

Women with asthma: a review of potential variables and preferred medical management

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Objectives: To summarize the potential variables that contribute to the increased risk of asthma in women, outline therapeutic strategies that address these variables, and review current treatment recommendations for both pregnant and nonpregnant women with asthma.

Data Sources: Literature searches (MEDLINE and cross-references) were performed using the keywords *asthma* and *women* in combination with the terms *compliance*, *depression*, *emergency department*, *hormones*, *menstruation*, *mortality*, *National Asthma Education and Prevention Program*, *osteoporosis*, *pregnancy*, *prevalence*, *smoking*, and *treatment*. Searches were limited to human studies with data published before 2005.

Study Selection: The author selected relevant articles for inclusion in this review.

Results: Fluctuations in sex hormones, menstruation, pregnancy, obesity, depression, medication nonadherence, and smoking may contribute to increased asthma symptoms or severity in women. Asthma control may be improved if physicians address conditions and behaviors associated with asthma variability and severity in women. Notably, asthma must be managed aggressively in pregnant women, because uncontrolled asthma can lead to perinatal complications. Asthma treatment in women is optimized through patient and physician adherence to national guideline recommendations, including provision of patient education and asthma action plans.

Conclusions: Multiple variables throughout the female life cycle may influence asthma control. Successful asthma management requires an ongoing partnership between the patient and her physician to address physiologic (eg, sex hormones, pregnancy, obesity, depression) and nonphysiologic (eg, smoking, medication nonadherence) factors that may contribute to decreased asthma control.

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INTRODUCTION

After a previous increase in incidence, asthma-related hospitalizations and deaths have decreased during the past few years in the United States. However, the asthma burden remains high.¹ In 2002, more than 20 million Americans had asthma.¹ Although females are 10% more likely than males to be diagnosed as having asthma in their lifetime,¹ differences in asthma prevalence between the sexes vary based on age. During childhood, the risk of asthma is greater in boys than in girls.² In 2002, the prevalence rate for current asthma among boys was more than 30% higher than that in girls.¹ By late adolescence to early adulthood, this childhood trend is reversed, such that asthma prevalence is disproportionately high among women.³ According to the American Lung Association, the prevalence rate for current asthma in women 18 years or older was almost 70% greater than that in men in 2002 (85.0 vs 50.5 cases per 1,000 persons, respectively).¹ An evaluation of asthma risk factors that was based on a 2000

telephone survey of 184,450 US adults 18 years or older similarly demonstrated an approximately 80% greater current asthma prevalence in women compared with men (adjusted odds ratio [OR], 1.91; 95% confidence interval [CI], 1.77–2.06).⁴ Figure 1 demonstrates the age-related reversal in the female-male prevalence of asthma among 60,694 patients with asthma enrolled from 1999 to 2000 in the Southern California Kaiser-Permanente Asthma Case Identification Database. In this patient cohort, asthma prevalence in women aged 23 to 64 years was almost 2-fold that in men (prevalence ratio, 65:35 for women vs men).³

In addition to greater asthma prevalence, women appear to have greater morbidity due to asthma. Studies have demonstrated more self-reported asthma symptoms,^{5,6} greater asthma medication use,^{6,7} and reduced quality of life^{6,8} in women compared with men. Additional studies suggest greater morbidity in women based on asthma-related emergency department (ED) visits and hospitalizations.^{3,9–15} In the cohort study by Schatz and Camargo,³ women aged 23 to 64 years with asthma were significantly more likely to have an outpatient or ED visit or to require hospitalization for asthma compared with men of the same age ($P < .001$). In another study, the rate of hospital admissions for women with asthma

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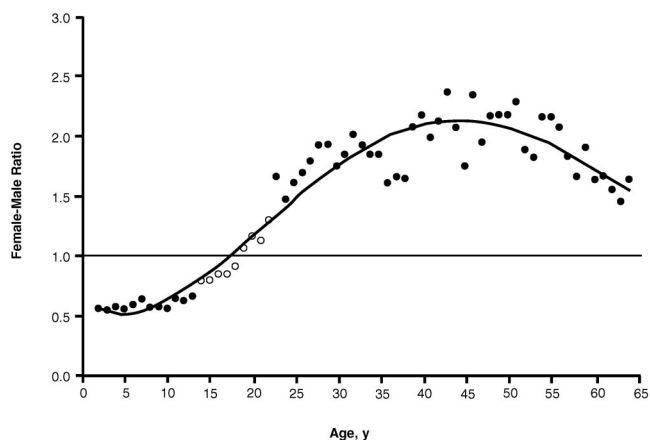


