there are no significant alterations in forced vital capacity, peak expiratory flow rate (PEFR) or forced expiratory volume in 1 second (FEV₁) in normal pregnancy. Shortness of breath at rest or with mild exertion is common and is often referred to as physiologic dyspnea of pregnancy. Asthma is characterized by paroxysmal or persistent symptoms including breathlessness, chest tightness, cough, and sputum production. The diagnosis of asthma is based upon a history of symptoms and spirometry. Patients with asthma will have an im-

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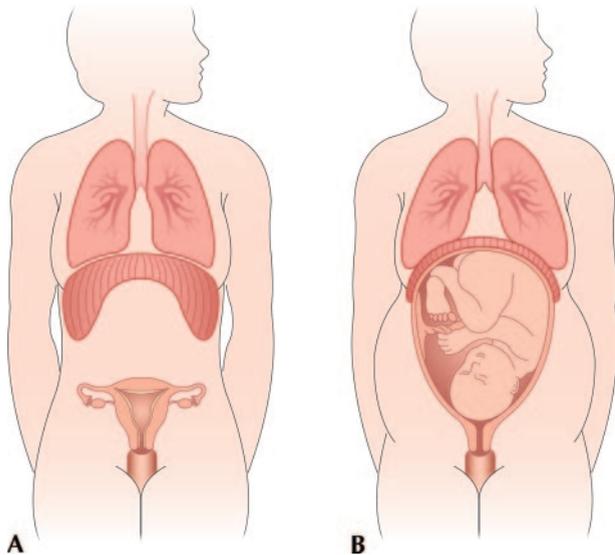


Fig. 1. Effect of enlarging pregnancy on the chest and pulmonary anatomy. A. Nonpregnant woman. B. Woman in third trimester of pregnancy. Illustration: John Yanson. Dombrowski. *Asthma and Pregnancy. Obstet Gynecol* 2006.

provement in FEV₁ after administration of a short-acting inhaled β_2 -agonist. They will also have increased sensitivity to inhaled methacholine, although this is not usually performed during pregnancy.

In 2004, the National Asthma Education and Prevention Program (NAEPP) Working Group on Asthma and Pregnancy defined mild intermittent, mild persistent, moderate persistent, and severe persistent asthma according to symptomatic exacerbations (wheezing, cough, dyspnea or all three) and objective tests of pulmonary function. The most commonly used measures are the PEF_R and FEV₁. The NAEPP guidelines did not list the need for regular medication to be a factor for classifying asthma severity during pregnancy. However, patients with mild asthma by NAEP criteria, but who required regular medications to control their asthma, were similar to those with moderate asthma with respect to asthma exacerbations.⁴ Pregnant patients requiring regular systemic corticosteroids to control asthma symptoms were similar to severe asthmatics with respect to exacerbations. Box, "Asthma Severity Classification," shows modified NAEPP asthma severity criteria

THE EFFECTS OF PREGNANCY ON ASTHMA

Asthma has been associated with considerable maternal morbidity. In a large prospective study, patients with mild asthma had an exacerbation rate of 12.6% and hospitalization rate of 2.3%; those with moderate asthma had an exacerbation rate of 25.7% and hospi-

Asthma Severity Classification

Mild Intermittent Asthma*

Symptoms twice per week or less
Nocturnal symptoms twice per month or less
PEFR or FEV₁ 80% predicted or more, variability less than 20%

Mild Persistent Asthma

Symptoms more than twice per week but not daily
Nocturnal symptoms more than twice per month
PEFR or FEV₁ 80% predicted or more, variability 20–30%

Moderate Persistent Asthma

Daily symptoms
Nocturnal symptoms more than once per week
PEFR or FEV₁ more than 60% to less than 80% predicted, variability more than 30%
Regular medications necessary to control symptoms

Severe Asthma

Continuous symptoms and frequent exacerbations
Frequent nocturnal symptoms
PEFR or FEV₁ 60% predicted or less, variability more than 30%
Regular oral corticosteroids necessary to control symptoms

* Information from National Institutes of Health, National Heart, Lung, and Blood Institute. National Asthma Education Program. Report of the Working Group on Asthma and Pregnancy: management of asthma during pregnancy.³²

talization rate of 6.8%; and severe asthmatics had exacerbation of 51.9% and hospitalization rate 26.9%.⁴ The effects of pregnancy on asthma are variable, and in a large prospective study, 23% improved and 30% become worse during pregnancy.⁴ One of the most important conclusions to be made from this study is that pregnant asthmatic patients, even with mild or well-controlled disease, need to be monitored by PEF_R and FEV₁ testing during pregnancy.

THE EFFECTS OF ASTHMA ON PREGNANCY

Existing studies on the effects of asthma on pregnancy outcomes have had inconsistent results with regard to maternal and perinatal outcomes. For example, asthma has been reported to be associated with increased perinatal mortality,⁵ hyperemesis gravidarum,⁶ hemorrhage,^{2,6,7} hypertension or preeclampsia,^{6–13} preterm birth,^{6,10,11,14–16}



hypoxia at birth,⁶ low birth weight,^{6,17} increased cesarean delivery,^{7,9,10,14,17} small for gestational age (SGA) or intrauterine growth restriction,^{10,11,18} gestational diabetes,^{7,14} and malformations.¹⁰ In contrast, asthma has also been reported NOT to be associated with preterm birth,^{2,5,17-20} birth injury,⁶ reduced gestational age,^{8,9,21-23} reduced mean birth weight,^{8,9,17,22-24} increased perinatal mortality,^{6,7,9,19,23,25} low Apgar score,⁹ neonatal respiratory difficulty,⁹ malformations,^{2,6,9,11,19} antepartum or postpartum hemorrhage or both,^{11,17,21} perinatal complications,^{12,17} gestational hypertension or preeclampsia,^{14,18,19,26} intrauterine growth restriction,^{14,19} increased cesarean delivery,^{2,20,25} low birth weight,^{2,19,20,21,25} gestational diabetes,^{2,12} or respiratory distress syndrome.²

Many of the older studies have a number of methodologic inadequacies, including low power, different inclusion criteria, lacking or inadequate control for confounders, little or no information regarding asthma severity, management, or control, and time frames that do not reflect current management. Until recently, there have been few large prospective studies of asthma during pregnancy.

