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Management of asthma during pregnancy

Diego J. Maselli, Sandra G. Adams, Jay I. Peters and Stephanie M. Levine

Abstract: Asthma is an inflammatory lung condition that is the most common chronic disease affecting pregnancy. The changes in pulmonary physiology during pregnancy include increased minute ventilation, decreased functional residual capacity, increased mucus production, and airway mucosa hyperemia and edema. Pregnancy is also associated with a physiological suppression of the immune system. Many studies have described the heterogeneous immune system response in women with asthma during pregnancy, which partly explains why asthma has been shown to worsen, improve, or remain stable in equal proportions of women during pregnancy. Asthma may be associated with poor maternal and fetal outcomes. However, better maternal and fetal outcomes are observed with better asthma control. Asthma controller medications are generally thought to be safe during pregnancy, but limited data are available for some of the medicines. Newer medications like omalizumab open avenues for the treatment of asthma, but also pose a challenge, as there is limited experience with their use. Therefore, a multidisciplinary approach, including obstetricians, asthma specialists, and pediatricians should collaborate with the patient to carefully weigh the risks and benefits to determine an optimal management plan for each individual patient. The aim of this review article is to summarize the most recent literature about the immunological changes that occur during pregnancy, physiological and clinical implications of asthma on pregnancy, and asthma management and medication use in pregnant women.

Keywords: asthma, management of asthma, pregnancy

Introduction

Asthma is a chronic inflammatory disorder characterized by airway hyperresponsiveness and variable airflow obstruction. The airway obstruction can be reversible either spontaneously or with therapy. Asthma remains a common condition affecting 300 million patients worldwide and 10% of the population in the United States, and has a great impact on healthcare costs [Braman, 2006; Masoli *et al.* 2004].

Asthma can affect up to 8% of pregnant women and often has a significant impact on pregnancy [Kwon *et al.* 2006]. Changes in pulmonary physiology, hormonal fluctuations, and immunological aspects of the maternal–fetal interactions may play a role in the changes in asthma symptoms and control. It is well established that asthma control varies for different patients during pregnancy; in approximately one-third of women their asthma improves, in one-third it does not change, and in the remaining third it clinically worsens

[Tamási *et al.* 2011]. Asthma may complicate pregnancy and is a challenging condition due to the changes in the pulmonary physiology, alterations in the immune system, possible fetal adverse effects of the medications, and other obstetric considerations, as we will discuss in detail in this review.

Pulmonary changes during pregnancy

As pregnancy progresses there are several changes in the pulmonary physiology. The minute ventilation (VE) is increased due to the effects of high progesterone levels and by the third trimester VE may be increased by 50% [Guy *et al.* 2004]. The rise in the VE is driven mainly by an increase in the tidal volume (TV), and to a lesser extent, by an increase in the respiratory rate. This, in turn, causes a respiratory alkalosis that is compensated by renal excretion of bicarbonate [typical arterial blood gas: pH 7.40–7.45, partial pressure of carbon dioxide (CO₂) 28–32 mmHg].

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The functional residual capacity (FRC) can be decreased by 10–25% [Goucher *et al.* 1956]. This is largely due to a progressive decrease in the expiratory reserve volume and residual volume caused by the enlarging uterus and diaphragmatic elevation (3–6 cm). An adaptation of the abdominal muscles and widening of the lower rib cage partially compensates for the diaphragmatic elevation. In addition, higher levels of estrogen during the third trimester may cause increased mucus production and airway mucosa hyperemia and edema. Despite these changes, other parameters of the pulmonary function, including forced expiratory volume in 1 s (FEV₁), forced vital capacity (FVC), FEV₁ to FVC ratio, and peak expiratory flow rate remain unchanged during pregnancy [Brancazio *et al.* 1997; Guy *et al.* 2004].

