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# Maternal asthma: Management strategies

## ABSTRACT

Asthma in pregnancy is common, and its prevalence is rising. Internists need to be aware of the effects of maternal asthma control on the health of the expectant mother and the baby. With the ever-present worry about medication use and teratogenicity in pregnant women, these patients are often undertreated for their asthma. This review focuses on effects of uncontrolled maternal asthma as well as appropriate management of maternal asthma in the outpatient setting and during exacerbations.

## KEY POINTS

The benefits of good adherence to asthma regimens during pregnancy outweigh the risks associated with the medications used.

For treatment of reflux disease in pregnant women with asthma, antacids (but not sodium bicarbonate, for fear of metabolic alkalosis) and sucralfate should be considered before a histamine 2 receptor antagonist such as ranitidine. Proton pump inhibitors should be considered only if reflux symptoms are refractory to other therapies.

Uncontrolled maternal asthma contributes to poor maternal and fetal outcomes. Management by a multidisciplinary team, including internist, obstetrician, pharmacist, nurse, allergist, and pulmonologist, improves care and outcomes.

**T**HE INCIDENCE OF MATERNAL ASTHMA is rising. Based on US national health surveys, the prevalence of asthma during pregnancy is between 3.7% and 8.4%.<sup>1</sup> It is the most common respiratory illness of pregnancy.<sup>2</sup> Hence, clinicians need to know how asthma affects the mother and the fetus. Appropriate care of asthma during pregnancy is based on several management principles, as reviewed here, and is key to ensuring good outcomes for the mother and the baby.

## ■ EFFECT OF PREGNANCY ON ASTHMA CONTROL

Asthma control can vary in pregnancy. About a third of asthmatic women experience a worsening of asthma control with pregnancy, a third remain unchanged, and another third have improvement in asthma symptoms.<sup>3</sup> The peak worsening of asthma tends to occur in the sixth month.<sup>4</sup> Asthma control also tends to be better in the last month of pregnancy.<sup>3</sup>

The peak expiratory flow rate was noted to increase with each trimester in a small study of 43 women.<sup>5</sup> The authors speculated that a rising progesterone level stimulates cyclic adenosine monophosphate to cause bronchodilation, thereby improving the expiratory flow rate and asthma control. Asthma control tends to follow the pattern experienced in the previous pregnancy: ie, if asthma worsened during the previous pregnancy, the same will be likely in the subsequent pregnancy.<sup>3</sup>

Two maternal factors that adversely affect asthma severity during pregnancy are the use of asthma medications contrary to guidelines such as those of the Global Initiative for Asthma (<http://ginasthma.org/2017-gina-report-global-strategy-for-asthma-manage->

ment-and-prevention) and inadequate control of asthma before becoming pregnant.<sup>6</sup> Pregnancy can bring on stress, and stress is known to worsen asthma. In addition, when patients themselves were interviewed to elucidate the reasons for poor adherence to asthma medications during pregnancy, concerns about medication use, especially corticosteroids, stood out.<sup>7</sup> A study based on prescription claims data showed that in the first trimester, there was a significant decline in asthma prescription medications (a 23% decline in inhaled corticosteroids, a 13% decline in short-acting bronchodilator agents, and a 54% decline in rescue corticosteroids).<sup>8</sup> Lack of physician education about management of asthma in pregnancy and discomfort with prescribing to pregnant women also affect asthma control.