There have been two recent, large, multicenter, prospective cohort studies evaluating the effects of maternal asthma perinatal outcomes.^{27,28} These studies were relatively unique in that they contained information regarding asthma severity and management. In 2003, Bracken and coworkers²⁷ reported that preterm delivery was not associated with asthma diagnosis or severity. However, need for treatment with oral corticosteroid or theophylline use was significantly associated with a reduction of gestational age at delivery. Small for gestational age was significantly increased among those with daily symptoms or moderate persistent severity. No specific medication type was observed to lead to an increased risk of fetal growth restriction. Preeclampsia was significantly increased among the cohort who had daily asthma symptoms and among those who required theophylline.²⁹ These data suggest that poor asthma control, by causing acute or chronic maternal hypoxia, may be the most remedial responsible factor and support the important generalization that adequate asthma control during pregnancy is important in improving maternal and fetal outcome.

The National Institute of Child Health and Human Development and National Heart, Lung, and Blood Institute (NHLBI) conducted a multicenter, prospective, observational cohort study involving 16 centers with preterm delivery less than 32 weeks as the primary outcome. Dombrowski et al²⁸ enrolled 873 subjects with mild asthma, 814 with moderate or

52 with severe asthma, and 881 nonasthmatic controls. There were no significant differences in the rates of preterm delivery less than 32 weeks or less than 37 weeks gestation. Of all outcomes explored (including preterm delivery, gestational diabetes, preeclampsia, preterm labor, chorioamnionitis, oligohydramnios, cesarean delivery, low birth weight, small for gestational age, and congenital malformations), only cesarean delivery rate was significantly increased in the group of moderate to severe asthma. Among the cohort with severe asthma, there was a significantly increased incidence of gestational diabetes and delivery less than 37 weeks compared with controls by logistic regression adjusted for confounding variables. Oral corticosteroid use was significantly associated with both preterm delivery less than 37 weeks and birth weight less than 2,500 g.³⁰ There were no significant differences for neonatal outcomes except for discharge diagnosis of neonatal sepsis among the group with mild asthma, a finding that may be related to type 1 error.

Participants in the National Institute of Child Health and Human Development and NHLBI study had excellent maternal and perinatal outcomes despite a high frequency of asthma exacerbations. These findings do not contradict the possibility that suboptimal control of asthma during pregnancy is associated with increased risk to the mother or baby. In fact, this study did find a relationship between lower FEV₁ during pregnancy and an increased risk of low birth weight and prematurity.³¹ Both studies indicate that classification of asthma severity with therapy tailored according to asthma severity can result in excellent perinatal and maternal outcomes. This generally confirms the findings of two earlier and smaller prospective cohort studies^{19,21} in which asthma was managed by asthma specialists.

PUTTING THE LITERATURE INTO PERSPECTIVE

There is considerable consistency among prospective studies of the effects of asthma on maternal and perinatal outcomes. Eight prospective studies reporting maternal and neonatal outcomes of at least 100 participants have been published in the English literature, in locations at or near sea level (Table 1). One can conclude from these studies that cohorts with mild or moderate asthma during pregnancy can have excellent maternal and perinatal outcomes. The two largest studies, by Dombrowski et al²⁸ and Bracken et al²⁷ reported an increase of preterm delivery less than 37 weeks gestation among subjects who had severe asthma, required



Table 1. Prospective Cohort Studies Reporting Obstetric and Neonatal Outcomes

Outcome	Dombrowski et al 2004 ²⁸ (N=1,739)	Bracken et al 2003 ²⁷ (N=872)	Stenius et al 1996 ²¹ (N=504)	Schatz et al 1995 ¹⁹ (N=486)	Mihrshahi et al 2003 ¹² (N=340)	Jana et al 1995 ²⁵ (N=182)	Stenius and Teramo 1988 ⁹ (N=181)	Minerbi-Codish et al 1998 ²⁰ (N=101)
Preterm less than 32 weeks	No	NR	NR	NR	NR	NR	NR	NR
Preterm less than 37 weeks	No (yes if severe)	No (yes if oral steroids)	No	No	No	No	NR	No
Preeclampsia	No	No (yes if daily symptoms)	No	No	No	NR	Yes	No
Cesarean delivery	Yes (if moderate or severe)	NR	Yes (if elective)	NR	No	No	Yes	No
Gestational diabetes	No (yes if severe)	NR	No	No	NR	NR	No	No
Small for gestational age	No	No (yes if daily symptoms)	NR	No	NR	NR	NR	No
Malformation	No	NR	No	No	NR	No	NR	No
Antenatal hemorrhage	NR	NR	No	NR	NR	No	No	NR
Postnatal hemorrhage	No	NR	NR	NR	NR	NR	NR	NR
RDS/HMD	No	NR	NR	No	NR	NR	No	NR
NEC	No	NR	NR	No	NR	NR	NR	NR
Perinatal death	No	NR	No	No	NR	No	No	NR
NICU admission	No	NR	No	NR	No	NR	No	NR

NR, not reported; RDS/HMD, respiratory distress syndrome/hyaline membrane disease; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit

“Yes” entries indicate significantly increased; “No” entries indicate no significant association.