Immunologic influence of asthma during pregnancy

During pregnancy there is a physiological suppression of the immune system. This occurs to protect the fetus from the mother when paternally originated antigens are expressed (semiallograft). This fetomaternal ‘tolerance’ is necessary for a normal gestation to complete. There are several cellular and humoral processes that allow this to occur and both regulatory T cells (Tregs) and natural killer (NK) cells appear to play important roles [Saito *et al.* 2007]. It has been shown that regulatory NK cells and Tregs inhibit fetal attack of maternal NK and T cells. This suppression of NK cells during pregnancy may explain why pregnant patients might develop more aggressive presentations of viral infections (e.g. hepatitis B, H1N1 influenza, etc.) [Palmer and Claman, 2002; Denney *et al.* 2010]. Interestingly, despite this ‘temporary immunodeficiency’, in general, most pregnant women react normally to most infections.

During pregnancy a shift towards a T-helper cell type 2 (Th2)-predominant inflammatory state has been described, and simultaneously, there is a Tregs suppression of a Th1 cell-induced fetal rejection [Saito *et al.* 2007]. This creates a high Th2/Th1 cytokine response. Asthma is also categorized as a Th2-predominant inflammatory state, but it remains unclear how the immune system of patients with asthma is affected by pregnancy and its consequences. Nevertheless, there have been observations in recent studies that have attempted to better characterize this response. A study by Toldi and colleagues confirmed the

presence of a high Th2/Th1 cell ratio in blood samples of healthy women without asthma during pregnancy and in nonpregnant women with asthma, but no further increases in this ratio were found in pregnant women with controlled asthma [Toldi *et al.* 2011]. These observations are in line with a study by Bohács and colleagues showing no additive activation of subpopulations of lymphocytes in pregnant women with asthma compared with those without asthma [Bohács *et al.* 2010]. These investigations suggest that pregnancy does not further augment an inflammatory response in already atopic individuals. By contrast, a study showed that interleukin-4 (IL-4; a Th2 cytokine) and interferon γ (IFN- γ ; a Th1 cytokine) synthesizing T lymphocytes were both increased in pregnant women with uncontrolled asthma in comparison to those without asthma [Tamási *et al.* 2005]. In fact, pregnant women with asthma had a 20-fold increase in IFN- γ -producing T cells compared with nonpregnant patients with the same severity of asthma. These findings imply that the cellular responses may change, especially in a disease with variation in activity (i.e. poorly controlled asthma). These studies also demonstrate the heterogeneous response of the immune system in women with asthma during pregnancy, and partly explain why asthma worsens, improves or remains stable in equal proportions of women during pregnancy.

Effects of asthma on pregnancy: maternal/fetal outcomes

Asthma is the most common chronic condition to affect pregnancy. Several studies in the past decades have identified asthma as a risk factor for both poor maternal and fetal outcomes. It is not clear whether these adverse consequences are an effect directly attributable to asthma, secondary to the medications used for asthma, socioeconomic status, or other factors that share common mechanisms with asthma.

Perhaps the most striking data come from a large meta-analysis that included 40 studies over various decades and over 1.5 million subjects [Murphy *et al.* 2011]. This study showed that maternal asthma was associated with increased risk of low birth weight infants [relative risk (RR) 1.46, 95% confidence interval (CI) 1.22–1.75], intrauterine growth restriction (IUGR) (RR 1.22, 95% CI 1.14–1.31), preterm delivery (RR 1.41, 95% CI 1.22–1.61), and preeclampsia (RR 1.54, 95% CI 1.32–1.81). Despite the inherent problems with

Table 1. Effect of pregnancy on asthma control.

Study	Total	Better		Unchanged		Worse		Undefined	
	N	N	%	N	%	N	%	N	%
Turner <i>et al.</i> [1980]	1054	306	29	516	49	232	22	–	–
Stenius-Aarniala <i>et al.</i> [1988]	198	36	18	79	40	83	42	–	–
Schatz <i>et al.</i> [1988a]	366	102	28	121	33	128	35	15	4
Kircher [2002]	568	193	34	148	26	204	36	23	4
Total	2186	637	29	864	39	647	30	38	2
Studies evaluating the changes in asthma symptoms during the course of pregnancy.									

this type of analysis, this study provides robust evidence on the negative impact of asthma during pregnancy. Even more worrisome were data obtained from over 4300 pregnancies in women with asthma evaluating congenital malformations [Blais and Forget, 2008]. Exacerbations during the first trimester of pregnancy were associated with an increased risk of congenital malformation (adjusted odds ratio 1.48, 95% CI 1.04–2.09). The reasons for these observations are complex and likely multifactorial.