**■ EFFECT OF ASTHMA ON MATERNAL AND FETAL OUTCOMES**

Studies of the effects of asthma on fetal and maternal outcomes have yielded mixed and conflicting results.<sup>9</sup> Adverse outcomes that have been shown to be associated with maternal asthma are listed in **Table 1**. Other studies have not demonstrated an association between asthma in pregnancy and maternal or fetal adverse events.<sup>9</sup> Such discrepant findings are due to differences in study population characteristics that make comparisons difficult. A meta-analysis involving more than 1.6 million asthmatic women showed maternal asthma was associated with a 40% greater risk of low birth weight and preterm delivery, a 50% greater risk of preeclampsia, and a 20% greater risk of the baby being small for its gestational age.<sup>10</sup>

The association of maternal asthma and preterm birth may pose short-term and long-term health risks to the child associated with prematurity.<sup>9</sup> Short-term risks with prematurity include infection, respiratory distress syndrome, brain injury, and necrotizing enterocolitis. Long-term risks include neurodevelopmental and behavioral sequelae. Furthermore, asthma exacerbations during pregnancy are associated with a twofold higher risk of low birth weight.<sup>11</sup> The benefits of good adherence to asthma regimens during

**TABLE 1**

**Uncontrolled asthma in pregnancy: Effects on mother and fetus**

**Maternal effects**

- Preeclampsia
- Pregnancy-induced hypertension
- Gestational diabetes
- Premature rupture of membranes
- Cesarean birth
- Chorioamnionitis
- Hyperemesis
- Postpartum hemorrhage

**Fetal effects**

- Perinatal death
- Preterm birth
- Low birth weight
- Intrauterine growth restriction
- Congenital malformations
- Admission to neonatal intensive care unit
- Hyperbilirubinemia
- Respiratory distress syndrome
- Transient tachypnea of the newborn
- Asphyxia
- Increased risk of intracerebral hemorrhage, anemia

Based in part on information in reference 9.

pregnancy outweigh the risks associated with frequent symptoms and exacerbations caused by untreated asthma.<sup>12</sup>

**■ OUTPATIENT MANAGEMENT OF MATERNAL ASTHMA**

**Goals**

In the 2004 update of the National Asthma Education and Prevention Program (NAEPP) Working Group Report on Managing Asthma During Pregnancy, goals focused mainly on adequate asthma control for maternal health and quality of life, as well as normal fetal maturation (**Table 2**),<sup>12</sup> goals similar to those in nonpregnant asthmatic women.

**Assessment and monitoring**

Monthly physician visits during pregnancy are recommended for assessment of symptoms and pulmonary function. If symptoms are uncontrolled, therapy must be stepped up, and any trigger for exacerbation, such as gastroesophageal reflux disease (GERD), exposure, or rhi-

**Benefits of adherence to asthma regimens during pregnancy outweigh the risks of drug treatment**

**TABLE 2**

**A definition of asthma control**

- Minimal or no chronic symptoms day or night
- Minimal or no exacerbations
- No limitation on activities
- Maintenance of normal or near-normal pulmonary function
- Minimal use of short-acting beta-agonists
- Minimal or no adverse effects from medications

Based on information in reference 12.

**Avoiding asthma triggers—eg, dander, dust mites, smoke—can decrease symptoms and allow for lower doses of medications**

nititis, must be treated and eliminated. NAEPP guidelines recommend baseline spirometry at the time of initial assessment.<sup>12</sup> At follow-up visits, spirometry is preferred, but measurement of the peak expiratory flow rate usually suffices. Such objective data can help differentiate dyspnea from asthma and from dyspnea that usually accompanies the physiologic changes of pregnancy. In addition, patients should be advised to monitor for adequate fetal activity. If asthma is uncontrolled or poorly controlled, serial fetal ultrasonography should be considered from 32 weeks of gestation, as well as after recovery from an asthma exacerbation. Regular monitoring of the pregnant asthmatic patient by a multidisciplinary team can improve outcomes.<sup>13</sup>

**Avoiding triggers**

Patients should be advised to avoid asthma triggers such as pet dander, dust mites, pollen, smoke, mold, and perfumes, as this can decrease symptoms and allow for use of lower doses of medications.<sup>12</sup> Additionally, smoking cessation must be strongly encouraged, not only to control maternal asthma, but also to prevent harm to the fetus.