Reprinted from Dombrowski MP. Outcomes of pregnancy in asthmatic women. *Immunol Allergy Clin North Am* 2006;26:81–92.

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oral corticosteroids, or both. In addition, two studies reported an increase in preeclampsia,^{9,27} although one of these only found this in patients with daily symptoms.²⁷ Three studies reported increased cesarean delivery,^{9,21,28} although one of these was only in patients with moderate to severe asthma.²⁸ One study reported an increased incidence of gestational diabetes with severe asthma,²⁸ and one found an increased risk of SGA in infants of mothers with daily asthma symptoms.²⁷

In contrast, there is much less consensus among retrospective studies of asthma in pregnancy. Nearly every possible pregnancy complication has been associated with asthma by at least one retrospective publication. In 1993, the National Asthma Education and Prevention Program of the NHLBI recommended anti-inflammatory treatment for pregnant women with moderate or severe asthma. Studies that enrolled patients after the 1993 NAEP recommendations tended to have fewer adverse pregnancy outcomes associated with asthma. This again supports the concept that optimal asthma management can mitigate adverse pregnancy out-

comes. Patients with poorly controlled asthma complicated by severe exacerbations are at significant risk for maternal and fetal morbidity and mortality.

A potential explanation for the inconsistencies among many studies with regard to the effect of asthma on obstetric and neonatal outcomes may include the fact that most studies of asthma during pregnancy did not attempt to classify asthma severity. Classification of asthma severity has important clinical implications with regard to asthma morbidity and tailoring optimal treatment regimens.^{32,33} Failure to classify severity may result in suboptimal asthma control, thereby increasing risks for adverse maternal or neonatal outcomes. Oral corticosteroid treatment per se may confound maternal and neonatal outcomes. Some positive findings may be due to chance or due to confounders such as ethnicity, smoking status, socioeconomic status, hypertension, and others. Asthma medications and poor asthma control leading to hypoxia have been hypothesized to explain some of these observations.³⁴ There are some data to support a correlation with poor asthma control indicated by increased hospi-



talization for exacerbations and decreased FEV₁ values with low birth weight and ponderal index.^{25,34,35} Studies have shown that patients with more severe asthma may have the greatest risk for complications during pregnancy,^{10,14,15,36} whereas better-controlled asthma is associated with decreased risks.^{19,27,28} Prospective studies have tended to find fewer significant adverse associations, possibly due to better asthma surveillance and treatment.

There are important caveats when interpreting this literature. The excellent maternal and perinatal outcomes were achieved at centers that tended to manage asthma actively in pregnancy. In addition, women who enroll in research studies tend to be more compliant and better motivated than the general public. The lack of finding more adverse outcomes among gravida with severe asthma may also be a function of the relatively small numbers of this cohort and the resulting lack of power to find adverse outcomes that were statistically significant. Nonetheless, these prospective studies are reassuring in their consensus of good pregnancy outcomes among women with asthma. However, these studies do not suggest that asthma should be considered to be a benign condition, because active asthma management was a part of these studies and may have affected outcomes.

ASTHMA MANAGEMENT

The ultimate goal of asthma therapy during pregnancy is to maintain adequate oxygenation of the fetus by prevention of hypoxic episodes in the mother. Other goals include to achievement of minimal or no maternal symptoms day or night, minimal or no exacerbations, no limitations of activities, maintenance of normal or near-normal pulmonary function, minimal use of short-acting β_2 -agonists, and minimal or no adverse effects from medications. Consultation or comanagement with an asthma specialist is appropriate, as indicated, for evaluation of the role of allergy and irritants, complete pulmonary function studies, or evaluation of the medication plan if there are complications in achieving the goals of therapy or the patient has severe asthma. A team approach is helpful if more than one clinician is managing the asthma and the pregnancy. The effective management of asthma during pregnancy relies on four integral components outlined below:

Objective Measures for Assessment and Monitoring

Subjective measures of lung function by either the patient or physician provides an insensitive and inaccurate assessment of airway hyperresponsiveness, airway inflammation, and asthma severity. The FEV₁ after a maximal inspiration is the single best measure of pulmonary function. When adjusted for confounders, a mean FEV₁ less than 80% predicted has been found to be significantly associated with increased preterm delivery less than 32 weeks and less than 37 weeks, and birth weight less than 2,500 g.³¹ However, measurement of FEV₁ requires a spirometer. The PEF_r correlates well with the FEV₁, and has the advantages that it can be measured reliably with inexpensive, disposable, portable peak flow meters (Fig. 2).

Patient self-monitoring of PEF_r provides valuable insight to the course of asthma throughout the day, assesses circadian variation in pulmonary function, and helps detect early signs of deterioration so that timely therapy can be instituted. Patients with persistent asthma should be evaluated at least monthly and those with moderate to severe asthma should have daily PEF_r monitoring.³⁷ The typical PEF_r in pregnancy should be 380–550 L/min. She should establish her “personal best” PEF_r, then calculate her individualized PEF_r zones: Green Zone more than 80% of personal best, Yellow Zone 50 to 80% of personal best, and Red Zone less than 50% of personal best PEF_r.



Fig. 2. Typical peak flow meter. Illustration: John Yanson.