Maternal hypoxemia and changes in the placental function during asthma have been offered as possible explanations for an increased incidence of IUGR and preterm delivery [Clifton *et al.* 2001; Murphy *et al.* 2003]. A study of 2123 women with asthma showed that lower FEV₁ was significantly associated with prematurity and preeclampsia [Schatz *et al.* 2006]. Because FEV₁ has been used as a marker of asthma control, these observations could be attributed to poor asthma control [Juniper *et al.* 1999]. In the study by Murphy and colleagues, it was also shown that the risk of preterm delivery was significantly reduced after an appropriate asthma treatment protocol was used, further reinforcing the need for appropriate asthma therapy during pregnancy [Murphy *et al.* 2011]. Other theories include a common pathway leading to hyperactivity of smooth muscle in the bronchial tree and uterus to explain an increased incidence of preterm labor in pregnant women with asthma [Kramer *et al.* 1995]. In addition, a possible association has been explored between asthma and preeclampsia related to mast cell infiltration [Siddiqui *et al.* 2008]. Despite the wide array of possible associations between asthma and pregnancy, it remains clear that better asthma control offers the best outcomes [National Heart, Lung, and Blood Institute *et al.* 2005].

Effects of pregnancy on asthma

It is difficult to predict how asthma control will evolve with pregnancy for any individual patient. Historically, asthma control improves, worsens or remains the same in equal proportions during pregnancy. By pooling a total of 2186 patients from four large series evaluating the effect of pregnancy on asthma control, we found that approximately 30% improved, 40% worsened, and 30% had no change in their symptoms (Table 1). The severity of baseline asthma, the frequency of exacerbations, and the level of control of asthma in prior pregnancies have also been used as predictors of how asthma will behave during pregnancy. A study classified the severity of asthma in 1739 pregnant women as mild, moderate or severe based on standard criteria, including FEV₁, symptoms, and rescue inhaler use [Schatz *et al.* 2003]. Schatz and colleagues demonstrated that 13%, 16%, and 52% of patients with at least one asthma exacerbation were classified at the onset of pregnancy as having mild, moderate, and severe asthma respectively, which supports a direct correlation between the severity of asthma and the frequency of exacerbations during pregnancy. Similar results have been reported in other series [Murphy *et al.* 2005]. Schatz and colleagues also noted that 30% of patients initially classified as having mild asthma were changed to the moderate or severe category, while 23% of patients with severe or moderate asthma were later categorized as having mild asthma as the pregnancy progressed [Schatz *et al.* 2003]. These findings suggest that, even though special attention should be paid to patients with severe asthma, others with milder severity of asthma must be followed closely as well, because of a relatively unpredictable course during pregnancy.

In addition to the severity of asthma, the occurrence of exacerbations has been associated with

the stage of pregnancy. While exacerbations can occur at any time during the course of the pregnancy and puerperium, studies have suggested a higher frequency of exacerbations during the late second and early third trimester [Stenius-Aarniala *et al.* 1996; Murphy *et al.* 2005; Schatz *et al.* 1988a]. Importantly, these studies suggest a possible protective effect during labor and delivery, as exacerbations tend to occur less frequently during this period [Jana *et al.* 1995; Schatz *et al.* 1988a]. Other risks associated with an increased rate of exacerbations include inadequate prenatal care, medication noncompliance, lack of inhaled corticosteroids when indicated, and obesity [Murphy and Gibson, 2011].