Figure 1. Ratio of female to male asthma patients aged 2 to 64 years in relation to age. The empty circles represent sex ratios between 14 and 22 years old. Reprinted with permission from Schatz and Camargo.³

aged 20 to 50 years was nearly 3-fold that for men.¹² Singh et al¹¹ also reported that ED visits for asthma were more frequent among women vs men (2:1), even though inhaled corticosteroid (ICS) use was more common among women than men during the 4 weeks before an ED visit (47% vs 36%, $P < .001$). Additionally, Cydulka et al¹⁵ reported that women who were pregnant ($n = 51$) were less likely than those who were not pregnant ($n = 500$) to receive systemic corticosteroids in the ED (44% vs 66%, $P = .002$) and at discharge (38% vs 64%, $P = .002$). Ultimately, in addition to the differences in ED visits and treatment, mortality rates are also higher in women than in men. Overall, the 2001 asthma mortality rate was 42% greater in women than in men. At that time, more than 65% of all 4,269 asthma-related deaths in the United States occurred in women. Black women experienced the highest rate of death due to asthma.¹

The purpose of this clinical review is to summarize the potential variables that contribute to the increased risk of asthma in women, outline therapeutic strategies that address these variables, and review current treatment recommendations for both pregnant and nonpregnant women with asthma. Literature searches (MEDLINE and cross-references) were performed using the keywords *asthma* and *women* in combination with the terms *compliance*, *depression*, *emergency department*, *hormones*, *menstruation*, *mortality*, *National Asthma Education and Prevention Program*, *osteoporosis*, *pregnancy*, *prevalence*, *smoking*, and *treatment*. Searches were limited to human studies with data published before 2005. The author selected relevant articles for inclusion in this review.

FACTORS THAT MAY INFLUENCE ASTHMA IN WOMEN

Physiologic Factors

Sex hormones. Changes in hormone levels that occur in females during puberty and at the onset of menstruation may

explain, in part, the reversal of the male-female asthma prevalence ratio that occurs from childhood to adulthood. Monthly worsening of asthma that occurs in conjunction with menstruation is well documented. Approximately 20% to 40% of women with asthma have been reported to experience worsening of asthma symptoms or pulmonary function during premenstrual and menstrual periods.^{16–21}

Reports of life-threatening perimenstrual asthma^{22,23} reflect the seriousness of this condition (Fig 2). Women who experience perimenstrual asthma have more severe symptoms and are hospitalized more frequently than women without perimenstrual asthma.^{16–18} Occasionally, perimenstrual asthma can lead to recurrent respiratory failure²⁴ or death.²⁵ Decreases in peak expiratory flow (PEF) have been observed in patients with premenstrual exacerbations of asthma before the onset or at the beginning of the menstrual cycle.^{16,18,19,21,26} In 2 patients with severe premenstrual asthma that did not respond to conventional treatment, including high-dose corticosteroids, administration of intramuscular progesterone eliminated the premenstrual decrease in PEF.²⁶

The mechanism of increased asthma severity in relation to menstruation is not known. Proposed mechanisms include reduced serum progesterone levels,²⁶ increased mucous secretions,²⁷ variation in prostaglandin synthesis,^{28,29} and abnormal β_2 -adrenoreceptor regulation.^{27,28} Although the effect of endogenous estrogen on the airway is not clearly defined, exogenous hormone may influence asthma in women. Troisi et al³⁰ found a dose-related increased risk of asthma among women enrolled in the Nurses' Health Study who used hormone replacement therapy for 10 or more years compared with those who never used postmenopausal hormones (relative risk [RR], 2.0; 95% CI, 1.39–2.87), suggesting that exogenous estrogen may affect the lung.