Dombrowski. Asthma and Pregnancy. Obstet Gynecol 2006.



Avoid or Control Asthma Triggers

Limiting adverse environmental exposures during pregnancy is important for controlling asthma. Irritants and allergens that provoke acute symptoms also increase airway inflammation and hyperresponsiveness. Avoiding or controlling such triggers can reduce asthma symptoms, airway hyperresponsiveness, and the need for medical therapy. Association of asthma with allergies is common; 75–85% of patients with asthma have positive skin tests to common allergens, including animal dander, house dust mites, cockroach antigens, pollens, and molds. Other common nonimmunologic triggers include tobacco smoke, strong odors, air pollutants, food additives such as sulfites, and certain drugs, including aspirin and β -blockers. Another trigger can be strenuous physical activity. For some patients, exercise-induced asthma can be avoided with inhalation of albuterol, 5–60 minutes before exercise.

Specific measures for avoiding asthma triggers include using allergen-impermeable mattress and pillow covers, removing carpeting, weekly washing of bedding in hot water, avoiding tobacco smoke, inhibiting mite and mold growth by reducing humidity, and leaving the house when it is vacuumed. Animal dander control includes weekly bathing of the pet, keeping furry pets out of the bedroom, or removing the pet from the home. Cockroaches can be controlled by poison or bait traps and eliminating exposed food or garbage.

Patient Education

Patients should be made aware that controlling asthma during pregnancy is especially important for the well being of the fetus. She should understand that she can reduce symptoms by limiting asthma triggers. The patient should have a basic understanding of the medical management during pregnancy, including self-monitoring of PEFRs and the correct use of inhalers. Patients

should be instructed on proper PEFR technique. She should make the measurement while standing, take a maximum inspiration and note the reading on the peak flow meter.

Pharmacologic Therapy

The goals of asthma therapy include: relieving bronchospasm, protect the airways from irritant stimuli, mitigating pulmonary and inflammatory response to an allergen exposure, and resolving the inflammatory process in the airways leading to improved pulmonary function with reduced airway hyperresponsiveness. Step-care therapeutic approach uses the least amount of drug intervention necessary to control a patient's severity of asthma.

ASTHMA PHARMACOTHERAPY

It is safer for pregnant women with asthma to be treated with asthma medications than it is for them to have asthma symptoms and exacerbations.³⁷ Current pharmacologic therapy emphasizes treatment of airway inflammation to decrease airway hyperresponsiveness and prevent asthma symptoms. Typical dosages of commonly used asthma medications are listed in Table 2. Low, medium, and high doses of inhaled corticosteroid are presented in Table 3.

Although it is assumed that asthma medications are equally effective during pregnancy, differences in maternal physiology and pharmacokinetics may affect the absorption, distribution, metabolism and clearance of medications during pregnancy. Endocrinologic and immunologic changes during pregnancy include elevations in free plasma cortisol, possible tissue refractoriness to cortisol,³⁸ and changes in cellular immunity.³⁹

Step Therapy

The step-care therapeutic approach increases the number and frequency of medications with increas-

Table 2. Typical Dosages of Asthma Medications

Medicine	Dosage
Albuterol MDI	2–8 puffs as needed
Salmeterol MDI	2 puffs bid
Fluticasone and salmeterol (Advair*) DPI	1 inhalation twice daily, dose depends on severity of asthma
Montelukast	10 mg tablet at night
Zafirlukast	20 mg twice daily
Prednisone	20–60 mg/d for active symptoms
Theophylline	Start 10 mg/kg orally, target serum levels of 5–12 μ g/mL (decrease dosage by half if treated with erythromycin or cimetidine)
Ipratropium MDI	4–8 puffs as needed
Nebulizer	3 mL (0.5 mg) every 30 min for 3 doses, then every 2–4 h, as needed
Cromolyn MDI	2–4 puffs three or four times daily

DPI, dry powder inhaler; MDI, metered-dose inhaler

* GlaxoSmithKline, Research Triangle, NC.



Table 3. Comparative Daily Doses for Inhaled Corticosteroids

Medicine	Metered Dose	Dosage Level		
		Low Dose	Medium Dose	High Dose
Beclomethasone MDI	42 µg/puff	4–12 puffs	12–20 puffs	More than 20 puffs
	84 µg/puff	2–6 puffs	6–10 puffs	More than 10 puffs
Triamcinolone MDI	100 µg/puff	4–10 puffs	10–20 puffs	More than 20 puffs
Budesonide DPI	200 µg/puff	1–2 puffs	2–3 puffs	More than 3 puffs
Fluticasone MDI	44 µg/puff	2–6 puffs		
	110 µg/puff	2 puffs	2–6 puffs	More than 6 puffs
	220 µg/puff		1–3 puffs	More than 3 puffs
Flunisolide MDI	250 µg/puff	2–4 puffs	4–8 puffs	More than 8 puffs

MDI, metered-dose inhaler; DPI, dry powder inhaler.

Note that total daily puffs is usually divided as a twice-daily or three times-daily regimen.