Treatment of asthma in pregnancy

Maintenance therapy

Patients with asthma who become pregnant should be considered as high risk and their medical management should be carried out in conjunction with obstetricians, asthma specialists, and pediatricians. The patients should be informed about the potential complications of asthma and what changes to expect in the respiratory system as the pregnancy progresses. In addition, as for all patients with asthma, emphasis should be placed on patient education, appropriate inhaler use, avoidance of asthma triggers, and early consultation if symptoms develop. A written asthma action plan should be established, especially in patients with moderate to severe asthma, describing in detail the measures to control asthma in the long term, how to appropriately respond to worsening symptoms and asthma exacerbations, and when to request emergency services [National Heart, Lung, and Blood Institute *et al.* 2005]. Well-informed patients may voice concerns regarding possible fetal side effects of asthma medications. They should be reassured and encouraged to be compliant with the regimens established by their healthcare professionals. The different classes of medications for asthma are generally regarded as safe (see individual discussion below), and even though they have potential side effects, better maternal and fetal outcomes are observed with better asthma control [Blais and Forget, 2008]. Patients who are current smokers should be strongly encouraged to stop smoking due to the well known adverse effects on the mother and fetus, and the association with poor asthma control [Salihu and Wilson, 2007; McCoy *et al.* 2006]. Moreover, second-hand smoke has been shown to

be equally detrimental and should be avoided in all patients [Oberg *et al.* 2011].

Conditions that may aggravate asthma such as allergic rhinitis and gastroesophageal reflux disease (GERD) should be aggressively treated [Schatz and Dombrowski, 2009]. Intranasal corticosteroids are the therapy of choice for allergic rhinitis due to their limited systemic effects [National Heart, Lung, and Blood Institute *et al.* 2005]. Leukotriene antagonists (LTAs) are also effective and considered safe during pregnancy (see discussion below). Second-generation antihistamines (e.g. loratadine, cetirizine) can be safely used, but combinations with pseudoephedrine are contraindicated due to potential fetal side effects (e.g. gastroschisis, intestinal atresia) [Piette *et al.* 2006]. GERD may occur in 30–50% of pregnancies [Majithia and Johnson, 2012]. Proton pump inhibitors are effective in treating GERD, and intrauterine exposure to these has not been associated with an increased risk for congenital malformations, perinatal mortality, or morbidity [Pasternak and Hviid, 2010; Majithia and Johnson, 2012].

Regular visits to evaluate asthma control are recommended for patients who require controller therapy during pregnancy. The evaluations should include objective assessment of lung function and validated assessment of symptoms (e.g. Asthma Control Test). Respiratory symptoms alone are not sensitive indicators of worsening asthma control, because most pregnant women have some degree of dyspnea as pregnancy advances [Guy *et al.* 2004]. A recent study showed that exhaled nitric oxide may be useful in monitoring and improving asthma control, but future studies are needed to validate these findings [Powell *et al.* 2011]. It is generally advocated to have monthly visits with the healthcare professionals who are managing the patient's asthma, but more frequent visits might be required if asthma remains uncontrolled. The therapy of pregnant women with asthma should follow a step-guided approach (Table 2), and if asthma control is not achieved by the current prescribed medications, then a 'step up' in therapy should be carried out following the established guidelines [National Heart Lung and Blood Institute, 2007; Global Initiative for Asthma, 2011]. Even though in nonpregnant patients with asthma a 'step down' is recommended if asthma control is maintained for at least 3 months, during pregnancy a 'step down' in therapy is generally not recommended because of the potential of losing asthma

Table 2. Therapy of asthma during pregnancy.

Step	Preferred therapy	Alternative therapy
1	As needed SABA*	–
2	Low-dose ICS	LTRA
3	Medium-dose ICS	LTRA
4	Low-dose ICS + LABA	Medium- or high-dose ICS Low-dose ICS + LABA + LTRA Low-dose ICS + LABA + theophylline [§]
5	Medium- or high-dose ICS + LABA	LTRA + theophylline [§]
6	Oral glucocorticoids	Omalizumab [‡]

Step-guided therapy for the control of asthma during pregnancy. When a step-up is considered for poor asthma control, it is recommended to confirm proper inhaler technique, compliance with the medications, and confirm that the symptoms are due to worsening asthma control.

*As needed SABA should be used in all steps.

[§]Sustained-release theophylline.

[‡]It is uncertain if omalizumab should be initiated during pregnancy, it may be maintained during pregnancy if the patient was already receiving omalizumab prior to pregnancy; however, there are no short- or long-term published data documenting its safety.