Pregnancy. On average, one third of pregnant women experience improvement in asthma symptoms during preg-

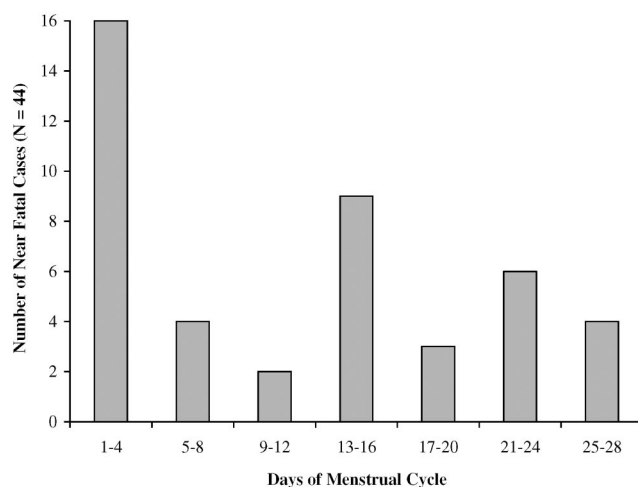


Figure 2. Women experiencing a near-fatal asthma episode on the first or other days in the menstrual cycle. Adapted with permission from the *Journal of Allergy and Clinical Immunology*.²²

nancy, one third experience worsening, and one third experience no change.³¹ Concordance between asthma course in 2 successive pregnancies has been demonstrated in 58.8% of women.³² The observation that asthma reverts to its prepregnancy course within 3 months of delivery in nearly three quarters of women further supports a specific effect of pregnancy on asthma.³²

Changing levels of the hormone progesterone may be a factor in both the improvement and worsening of asthma symptoms. In women who experience overall improvement in asthma during pregnancy, increasing levels of progesterone and estrogen coincide with decreasing symptoms.³² Bronchial smooth muscle relaxation caused by these hormones may contribute to diminished asthma severity in this group of women, who might be particularly sensitive to these effects.³² The positive effects of progesterone on asthma during pregnancy may be diminished in some patients because of the hormone's simultaneous effects on the smooth muscle of the lower esophageal sphincter, which may lead to increased gastric acid in the esophagus, a known trigger of bronchoconstriction.^{28,33} Asthma worsening characterized by nocturnal symptoms has been observed in association with the development of heartburn during pregnancy; nocturnal symptoms correlate with the timing of greatest reflux.³³

Fetal sex also may influence maternal asthma. Beecroft et al³⁴ reported a tendency of asthma symptoms to decrease in women giving birth to boys and to increase in women giving birth to girls. Patient-reported differences between women giving birth to girls and those giving birth to boys were significant for shortness of breath, nocturnal awakening, and general asthma symptoms. The authors suggest that a surge in androgen production by the male fetus at the time that most women completed the questionnaire (12 to 16 weeks' gestation) might be responsible for this difference.

Obesity. Numerous studies have demonstrated an association between obesity and asthma.^{4,35–40} In one prospective study, preadolescent girls becoming obese were at a higher risk of developing recurrent wheezing.⁴¹ In obese patients, weight reduction by diet or surgery (mean weight reduction of 13.7–45 kg) coincides with improvements in pulmonary function^{42,43} and asthma-related quality of life,^{43,44} as well as reductions in symptoms,^{43,45} exacerbations,^{43,45} asthma medication requirements,^{43–45} and hospitalizations.⁴⁴ In a study by MacGregor and Greenburg,⁴⁵ obese patients experienced improvements in asthma control (fewer symptoms and exacerbations, with reduced medication use) after surgically induced weight loss. Of patients taking daily asthma medication before this surgery, 42% stopped taking their medication and 18.5% received less medication after weight reduction. Patients who regained the weight during follow-up experienced an increase in exacerbations, which again subsided on further weight loss, supporting a causal relationship between obesity and asthma.

The results of several studies demonstrate that obesity increases the risk or severity of asthma to a greater degree in females (ORs, 1.8–2.1) vs males (ORs, 1.1–1.9).^{35,37,39,46} Sev-

eral hypotheses have been put forward to explain the stronger association in females. These hypotheses include (1) enhanced effects of estrogen on asthma due to greater bioavailability in obese women,³⁹ (2) reduction in bronchial smooth muscle relaxation due to reduced levels of progesterone in obese women vs men,⁴⁶ and (3) increased asthma risk due to greater allergen sensitivity in overweight girls vs boys.⁴¹

Depression. Depression is more evident in patients with asthma than in healthy subjects ($P < .05$).⁴⁷ Among adult patients with asthma, depression is more evident among women than men ($P < .05$).^{14,47,48} Depression has been shown to have a significant positive correlation with patient-reported asthma symptoms and a negative correlation with quality of life.^{49,50} Furthermore, depression is a risk factor for death due to asthma.^{51,52} In the studies by Hessel et al⁵¹ and Tough et al,⁵² patients who died of asthma were approximately 3-fold more likely to experience depression compared with control patients. Although the mechanism by which depression might contribute to asthma-related morbidity and mortality has not been established, depression has been associated with impaired voluntary activation of the diaphragm (which may be of physiologic relevance during an acute exacerbation),⁵³ medication nonadherence,^{54,55} and smoking.⁵⁴