Table 4. Medical Management of Asthma

Type	Management	
	Preferred	Alternative
Mild intermittent asthma	No daily medications; albuterol as needed	
Mild persistent asthma	Low-dose inhaled corticosteroid	Cromolyn, leukotriene receptor antagonist, or theophylline (serum level 5–12 µg/mL)
Moderate persistent asthma	Low-dose inhaled corticosteroid and salmeterol or medium-dose inhaled corticosteroid or (if needed) medium-dose inhaled corticosteroid and salmeterol	Low-dose or (if needed) medium-dose inhaled corticosteroid and either leukotriene receptor antagonist or theophylline (serum level 5–12 µg/mL)
Severe persistent asthma	High-dose inhaled corticosteroid and salmeterol and (if needed) oral corticosteroid	High-dose inhaled corticosteroid and theophylline (serum level 5–12 µg/mL) and oral corticosteroid if needed

Albuterol 2–4 puffs as needed for peak expiratory flow rate or forced expiratory volume in 1 second less than 80%, asthma exacerbations, or exposure to exercise or allergens; oral corticosteroid burst if inadequate response to albuterol regardless of asthma severity. Information from National Institutes of Health, National Heart, Lung, and Blood Institute. National Asthma Education Program. Report of the Working Group on Asthma and Pregnancy: management of asthma during pregnancy.³²

ing asthma severity (Table 4). Based on the severity of asthma, medications are considered to be “preferred” or “alternative.” Patients not optimally responding to treatment should be stepped up to more intensive medical therapy. Once control is achieved and sustained for several months, a step-down approach can be considered, but should be undertaken cautiously and gradually to avoid compromising the stability of the asthma control. For some patients, it may be prudent to postpone until after birth attempts to reduce therapy that is effectively controlling the patient’s asthma.³⁷ In the case of patient who had a favorable response to an alternative drug before becoming pregnant, it would be preferable to maintain the therapy that successfully controlled the patient’s asthma before pregnancy. However, when initiating new treat-

ment for asthma during pregnancy, preferred medications should be considered rather than alternative treatment options.³⁷

A burst of oral corticosteroids is indicated for exacerbations not responding to initial β_2 agonist therapy regardless of asthma severity. Additionally, patients who require increasing inhaled albuterol therapy to control their symptoms may benefit from oral corticosteroids. In such cases, a short course of oral prednisone, 40 mg to 60 mg per day for one week followed by 7 to 14 days of tapering may be effective.

Inhaled Corticosteroids

Inhaled corticosteroids are the preferred treatment for the management of all levels of persistent asthma during pregnancy.³⁷ Airway inflammation is present



in nearly all cases, therefore inhaled corticosteroids have been advocated as first-line therapy for patients with mild asthma.⁴⁰ The use of inhaled corticosteroids among nonpregnant asthmatics has been associated with a marked reduction in fatal and near-fatal asthma.⁴¹ Inhaled corticosteroids produce clinically important improvements in bronchial hyperresponsiveness that appear dose related,⁴² and include prevention of increased bronchial hyperresponsiveness after seasonal exposure to allergen.^{43,44} Continued administration is also effective in reducing the immediate pulmonary response to an allergen challenge. In a prospective observational study of 504 pregnant subjects with asthma, 177 patients were not initially treated with either inhaled budesonide or inhaled beclomethasone.²¹ This cohort had a 17% acute exacerbation rate compared with only a 4% rate among those treated with inhaled corticosteroids from the start of pregnancy.

The NAEPP Working Group reviewed 10 studies including 6,113 patients who took inhaled corticosteroids during pregnancy for asthma.³⁷ There is no evidence linking inhaled corticosteroid use and increases in congenital malformations or adverse perinatal outcomes. Included among these studies was the Swedish Medical Birth Registry that had 2,014 infants whose mothers had used inhaled budesonide in early pregnancy.⁴⁵ Because there are more data on using budesonide during pregnancy than on using other inhaled corticosteroids, the NAEPP considered budesonide to be a preferred medication. However, if a woman is well controlled by a different inhaled corticosteroid before pregnancy, it seems reasonable to continue that medication during pregnancy. All inhaled corticosteroids are currently labeled Food and Drug Administration pregnancy class C, except budesonide is class B.

Inhaled Beta₂-Agonists

Inhaled β_2 -agonists are currently recommended for all degrees of asthma during pregnancy.^{37,46} Albuterol has the advantage of a rapid onset of effect in the relief of acute bronchospasm by way of smooth muscle relaxation, and is an excellent bronchoprotective agent for pretreatment before exercise. Salmeterol and formoterol are long-acting preparations. Beta₂-agonists are associated with tremor, tachycardia, and palpitations. They do not block the development of airway hyperresponsiveness.⁴⁷ Indeed, a comparison of an inhaled glucocorticoid, budesonide, with the inhaled terbutaline, raised the question whether routine use of terbutaline could result in increased airway hyperresponsiveness.⁴⁰ An increased frequency of

bronchodilator use could be an indicator of the need for additional anti-inflammatory therapy; chronic use of short acting β_2 -agonists has been associated with an increased risk of death.^{46,48} Beta₂-agonists seem to be safe based upon a NAEPP review of six published studies with 1,599 women with asthma who took β_2 -agonists during pregnancy.³⁷ Additionally, in a large prospective study, no significant relationship was found between the use of inhaled β_2 -agonists (N=1,828) and adverse pregnancy outcomes.³⁰

Cromolyn

Cromolyn sodium is virtually devoid of significant side effects; it blocks both the early and late phase pulmonary response to allergen challenge as well as preventing the development of airway hyperresponsiveness.⁴⁷ Cromolyn does not have any intrinsic bronchodilator or antihistaminic activity. Compared with inhaled corticosteroids the time to maximal clinical benefit is longer for cromolyn. Cromolyn seems to be less effective than inhaled corticosteroids in reducing objective and subjective manifestations of asthma. Cromolyn seems to be safe during pregnancy³⁰ and is an alternative treatment for mild persistent asthma.³⁷