**MANAGEMENT OF SPECIFIC TRIGGERS**

**GERD**

Reflux disease often worsens during pregnancy, and it can coexist with asthma and can also exacerbate it.<sup>14</sup> Optimal control of GERD helps maintain adequate asthma control. For mild reflux symptoms, lifestyle modifications such

as elevating the head of bed, avoiding eating too close to bedtime, and avoiding foods that cause heartburn may be adequate.<sup>15,16</sup> If medications are needed, antacids (but not sodium bicarbonate, for fear of metabolic alkalosis) and sucralfate should be considered before using a histamine 2 receptor antagonist such as ranitidine. Proton pump inhibitors should be considered only if reflux symptoms are refractory to other therapies.

**Allergic rhinitis**

Intranasal corticosteroids are effective against allergic rhinitis in pregnancy (Table 3).<sup>12</sup> Montelukast, a leukotriene receptor antagonist, can be used, but data to support its use for allergic rhinitis in pregnancy are limited.

Among antihistamines, second-generation drugs such as cetirizine or loratadine can be considered.<sup>12</sup> Oral decongestants such as pseudoephedrine in early pregnancy are associated with a rare congenital fetal abnormality called gastroschisis, caused by vascular disruption.<sup>17</sup> Hence, if a nasal decongestant is required in early pregnancy, a local therapy such as an intranasal corticosteroid, short-term oxymetazoline, or an external nasal dilator may be considered.<sup>12</sup> These therapies must be combined with avoidance of allergens whenever possible.

**Allergies**

Diagnostic allergy and skin tests during pregnancy pose a risk of anaphylaxis and thus should be avoided. Instead, the focus should be on obtaining a thorough medical history about exposures and eliminating specific asthma triggers. It is also inadvisable to start allergen immunotherapy during pregnancy because of the risk of anaphylaxis and the effect of treatment on the mother and fetus.<sup>18</sup> However, maintenance doses of allergen immunotherapy can be continued during pregnancy.<sup>18</sup>

**Patient education**

Because of concern about the risks of taking medications during pregnancy, many women with asthma stop using their inhalers during pregnancy, thus compromising asthma control.<sup>8,13</sup> The physician and multidisciplinary team must use every opportunity to emphasize the importance of good asthma control during pregnancy. Inhaler technique should also be reviewed and, if defective, corrected.

Again, trigger avoidance and tobacco cessation should be addressed.

**Drugs**

The NAEPP recommendations state that asthma therapy should be continued during pregnancy, as it is safer both for mother and fetus to avoid exacerbations and uncontrolled asthma.<sup>12</sup> Despite this, 25% of primary care physicians instruct their patients to decrease or discontinue their inhaled corticosteroid during pregnancy.<sup>19</sup> As with asthma in general, treatment should involve using the lowest dose of drugs that achieves adequate control of symptoms.

In 2015, the US Food and Drug Administration (FDA) amended the labeling rule for medications used in pregnancy and lactation. The previous risk categories A (safest), B, C, D, and X (highest risk) are in the process of being removed from labels for all human prescription drugs and biologic products, to be replaced with a summary of the risks of taking the drug during pregnancy and lactation, a discussion of the data supporting the use, and relevant information to help healthcare providers make prescribing decisions and counsel women about the use of drugs during pregnancy and lactation ([www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm](http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm)).

■ **ROLES OF CONTROLLER THERAPY AND RESCUE THERAPY**

**Inhaled corticosteroids**

Inhaled corticosteroids are the mainstay of asthma controller therapy during pregnancy. A meta-analysis of 16 studies showed no increased risk of congenital malformations, cesarean delivery, or stillbirth among mothers who used these agents during pregnancy.<sup>20</sup> Because there are more safety data for budesonide, it is currently the preferred inhaled corticosteroid during pregnancy.<sup>9</sup> However, if a patient's asthma is controlled with a different corticosteroid before pregnancy, that agent may be continued during pregnancy, especially if it is thought that switching formulations could adversely affect asthma control.<sup>12</sup> This is mainly because current data do not prove that other inhaled corticosteroids are unsafe.