Nonphysiologic Factors

Smoking. Smoking is associated with reduced pulmonary function⁵⁶ and increased asthma prevalence.^{4,5,57} The relationship between tobacco use and asthma is linear, such that heavy or long-term smokers demonstrate a greater prevalence of asthma,⁵ increased symptoms,⁵⁷ and lower lung function^{57,58} compared with smokers with a lower total tobacco consumption. Importantly, cessation of smoking can result in a reversal of smoking-induced lung function changes,⁵⁹ but the extent of this reversal depends on the duration of smoking and the degree of lung function decline at the time of cessation.⁵⁹

Studies indicate that females are more sensitive to the lung function effects of smoking than males.^{5,58,60} In the study by Langhammer et al,⁵ current asthma was reported more frequently in women who ever smoked compared with men (6.4% vs 5.7%, $P = .005$). The prevalence of current asthma in women, but not men, increased with increasing daily tobacco use; self-reported asthma prevalence in women smoking more than 20 cigarettes per day reached 10.4%.⁵

Nonadherence to medication and treatment guidelines. Nonadherence to national asthma treatment guidelines is common^{61,62} and can result in increased asthma-related morbidity⁶³ and mortality.⁶⁴ A retrospective analysis of Medicaid data demonstrated that only 36% of asthma patients received a prescription for an inhaled short-acting β_2 -adrenergic agonist, with less than 10% of those who used these medications on a daily basis receiving continuous ICS therapy. This nonadherence to guidelines (ie, daily use of a rescue medication in the absence of an ICS) was associated with an increased risk of an asthma-related hospitalization (OR, 1.5; $P < .05$).⁶³ The cause of medication nonadherence may be multifactorial. Psychological factors (eg, depression, poor

coping strategies, disease denial) and complicated therapeutic regimens can contribute to decreased patient adherence to prescribed therapy.^{54,65} Among older women with asthma, medication nonadherence has been associated with severe asthma, lower socioeconomic status, current smoking, earlier asthma onset, and comorbid medical conditions.⁶⁶

Concern over adverse effects also may limit patient adherence to prescribed medications.⁶⁷ In pregnant women, heightened concern for the fetus may cause discontinuation of recommended treatments.⁶⁸ Unfortunately, discontinued use of asthma medications is a precipitating factor for acute exacerbations during pregnancy.⁶⁹ In one study, 17.5% of pregnant women who were not initially treated with an ICS had an acute attack compared with 3.9% of those who received an ICS throughout pregnancy. The risk of exacerbation during pregnancy in women using ICSs was 22% of the risk (RR, 0.22; 95% CI, 0.11–0.44) in women not using ICSs.⁷⁰ As previously described, pregnant women were less likely to receive ED treatment with systemic corticosteroids for an asthma exacerbation than nonpregnant women.¹⁵ These pregnant patients were 2.9 times more likely than nonpregnant patients to report an ongoing asthma exacerbation within 2 weeks of the ED visit ($P = .02$).¹⁵ Physicians may be less likely to prescribe appropriate long-term medications because of perceived risks to the fetus.

Some studies suggest that women may be less likely than men to adhere to recommended asthma medications.^{71,72} In a study by Krishnan et al,⁷² men were less likely to possess an ICS than women, but men who did have one were more likely to use it on a daily basis. Verification of sex-based differences in medication prescribing patterns and adherence requires further investigation.

Other factors. Differences in asthma symptom perception or disease management may account for some of the apparent disparity in asthma-related morbidity between the sexes. In a study of patients enrolled in a large health maintenance organization, Osborne et al⁶ reported that, despite similar airflow obstruction measured as percent predicted postbronchodilator forced expiratory volume in 1 second (FEV₁) and greater prebronchodilator FEV₁, women aged 35 to 55 years with asthma reported more asthma symptoms ($P = .002$) and reduced quality of life ($P \leq .016$ for physical functioning, social functioning, and bodily pain) compared with men.⁶ Women also reported more health care utilization ($P = .002$) and greater use of asthma medications ($P < .01$). Whether these differences reflect sex-specific differences in asthma severity, symptom perception, or tendency to seek medical attention is not clear.