Theophylline

Theophylline is an alternative treatment for mild persistent and an adjunctive treatment for the management of moderate and severe persistent asthma during pregnancy.³⁷ Subjective symptoms of adverse theophylline effects including, insomnia, heartburn, palpitations, and nausea, may be difficult to differentiate from typical pregnancy symptoms. High doses have been observed to cause jitteriness, tachycardia, and vomiting in mothers and neonates (Yeh TF, Pildes RS. Transplacental aminophylline toxicity in a neonate [letter]. *Lancet* 1977;1:910).⁴⁹ New dosing guidelines have recommended that serum theophylline concentrations be maintained at 5–12 $\mu\text{g}/\text{mL}$ during pregnancy.³⁷ Theophylline can have significant interactions with other drugs, which can cause decreased clearance with resultant toxicity. For instance, cimetidine can cause a 70% increase in serum levels, while erythromycin use can increase theophylline serum levels by 35%.⁵⁰ The main advantage of theophylline is the long duration of action, 10 to 12 hours with the use of sustained-release preparations, which is especially useful in the management of nocturnal asthma.⁵¹ Theophylline is only indicated for chronic therapy and is not effective for the treatment of acute exacerbations during pregnancy.⁵² Theophylline has anti-inflammatory actions⁵³ that may be



mediated from inhibition of leukotriene production and its capacity to stimulate PGE₂ production.⁵⁴ Theophylline may potentiate the efficacy of inhaled corticosteroids.⁵⁵

The NAEPP reviewed eight human studies that had a total of 660 women with asthma who took theophylline during pregnancy.³⁷ These studies and clinical experience confirm the safety of theophylline at a serum concentration of 5–12 µg/mL during pregnancy. In a recent randomized controlled trial, there were no differences in asthma exacerbations or perinatal outcomes in a cohort receiving theophylline compared with the cohort receiving inhaled beclomethasone.^{56,57} However, the theophylline cohort had significantly more reported side effects and discontinuation of study medication and an increased proportion of those with an FEV₁ less than 80% predicted.

Leukotriene Moderators

Leukotrienes are arachidonic acid metabolites that have been implicated in transducing bronchospasm, mucous secretion and increased vascular permeability.⁵⁸ Bronchoconstriction associated with aspirin ingestion can be blocked by leukotriene receptor antagonists.⁵⁹ Treatment with leukotriene receptor antagonist montelukast has been shown to improve pulmonary function significantly as measured by FEV₁.⁵⁸ The leukotriene receptor antagonists zafirlukast (Accolate, AstraZeneca LP, Wilmington, DE), and montelukast (Singulair, Merck & Co., Inc., West Point, PA) are both pregnancy category B. It should be noted that there are minimal data regarding the efficacy or safety of these agents during human pregnancy. Leukotriene receptor antagonists are an alternative treatment for mild persistent and an adjunctive treatment for the management of moderate and severe persistent asthma during pregnancy.³⁷

Oral Corticosteroids

The NAEPP Working Group reviewed eight human studies including one report of two meta-analyses.³⁷ The majority of participants in these studies did not take oral corticosteroids for asthma, and the length, timing, and dose of exposure to the drug were not well described. The panel concluded that findings from the current evidence review are conflicting. Oral corticosteroid use during the first trimester of pregnancy is associated with a three-fold increased risk for isolated cleft lip with or without cleft palate, with a background incidence of about 0.1%, thus the excess risk attributable to oral steroids would be 0.2–0.3%.⁶⁰ Oral corticosteroid use during pregnancy in patients

who have asthma has been associated with an increased incidence of preeclampsia, preterm delivery, and low birth weight.^{14,19,27,30,60} A recent prospective study found that systemic corticosteroids resulted in a deficit of about 200 g in birth weight compared with controls and those exclusively treated with β₂-agonists.⁶¹ However, it is difficult to separate the effects of the oral corticosteroids on these outcomes from the effects of severe or uncontrolled asthma.

Because of the uncertainties in these data and the definite risks of severe uncontrolled asthma to the mother and fetus, the NAEPP Working Group recommends the use of oral corticosteroids when indicated for the long-term management of severe asthma or exacerbations during pregnancy.³⁷ For the treatment of acute exacerbations, methylprednisolone, or other corticosteroids, may be given up to 120–180 mg per day in three or four divided doses; once the PEFR reaches 70% of personal best the daily dosage of parenteral or oral corticosteroid, such as prednisone, could be dropped to 60–80 mg per day.³⁷

Management of Allergic Rhinitis

Rhinitis, sinusitis, and gastroesophageal reflux may exacerbate asthma symptoms, and their management should be considered an integral aspect of asthma care. Intranasal corticosteroids are the most effective medications for control of allergic rhinitis. Loratadine (Claritin, Schering Corporation, Kenilworth, NJ) or cetirizine (Zyrtec, Pfizer Inc., New York, NY) are recommended second-generation antihistamines. Oral decongestant ingestion during the first trimester has been associated with gastroschisis; therefore, inhaled decongestants or inhaled corticosteroids should be considered before use of oral decongestants.³⁷ Immunotherapy is considered safe during pregnancy, but because of the risk of anaphylaxis, initiation of immunotherapy is not recommended during pregnancy.

ANTENATAL MANAGEMENT

Patients with moderate and severe asthma should be considered to be at risk for pregnancy complications. Adverse outcomes can be increased by underestimation of asthma severity and undertreatment of asthma. The first prenatal visit should include a detailed medical history with attention to medical conditions that could complicate the management of asthma, including active pulmonary disease. The patient should be questioned about smoking history and the presence and severity of symptoms, episodes of nocturnal asthma, the number of days of work missed, and emergency care visits due to asthma. Asthma severity should be determined (see box, “Asthma



Severity Classification”). The type and amount of asthma medications including the number of puffs of β_2 -agonists used each day should be noted.