**TABLE 3**

**Drug therapy of maternal asthma: Former pregnancy risk categories**

<b>Drug</b>	<b>Category<sup>a</sup></b>
<b>Short-acting beta-agonist</b>	
Albuterol	C
<b>Long-acting beta-agonists</b>	
Formoterol	C
Salmeterol	C
<b>Inhaled corticosteroids</b>	
Budesonide (inhalation)	B
Fluticasone (inhalation)	C
<b>Leukotriene modifiers</b>	
Montelukast, zafirlukast	B
Zileuton	C
<b>Monoclonal antibody</b>	
Omalizumab	B
<b>Xanthine derivative</b>	
Theophylline	C
<b>Intranasal corticosteroids</b>	
Intranasal budesonide	B
Intranasal fluticasone	C
Intranasal mometasone	C
Intranasal triamcinolone	C

<sup>a</sup> Former US Food and Drug Administration risk category (see **Drugs**, this page).

**Inhaled beta-agonists**

Inhaled beta-agonists, both short-acting and long-acting, are used for rescue therapy. Albuterol is the preferred short-acting agent for rescue therapy in pregnant women with asthma.<sup>12</sup> Meta-analysis has shown no increased risk of major or minor congenital malformations in pregnant patients who use bronchodilators.<sup>20</sup> Long-acting beta-agonists typically are used as add-on therapy when asthma cannot be controlled by an inhaled corticosteroid. They should not be used without a controller medication (ie, an inhaled corticosteroid).

Guidelines for rescue therapy are similar to those for nonpregnant asthmatic patients. Although data are limited as to the gestational effects of long-acting beta-agonists (ie, formoterol, salmeterol), it can be assumed that the toxicologic and pharmacologic profiles are similar to those of the short-acting bronchodilators. Thus,

**Based on a systematic review, 20% of pregnant women with asthma require an intervention for an exacerbation during pregnancy**

**TABLE 4**

**Management of asthma exacerbations in pregnancy**

Monitor to ensure the maternal oxygen saturation remains above 95%

Consider systemic (oral) corticosteroids

Administer rescue therapy with a short-acting beta-agonist

Consider hospital admission if symptoms do not improve with emergency room care

Consider admission to intensive care unit and mechanical ventilation if symptoms are severe or if patient shows signs of impending respiratory failure

Carefully monitor fetal health

the safety of albuterol can be extended potentially to the long-acting beta-agonists.<sup>12</sup>

**Combining controller and rescue therapy**

When asthma is not adequately controlled on inhaled corticosteroids, a long-acting beta-agonist can be added or the dose of corticosteroid can be increased. The 2004 NAEPP guidelines stated that based on available literature, there was no clear advantage of one option over the other.<sup>12</sup> A study that compared the 2 approaches found no difference in rates of congenital malformations.<sup>21</sup>

**Leukotriene receptor antagonists**

There is little in the literature regarding the use of leukotriene receptor antagonists during pregnancy. However, animal safety data are reassuring,<sup>12</sup> and human studies have not found a higher risk of major congenital malformations.<sup>22,23</sup> Thus, they are an alternative for patients whose asthma has been well controlled on these agents before pregnancy. Montelukast and zafirlukast are in former FDA pregnancy risk factor category B (probably safe) (Table 3). However, 5-lipoxygenase inhibitors such as zileuton are contraindicated based on animal studies showing teratogenicity.<sup>24</sup>

**Omalizumab**

Omalizumab, a recombinant anti-immunoglobulin E antibody, can be used for allergic asthma not controlled with inhaled cortico-

steroids (Table 3). An analysis of the omalizumab pregnancy registry<sup>25</sup> found no significant increase in the rate of major congenital malformations, prematurity, or babies small for gestational age in asthmatic women taking omalizumab 8 weeks before conception or during pregnancy vs pregnant asthmatic women not taking omalizumab. However, this drug carries a risk of anaphylaxis and so should not be started during pregnancy.<sup>25</sup>

**Theophylline**

Because of potential toxicity, use of theophylline during pregnancy requires careful monitoring to ensure the serum concentration remains between 5 and 12 µg/mL.<sup>12</sup> Drug interactions are also common: for example, alcohol may increase the serum concentration of theophylline, and theophylline may increase the toxic effect of formoterol.