In a study of adult patients who presented to the ED for acute asthma, Singh et al¹¹ reported a female-male ratio of approximately 2:1. Exacerbations in women who presented to the ED were more frequently mild to moderate in severity based on percent predicted PEF, whereas exacerbations in men were more frequently severe ($P < .001$).¹¹ Despite similar emergency treatment and significantly bet-

ter pulmonary function after treatment, women were more likely than men to be admitted to the hospital (OR, 2.2; 95% CI, 1.3–4.0).¹¹ When PEF was compared with reported symptoms in 1,291 men and women who presented to the ED, women were significantly more likely than men with similar levels of obstruction to report more severe symptoms and activity limitations ($P < .05$).⁷

MANAGING ASTHMA IN WOMEN

Key Components

In their first and subsequent reports (Table 1), the National Asthma Education and Prevention Program (NAEPP) identified 4 components for effective asthma management: (1) evaluation and monitoring of asthma, (2) control of factors that contribute to asthma severity, (3) patient education for a partnership in asthma care, and (4) pharmacologic therapy using a stepwise approach.^{73,74} Following these guidelines, the clinician must first establish a diagnosis of asthma based on the woman's medical history, physical examination, spirometry results, and the exclusion of alternative diagnoses.⁷³

Multiple factors that potentially affect asthma severity in women need to be addressed and controlled. Because women with asthma appear to be particularly susceptible to the adverse effects of obesity and smoking, physicians must ensure that their female patients who smoke or are obese fully understand the increased risk of asthma-related morbidity associated with these factors. These patients should be encouraged to participate in weight loss or smoking cessation programs. Women with asthma who are diagnosed as having depression should receive concomitant treatment for this condition, because successful treatment of depression may result in improved asthma symptoms and medication adherence.⁷⁶

To maximize the effectiveness of interventions, patient education should be tailored to the specific needs of each woman. Women should be provided with basic education regarding the pathophysiology of asthma, potential symptom triggers, and the actions, benefits, and potential risks of controller and reliever medications. It is also important to review how to manage an exacerbation and, most importantly, the negative consequences of uncontrolled asthma. The use of written action plans may be especially beneficial for those women who experience cyclic fluctuations in asthma severity with menstruation. Enabling patients to take a more active role in the management of their disease and feel more in control may lead to improved adherence,⁷⁶ decreased morbidity,^{76,77} improved quality of life,⁷⁷ and decreased health care utilization^{77,78} and asthma-related costs.⁷⁸

Current NAEPP guidelines recommend a stepwise approach to pharmacologic therapy based on asthma severity. In patients with mild to severe persistent asthma, ICSs are the preferred treatment for long-term control of asthma. Evidence indicates that the clinical effectiveness of ICS therapy clearly outweighs the potential risks.^{73,79,80}

Table 1. General and Pregnancy-Specific Asthma Treatment Guidelines

Guideline	Description	Date
<i>NAEPP Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma</i>	General approach to diagnosis and recommendations for treatment centered around 4 key components of effective asthma management ⁷³	1991
<i>NAEPP Report of the Working Group on Asthma and Pregnancy: Management of Asthma During Pregnancy</i>	Comprehensive review of data with recommendations for pharmacologic and nonpharmacologic management of asthma during pregnancy ⁷⁴	1993
<i>NAEPP Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma</i>	Comprehensive guide to diagnosing and managing asthma based on recent literature review; revised severity classification	1997
<i>ACOG/ACAAI Position Statement: The Use of Newer Asthma and Allergy Medications During Pregnancy</i>	Adapted the 1993 NAEPP Asthma and Pregnancy Report to the 1997 NAEPP asthma severity classifications ⁷⁵	2000
<i>NAEPP Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma. Update on Selected Topics—2002</i>	Evidenced-based update on pharmacologic treatment recommendations ⁷⁴	2002
<i>NAEPP Working Group Report on Managing Asthma During Pregnancy: Recommendations for Pharmacologic Treatment—2004</i>	Evidenced-based update on the pharmacologic management of asthma during pregnancy with highlights of the 3 other components of asthma management ⁷⁴	2004

Abbreviations: ACAAI, American College of Asthma, Allergy and Immunology; ACOG, American College of Obstetrics and Gynecology; NAEPP, National Asthma Education and Prevention Program.