Gravidas with moderate or severe asthma should have scheduling of prenatal visits based upon clinical judgment. In addition to routine care, monthly or more frequent evaluations of asthma history (emergency visits, hospital admissions, symptom frequency, severity, nocturnal symptoms, medications, dosages, and compliance) and pulmonary function (FEV_1 or PEFr) are recommended. Patients should be instructed on proper dosing and administration of their asthma medications.

Daily peak flow monitoring should be considered for patients with moderate to severe asthma, and especially for patients who have difficulty perceiving signs of worsening asthma.³⁷ It may be helpful to maintain an asthma diary containing daily assessment of asthma symptoms, including peak flow measurements, symptoms and activity limitations, indication of any medical contacts initiated, and a record of regular and as-needed medications taken. Identifying and avoiding asthma triggers can lead to improved maternal well-being with less need for medications. Specific recommendations can be made for appropriate environmental controls, based upon the patient’s history of exposure and, when available, skin test reactivity to asthma triggers.

Women who have moderate or severe asthma during pregnancy also may benefit from additional fetal surveillance in the form of ultrasound examinations and antenatal fetal testing. Because asthma has been associated with intrauterine growth restriction and preterm birth, it is useful to establish pregnancy dating accurately by first trimester ultrasonography where possible. In the opinion of the Working Group,³⁷ the evaluation of fetal activity and growth by serial ultrasound examinations may be considered for women who have suboptimally controlled asthma, with moderate to severe asthma (starting at 32 weeks), and after recovery from a severe asthma exacerbation. The intensity of antenatal surveillance of fetal well-being should be considered on the basis of the severity of the asthma as well as any other high-risk features of the pregnancy that may be present. All patients should be instructed to be attentive to fetal activity.

Home Management of Asthma Exacerbations

An asthma exacerbation that causes minimal problems for the mother may have severe sequelae for the fetus. Indeed, abnormal fetal heart rate tracing may be the initial manifestation of an asthmatic exacerbation. A maternal PO_2 less than 60 or hemoglobin saturation

less than 90% may be associated with profound fetal hypoxia. Therefore, asthma exacerbations in pregnancy should be aggressively managed. Patients should be given an individualized guide for decision-making and rescue management, and educated to recognize signs and symptoms of early asthma exacerbations such as coughing, chest tightness, dyspnea, or wheezing, or by a 20% decrease in their PEFr. This is important so that prompt home rescue treatment may be instituted to avoid maternal and fetal hypoxia. In general, patients should use inhaled albuterol 2–4 puffs every 20 minutes up to one hour (see box, “Home Management of Acute Asthma Exacerbations”). A good response is considered if symptoms are resolved or become subjectively mild, normal activities can be resumed, and the PEFr is more than 70% of personal best. The patient should seek further medical attention if the response is incomplete, or if fetal activity is decreased.

Home Management of Acute Asthma Exacerbations*

Use albuterol metered-dose inhaler (MDI) 2–4 puffs and measure peak expiratory flow rate (PEFr)

Poor response:

PEFr less than 50% predicted, or severe wheezing and shortness of breath, or decreased fetal movement, repeat albuterol 2–4 puffs by MDI and obtain emergency care.

Incomplete response:

PEFr is 50–80% predicted or if persistent wheezing and shortness of breath, then repeat albuterol treatment 2–4 puffs MDI at 20-minute intervals up to two more times. If repeat PEFr 50–80% predicted or if decreased fetal movement, contact caregiver or go for emergency care.

Good response:

PEFr more than 80% predicted, no wheezing or shortness of breath, and fetus is moving normally. May continue inhaled albuterol 2–4 puffs MDI every 3–4 hours as needed

* Information from National Institutes of Health, National Heart, Lung, and Blood Institute. National Asthma Education Program. Report of the Working Group on Asthma and Pregnancy: management of asthma during pregnancy.³²

Hospital and Clinic Management

The principal goal should be the prevention of hypoxia. Measurement of oxygenation by pulse oximetry is essential, arterial blood gases should be obtained if oxygen saturation remains less than 95%, but chest



X-rays are not commonly needed. Continuous electronic fetal monitoring should be initiated if gestation has advanced to point of potential fetal viability. Albuterol (2.5 mg to 5 mg every 20 minutes for three doses, then 2.5 mg to 10 mg every 1–4 hours as

needed, or 10–15 mg/h continuously) should be delivered by nebulizer driven with oxygen.³⁷ Occasionally, nebulized treatment is not effective because the patient is moving air poorly, in such cases, terbutaline 0.25mg can be administered subcutane-

Emergency Department and Hospital-Based Management of Asthma Exacerbation

Initial assessment and treatment

- History and examination (auscultation, use of accessory muscles, heart rate, respiratory rate), peak expiratory flow rate (PEFR) or forced expiratory volume in 1 second (FEV₁), oxygen saturation, and other tests as indicated.
- Initiate fetal assessment (consider fetal monitoring and/or biophysical profile if fetus is potentially viable)
- If severe exacerbation (FEV₁ or PEFR less than 50% with severe symptoms at rest) then high-dose albuterol by nebulization every 20 minutes or continuously for 1 hour and inhaled ipratropium bromide and systemic corticosteroid
- Albuterol by metered-dose inhaler or nebulizer, up to three doses in first hour
- Oral corticosteroid if no immediate response or if patient recently treated with systemic corticosteroid
- Oxygen to maintain saturation more than 95%
- Repeat assessment: symptoms, physical examination, PEFR, oxygen saturation
- Continue albuterol every 60 minutes for 1–3 hours provided there is improvement