**Systemic corticosteroids**

Pregnant women with asthma that is not well controlled despite the therapies described above may require a daily oral corticosteroid such as prednisone to achieve adequate control. Oral steroids are also a mainstay of treatment of asthma exacerbation.

Although use of corticosteroids in the first trimester was associated with orofacial cleft in infants,<sup>12</sup> these studies did not include many women with asthma. In 2011, a nationwide cohort study from Denmark showed no increase in the risk of orofacial cleft with the use of corticosteroids during pregnancy.<sup>26</sup>

Preeclampsia, low birth weight, and preterm delivery have been described with corticosteroid use in pregnancy. It is not known whether these problems were a result of corticosteroid use or were due to the uncontrolled nature of the underlying condition that led to the steroid use. Since the risk of uncontrolled asthma to mother and fetus outweighs the risk of systemic corticosteroids, these drugs are recommended when indicated for management of maternal asthma.<sup>12</sup>

**ACUTE EXACERBATIONS REQUIRE AGGRESSIVE MANAGEMENT**

Based on a systematic review, 20% of pregnant women with asthma require some intervention for an asthma exacerbation during pregnancy,

**Exacerbations are more common late in the second trimester and are unlikely to occur during labor or delivery**

and 5.8% are admitted to the hospital for an exacerbation.<sup>11</sup> Exacerbations were associated with a higher risk of low birth weight compared with rates in women without asthma.

Exacerbations are more common late in the second trimester and are unlikely to occur during labor and delivery.<sup>2</sup> The incidence of exacerbations increases with the severity of asthma, from 8% in mild asthma, to 47% in moderate asthma, to 65% in severe asthma.<sup>27</sup> Risk factors for exacerbations include poor prenatal care, obesity, and lack of appropriate treatment with inhaled corticosteroids.<sup>2</sup> The main triggers are viral respiratory infections and noncompliance with inhaled corticosteroid therapy.<sup>11</sup>

Asthma exacerbations during pregnancy should be managed aggressively (Table 4),<sup>12</sup> as the risk to the fetus of hypoxia far outweighs any risk from asthma medications. Close collaboration between the primary care physician and the obstetrician allows closer monitoring of mother and fetus.

The goal oxygen saturation must be above 95%.<sup>12</sup> Signs of acute respiratory failure in a preg-

nant patient include a partial pressure of arterial oxygen less than 70 mm Hg or a partial pressure of carbon dioxide greater than 35 mm Hg.

In a multicenter study comparing nonpregnant and pregnant women visiting the emergency room for asthma exacerbations,<sup>28</sup> pregnant women were less likely to be prescribed systemic corticosteroids either in the emergency room or at the time of hospital discharge, and they were also more likely to describe an ongoing exacerbation at 2-week follow-up. However, a recent study showed a significant increase in systemic corticosteroid treatment in the emergency room (51% to 78% across the time periods, odds ratio 3.11, 95% confidence interval 1.27–7.60,  $P = .01$ ). There was also an increase in steroid treatment at discharge (42% to 63%, odds ratio 2.49, 95% confidence interval 0.97–6.37,  $P = .054$ ), though the increase was not statistically significant.<sup>29</sup> Although emergency room care for pregnant asthmatic women has improved, this group concluded that further improvement is still warranted, as 1 in 3 women is discharged without corticosteroid treatment. ■

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