ICS, inhaled corticosteroids; LABA, long-acting β_2 agonist; LTRA, leukotriene-receptor antagonist; SABA, short-acting β_2 agonist.

control during this high-risk period [Dombrowski and Schatz, 2008]. In addition, every pregnant woman with asthma who develops worsening dyspnea should be carefully evaluated to rule out other conditions, including venous pulmonary embolism, amniotic fluid embolism, pulmonary edema, and pneumonia.

Treatment for acute exacerbations

The evaluation of pregnant women with asthma in the emergency room setting should be similar to that of other patients with asthma, but careful considerations regarding the pregnancy should be undertaken. An obstetrician experienced in high-risk pregnancies and an asthma specialist should be involved in the care of these patients, especially when they have moderate to severe asthma. Careful monitoring and prompt therapy should be initiated once other etiologies have been reasonably ruled out and it is established that a patient is having an asthma exacerbation. Bedside peak flow measurements should be obtained and compared with previous measurements or usual predicted values if possible. If the patient is taking theophylline, a level should be measured to rule out toxicity. Arterial blood gases should be measured, but it should be remembered that during pregnancy there is a baseline compensated respiratory alkalosis, and a normal arterial CO_2 of 40 mmHg may indicate relative hypercapnia and signs of fatigue.

Treatment should be started promptly. Inhaled albuterol treatments of 2.5 mg every 20 min should be established followed by the administration of oral or intravenous corticosteroids. Nebulized ipratropium bromide at 0.25–5 mg every 30 min for three doses should also be added to this regimen if the patient has an FEV_1 less than 40% or initially does not respond to albuterol. If the patient has a moderate or severe exacerbation, they should be observed to evaluate their response in a monitored bed. Patients in the advanced stages of pregnancy will require close maternal–fetal monitoring. A biophysical profile, including a nonstress test for reactive fetal heart rate, measurement of the amniotic fluid volume by ultrasound, observation for the presence of gross movements and of fetal breathing movements, and fetal heart tones should be performed in patients with a viable fetus [Schatz and Dombrowski, 2009]. Evaluation of the response to therapy should be done every 30–60 min, and a decision regarding admission or discharge should be reached ideally 4 h after the initial evaluation. If the patient responds appropriately to therapy and is discharged from the hospital, a 5–10-day course of prednisone (40–80 mg per day in a single or divided dose) should be prescribed to prevent early recurrence of symptoms. However, patients who have a moderate to severe exacerbation, or do not respond readily to therapy, should be hospitalized. In one study, 5.8% of pregnant women with asthma required hospitalization for exacerbations

during the course of the pregnancy [Murphy *et al.* 2006].

Endotracheal intubation and admission to the intensive care unit (ICU) should be considered if the patient continues to worsen despite maximal therapy. Potential indications for admitting a pregnant woman with asthma to the ICU include if her FEV₁ is less than 25% of predicted or if her FEV₁ improves less than 10% after treatment. Maternal hypoxia should be corrected as quickly as possible with a target oxygen saturation of 95% to prevent any possible fetal hypoxia [Schatz and Dombrowski, 2009]. Systemic administration of epinephrine should be avoided during pregnancy because of its teratogenic effects and placental and uterine vessel vasoconstriction. Terbutaline (a β_2 agonist) can be administered subcutaneously, 0.25 mg every 15–30 min for three doses, if the bronchoconstriction does not improve. Intravenous magnesium sulfate given at 1–2 g over 30 min can be considered because of its proven benefits in the pulmonary function of patients with severe acute asthma exacerbations [Silverman *et al.* 2002]. A helium–oxygen mixture (70:30 or 60:40) can be considered during the management of acute asthma to improve the delivery of medications to the distal airways and reduce the work of breathing [Ho *et al.* 2003]. The helium–oxygen mixture has had positive results in women with asthma during pregnancy [McGarvey and Pollack, 2008; George *et al.* 2001]. Adequate volume resuscitation should be carried out to prevent changes in the fetal–placental blood flow. In patients who are in the third trimester who, despite maximal therapy, continue to deteriorate, there have been reports of the pregnancy having to be terminated or the baby delivered prematurely via caesarian section as a life-saving measure to achieve asthma control [Elsayegh and Shapiro, 2008].