After asthma is diagnosed and treatment initiated, the patient's symptoms and lung function should be reassessed at 1- to 6-month intervals.⁸¹ During these follow-up visits, delivery device technique and patient adherence should be reviewed. Furthermore, physicians should be proactive in assessing for adverse events, because patients may be unaware of potential disease-drug interactions. For example, although a definitive association between ICS use and decreased bone mineral density has not been established,^{81,82} periodic bone mineral density analysis may be warranted and can indicate the need for additional treatment if osteopenia or osteoporosis is identified.⁸³ Physicians should, at a minimum, recommend that postmenopausal women who receive ICS therapy take daily calcium supplements.⁷³ Similarly, the effects of asthma treatment on other comorbid conditions, and vice versa, should be regularly reviewed.

Management of Asthma During Pregnancy and Lactation

Asthma should be treated aggressively in both pregnant and nonpregnant women. Despite contradictory results from some studies,⁷⁴ data suggest that asthma during pregnancy may lead to adverse maternal and fetal outcomes, including preeclampsia,^{84–86} hypertension,^{87,88} preterm labor,^{85,87–89} low birth weight,^{85,87,88} and even perinatal death.⁸⁵ However, the risks for the fetus and the mother are decreased when asthma is well controlled during pregnancy.^{74,90–92}

Recommendations for the management of asthma during pregnancy have evolved based on changes in the classification and treatment of asthma and the availability of new medications and current evidence about the safety of those medications during pregnancy (Table 1).⁷⁴ The NAEPP concluded in a review of the available evidence that “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.”⁷⁴ A summary of the recently updated NAEPP guidelines published in 2005 includes recommendations for the management of asthma during pregnancy and lactation^{74,93} (Table 2).

ICSs are the recommended first-line controller therapy for pregnant women based on proven efficacy in asthma control and because no studies in humans have shown an association between ICS use and perinatal complications.⁷⁴ Studies demonstrate that ICS use during pregnancy decreases asthma exacerbations,^{70,94} hospitalizations,^{95,96} and readmissions.^{94,97}

The US Food and Drug Administration (FDA) pregnancy category ratings provide an additional source of information about medication use during pregnancy (Table 3). Because this system is based heavily on animal exposure data, does not include all of the published gestational data, and fails to consider the route of administration or efficacy of a drug, it is under revision by the FDA.^{74,98} Nonetheless, the system includes results available from large epidemiologic studies in its category ratings. There are no category A asthma medications; however, category B products are available (Table 4).

The NAEPP ICS recommendations and the category B rating for budesonide are based on the preponderance of data available on its use during pregnancy.⁷⁴ Swedish Medical Birth Registry data from 2,014 infants whose mothers used inhaled budesonide during early pregnancy demonstrated that the rate of congenital malformations among these infants (3.8%; 95% CI, 2.9%–4.6%) was similar to that observed for the general population (3.5%; CI not provided).⁹⁹ Analysis of data that included an additional 520 infants reported similar findings (3.6% rate of congenital malformations among both groups).¹⁰⁰ More recently, registry data from 2,968 infants of

Table 2. National Asthma Education and Prevention Program Guidelines for the Management of Asthma During Pregnancy (2004)

	Classify severity: clinical features before treatment or adequate control		Daily medications required to maintain long-term control
	Daytime symptoms/nighttime symptoms	PEF or FEV ₁ /PEF variability	
Step 4: severe persistent	Continual/frequent	≤60%/>30%	· Preferred treatment: - High-dose inhaled corticosteroid* - AND - Long-acting inhaled β_2-adrenergic agonist - AND, if needed, - Corticosteroid tablets or syrup long-term (2 mg/kg daily, generally do not exceed 60 mg/d). (Make repeat attempts to reduce systemic corticosteroid and maintain control with high-dose inhaled corticosteroid.*) · Alternative treatment: - High-dose inhaled corticosteroid* - AND - Sustained-release theophylline to serum concentration of 5–12 μg/mL
Step 3: moderate persistent	Daily/>1 night per week	>60% to <80%/>30%	· Preferred treatment: - EITHER - Low-dose inhaled corticosteroid* and long-acting β_2-adrenergic agonist - OR - Medium-dose inhaled corticosteroid* - If needed (particularly in patients with recurring severe exacerbations): - Medium-dose inhaled corticosteroid* and long-acting inhaled β_2-adrenergic agonist · Alternative treatment: - Low-dose inhaled corticosteroid* and either theophylline or leukotriene receptor antagonist† - If needed: - Medium-dose inhaled corticosteroids* and either theophylline or leukotriene receptor antagonist†
Step 2: mild persistent	>2 times per week but <1 time per day/>2 nights per month	≥80%/20%–30%	· Preferred treatment: - Low-dose inhaled corticosteroid* · Alternative treatment (listed alphabetically): cromolyn, leukotriene receptor antagonist,† OR sustained-release theophylline to serum concentration of 5–12 μg/mL
Step 1: mild intermittent	≤2 days per week/≤2 nights per month	≥80%/<20%	· No daily medication needed
Quick relief	· Short-acting bronchodilator: 2–4 puffs short-acting inhaled β_2-adrenergic agonist‡ as needed for symptoms.		
All patients	· Intensity of treatment will depend on severity of exacerbation; up to 3 treatments at 20-minute intervals or a single nebulizer treatment as needed. Course of systemic corticosteroid may be needed. · Use of short-acting inhaled β_2-adrenergic agonist‡ >2 times a week in intermittent asthma (daily, or increasing use in persistent asthma) may indicate the need to initiate (increase) long-term control therapy.		