Repeat assessment

- Symptoms, physical examination, PEFR, oxygen saturation, other tests as needed
- Continue fetal assessment

Good response

- FEV₁ or PEFR 70% or more
- Response sustained 60 minutes after last treatment
- No distress
- Physical examination is normal
- Reassuring fetal status
- Discharge home

Incomplete response

- FEV₁ or PEFR 50% or more but less than 70%
- Mild or moderate symptoms
- Continue fetal assessment until patient is stabilized
- Monitor FEV₁ or PEFR, oxygen saturation, pulse
- Continue inhaled albuterol and oxygen
- Inhaled ipratropium bromide
- Systemic (oral or intravenous) corticosteroid
- Individualize decision for hospitalization

Poor response

- FEV₁ or PEFR less than 50%
- P_{co2} more than 42 mm Hg
- Physical examination: symptoms severe, drowsiness, confusion
- Continue fetal assessment
- Admit to intensive care unit Intravenous corticosteroid



Impending or actual respiratory arrest

- Admit to intensive care unit
- Intubation and mechanical ventilation with 100% oxygen
- Nebulized albuterol plus inhaled ipratropium bromide
- Intravenous corticosteroid

Intensive care unit

- Inhaled albuterol hourly or continuously plus inhaled ipratropium bromide
- Intravenous corticosteroid
- Oxygen
- Possible intubation and mechanical ventilation
- Continue fetal assessment until patient stabilized

Discharge home

- Continue treatment with albuterol
- Oral systemic corticosteroid if indicated
- Initiate or continue inhaled corticosteroid until review at medical follow-up
- Patient education
 - Review medicine use
 - Review and initiate action plan
 - Recommend close medical follow-up

Information from National Institutes of Health, National Heart, Lung, and Blood Institute. National Asthma Education Program. Report of the Working Group on Asthma and Pregnancy: management of asthma during pregnancy.³²

ously every 15 minutes for three doses. The patient should be assessed for general level of activity, color, pulse rate, use of accessory muscles, and airflow obstruction determined by auscultation and FEV₁, PEF_R, or both before and after each bronchodilator treatment. Guidelines for the management of asthma exacerbations are presented in the box, “Emergency Department and Hospital-Based Management of Asthma Exacerbation.”

LABOR AND DELIVERY MANAGEMENT

Asthma medications should not be discontinued during labor and delivery. Although asthma is usually quiescent during labor, consideration should be given to assessing PEF_Rs upon admission and at 12-hour intervals. The patient should be kept hydrated and should receive adequate analgesia to decrease the risk of bronchospasm. If systemic corticosteroids have been used in the previous four weeks, then intravenous corticosteroids (eg, hydrocortisone 100 mg every 8 hours) should be administered during labor and for the 24-hour period after delivery to prevent adrenal crisis.³⁷ An elective delivery should be postponed if the patient is having an exacerbation.

It is rarely necessary to perform a cesarean delivery for an acute asthma exacerbation. Usually, maternal and fetal compromise will respond to ag-

gressive medical management. Occasionally, delivery may improve the respiratory status of a patient with unstable asthma who has a mature fetus. Prostaglandin E₂ or E₁ can be used for cervical ripening, the management of spontaneous or induced abortions, or postpartum hemorrhage, although the patient’s respiratory status should be monitored.⁶² Carboprost (15-methyl PGF₂-α) and ergonovine and methylergonovine (Methergine, Novartis Pharmaceuticals Corporation, East Hanover, NJ) can cause bronchospasm.⁶³ Magnesium sulfate is a bronchodilator, but indomethacin can induce bronchospasm in the aspirin-sensitive patient. There are no reports of the use of calcium channel blockers for tocolysis among patients with asthma, although an association with bronchospasm has not been observed with wide clinical use.

Lumbar anesthesia has the benefit of reducing oxygen consumption and minute ventilation during labor.⁶⁴ Fentanyl may be a better analgesic than meperidine, which causes histamine release, but meperidine is rarely associated with the onset of bronchospasm during labor. A 2% incidence of bronchospasm has been reported with regional anesthesia.⁶⁵ Ketamine is useful for induction of general anesthesia because it can prevent bronchospasm.⁶⁶ Communication between the obstetric, anesthetic, and pediatric care givers is important for optimal care



Breastfeeding

In general, only small amounts of asthma medications enter breast milk. Prednisone, theophylline, antihistamines, beclomethasone, β_2 agonists, and cromolyn are not considered to be contraindications for breastfeeding.^{37,67} However, among sensitive individuals, theophylline may cause toxic effects in the neonate, including vomiting, feeding difficulties, jitteriness, and cardiac arrhythmias.

SUMMARY

Asthma is an increasingly common problem during pregnancy. Mild and moderate asthma can be associated with excellent maternal and perinatal pregnancy outcomes, especially if patients are managed according to contemporary NAEPP recommendations. Severe and poorly controlled asthma may be associated with increased prematurity, need for cesarean delivery, preeclampsia, and growth restriction. Severe asthma exacerbations can result in maternal morbidity and mortality and can have commensurate adverse pregnancy outcomes. The management of asthma during pregnancy should be based upon objective assessment, trigger avoidance, patient education, and step-therapy. Asthma medications should be continued during pregnancy and while breastfeeding.

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