Abbreviations: FEV₁, forced expiratory volume in 1 second; PEF, peak expiratory flow.

* There are more data on using budesonide during pregnancy than other inhaled corticosteroids.

† There are minimal data on using leukotriene receptor antagonists in humans during pregnancy, although there are reassuring animal data submitted to the Food and Drug Administration.

‡ There are more data on using albuterol during pregnancy than other short-acting inhaled β_2 -adrenergic agonists.

Table 3. Food and Drug Administration Pregnancy Risk Categories*

Category	Description
A	Adequate studies in pregnant women have not demonstrated a risk to the fetus in the first trimester of pregnancy, and there is no evidence of risk in later trimesters.
B	Animal studies have not demonstrated a risk to the fetus, but there are no adequate studies in pregnant women. or Animal studies have shown an adverse effect, but adequate studies in pregnant women have not demonstrated a risk to the fetus in the first trimester of pregnancy, and there is no evidence of risk in later trimesters.
C	Animal studies have shown an adverse effect on the fetus, but there are no adequate studies in humans; the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks. or There are no animal reproduction studies and no adequate studies in humans.
D	There is evidence of human fetal risk, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks.
X	Studies in animals or humans demonstrate fetal abnormalities, or adverse reaction reports indicate evidence of fetal risk. The risk of use in a pregnant woman clearly outweighs any possible benefit.

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Table 4. Pregnancy Category Ratings of Medications Commonly Used to Treat Asthma

Medication	Pregnancy category
Anticholinergic agents Ipratropium (Atrovent)*	B
Bronchodilators	
Albuterol (Proventil HFA, Ventolin HFA)	C
Formoterol (Foradil)	C
Salmeterol (Serevent, Serevent Diskus)	C
Inhaled corticosteroids	
Beclomethasone HFA (QVAR)	C
Budesonide (Pulmicort Turbuhaler, Pulmicort Respules†)	B
Fluticasone (Flovent)	C
Mometasone (Asmanex)	C
Triamcinolone (Azmacort)	C
Leukotriene receptor antagonists	
Montelukast (Singulair)	B
Zafirlukast (Accolate)	B
Mast cell stabilizers	
Cromolyn (Intal)	B
Methylxanthines	
Theophylline (Uniphyll)	C
Combination products	
Fluticasone and salmeterol (Advair Diskus)	C
Anti IgE monoclonal antibody Omalizumab (Xolair)	B

* Atrovent is indicated for maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease; no labeled indication for treatment of asthma.

† Pulmicort Respules is indicated for children aged 1 to 8 years.

mothers who used inhaled budesonide during early pregnancy demonstrated that these women gave birth to infants of normal gestational age, birth weight, and length, with no increased risk of stillbirth or multiple births compared with all women in the study population (N = 293,948).¹⁰¹ Limited

data on use during pregnancy are available for beclomethasone dipropionate. Studies conducted in women who received beclomethasone during pregnancy nonetheless demonstrated safety in terms of perinatal outcomes and congenital malformations. Few or no data are available for other ICSs.⁷⁴

The NAEPP guidelines for the management of asthma during pregnancy state that budesonide is the preferred ICS for pregnant women with mild or moderate persistent asthma.⁷⁴ However, because no evidence exists to indicate that other ICSs are unsafe during pregnancy, patients whose asthma is well controlled before pregnancy using an ICS other than budesonide may continue taking that medication.⁷⁴ Finally, the use of budesonide is preferred in patients with severe persistent asthma if the ICS needs to be increased to the high-dose range.⁷⁴

Among the alternatives and adjuncts to ICS therapy listed in Table 2, cromolyn has been used safely during pregnancy and is a reasonable alternative for mild persistent asthma if it is effective for disease control.⁷⁴ Based on decades of use, theophylline is considered a safe alternative or add-on therapy for use during pregnancy, provided serum concentrations are maintained between 5 and 12 $\mu\text{g/mL}$.⁷⁴ Leukotriene receptor antagonists, including zafirlukast and montelukast, may also be considered as alternative, but not preferred, long-term-control medication for mild persistent asthma or as add-on therapy for moderate persistent asthma. Although they are rated pregnancy category B because of a lack of animal teratogenic effects, only minimal human pregnancy data exist for these agents at this time.⁷⁴ Furthermore, the leukotriene lipooxygenase inhibitor zileuton should be avoided during pregnancy, because there are no adequate and well-controlled studies in pregnant women and animal studies demonstrated developmental adverse events, such as reduced body weight, skeletal variations, and cleft palates.^{74,102}

Despite limited observational data on the safety of long-acting β_2 -adrenergic agonists (LABAs) during pregnancy, these agents are still the preferred add-on therapy because of

their well-documented efficacy in well-controlled randomized clinical trials of nonpregnant patients. Although no data exist on which to base selection of a preferred LABA, salmeterol has been available longer than any other LABA.⁷⁴ FDA concerns regarding the long-term use of LABAs potentially resulting in a higher risk of severe exacerbation in some patients should be considered when making therapeutic decisions.^{103,104} The NAEPP states that "some clinicians may prefer increasing the dose of ICS, for which data on use during pregnancy exist, rather than adding a second medication."⁷⁴

Albuterol is the recommended quick-relief medication for as-needed treatment of symptoms and exacerbations at all steps of asthma severity.⁷⁴ Reassuring human safety data regarding albuterol use during pregnancy have been demonstrated in 6 studies. Of the 6,667 women included in these studies, 1,559 were women with asthma who received β_2 -adrenergic agonists, primarily albuterol, with no evidence of fetal injury.⁷⁴

Finally, the use of oral corticosteroids during the first trimester may increase the risk of oral clefts. A meta-analysis of 4 case-control studies that specifically examined the risk of oral clefts demonstrated a greater than 3-fold increase in risk (OR, 3.35; 95% CI, 1.97–5.69), particularly when the fetus was exposed to oral corticosteroids during the first trimester.¹⁰⁵ In addition to those 4 studies, the NAEPP included 3 additional studies, which evaluated 213 women who had used oral corticosteroids, in their evidence-based review. The NAEPP concluded that the evidence on the overall safety of oral corticosteroid use during pregnancy is conflicting. They noted that few women with oral corticosteroid-dependent asthma were included in these trials; data on dose, duration of therapy, and timing of exposure were lacking; and the available data made it challenging to separate out the drug-associated from disease-associated effects. The risk of cleft palate would appear to be small compared with the benefits of oral or intravenous steroids when required for treatment of severe asthma. Thus, the risk of severe asthma for the mother and fetus can be greater than the potential risks of the treatment.⁷⁴ Clinician judgment and patient education regarding potential benefits and risks of these therapies are advised.

In addition to pharmacologic therapy, management of asthma in pregnant women requires attention to other NAEPP management components, including the use of objective measures for assessing and monitoring asthma, avoidance of factors that contribute to asthma severity, and patient education.⁷⁴ Controlling environmental triggers, particularly tobacco smoke, also can help improve maternal well-being.⁷⁴ For optimal treatment, a team approach with the asthma care provider, the obstetrical care provider, and the patient can help ensure maternal health and normal fetal maturation.⁷⁴

CONCLUSION

Physicians should be aware of the significant burden of asthma in women. Multiple variables may influence asthma control throughout the female life cycle. Successful asthma

management requires an ongoing partnership between the patient and her physician to address physiologic (eg, sex hormones, obesity, pregnancy, depression) and nonphysiologic (eg, smoking, medication nonadherence) factors that may contribute to decreased asthma control. The risks of uncontrolled asthma for pregnant and nonpregnant women are generally greater than the risks of currently available asthma treatments. Increasing awareness of the issues unique to the management of asthma in women will help decrease the burden of this common, potentially life-threatening disease.

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