Invasive mechanical ventilation (IMV) may be required if the patient does not respond to therapy. IMV is indicated in patients who develop hypoxia that is refractory to noninvasive modes of oxygenation, severe respiratory acidosis, altered mental status, or maternal fatigue. The endotracheal intubation is preferably done through the oral airway. Because of a decreased FRC and increased oxygen consumption in pregnancy, apnea at the time of intubation may cause a steep decline in arterial oxygen content. Once an endotracheal airway is secured, IMV can be initiated using a target TV of 6–10 ml/kg. This relatively low

TV is recommended to prevent respiratory alkalosis and barotrauma, but studies in patients with asthma who required mechanical ventilation with a TV of 12 ml/kg did not show an increased rate of complications [Peters *et al.* 2012]. Longer expiratory times and lower respiratory rates may be required to prevent dynamic hyperinflation and prevent volutrauma and barotrauma, and case reports of permissive hypercapnic ventilation have been described [Shapiro, 2002]. Invasive or noninvasive monitoring of the volume status of the patient is recommended while the patient is on IMV to prevent pulmonary edema and ensure adequate tissue perfusion, particularly in fetal–placental circulation. The compression of the vena cava by the enlarging uterus while in a supine position may cause a decrease in the cardiac preload. This results in a decreased cardiac output and may lead to hypotension. By elevating the right hip (10–15 cm) the uterus can be displaced, thus relieving the compression of the vena cava [Mighty, 2010]. Sedation can be achieved using either benzodiazepines or propofol. Nutritional support should be started as soon as possible given the higher metabolic needs of pregnancy, but caution should be exercised because this may cause further elevation of CO₂ leading to worsening acidosis [Van den Berg and Stam, 1988].

Labor and delivery and other obstetric considerations

As mentioned above, it appears that during the period close to term, the frequency of asthma exacerbations is decreased. However, this remains a period of high risk for women with asthma. Women with adequate asthma control should continue to take their medications without changes. However, those experiencing asthma exacerbations during labor and delivery should be treated promptly and closely observed. During this period it is paramount to dismiss other causes of dyspnea because other diagnoses (i.e. pulmonary edema or pulmonary embolism) might become more common and delays in the treatment of these may have serious consequences.

The medications used during labor and delivery deserve special consideration when administered to women with asthma. In women with preterm labor, treatment with systemic β_2 agonists (e.g. terbutaline) should generally be avoided since there are few data to support the benefit in patients receiving inhaled β_2 agonists (e.g. albuterol) and

this may potentiate adverse effects such as tocolytic pulmonary edema, but can be considered in extreme situations. An alternative treatment could be intravenous magnesium sulfate because of its potentially beneficial dual effect [Silverman *et al.* 2002]. Morphine is not the preferred agent to treat pain due to its potential release of histamine that could affect asthma control and because of potential respiratory depression. Fentanyl is the preferred agent to treat pain because of its safer profile. If the patient has received significant oral corticosteroids in the months prior to delivery, then stress-dose corticosteroids should be considered to prevent potential complications from adrenal insufficiency [Hardy-Fairbanks and Baker, 2010]. Indomethacin should not be used in patients who have known reactions to aspirin or other nonsteroidal anti-inflammatory agents because it may cause bronchospasm. Oxytocin and prostaglandins E₁ and E₂ can be used safely for obstetric purposes, but prostaglandin F_{2 α} and the ergonovine compounds are known to cause bronchospasm and should not be used [Stenius-Aarniala *et al.* 1988]. After delivery, asthma symptoms may improve significantly, but despite this, therapy should not be discontinued in order to maintain asthma control.

Medications used for asthma control during pregnancy

There are several classes of medications used to achieve asthma control (Table 3). Most therapies are generally considered safe, but there are some considerations that have to be examined in detail. The caregiver should provide the patient with information regarding the potential risks of these medications to the mother and fetus. In addition, because there are several medications within each class, the lactation safety profile of a particular medication may influence the decision when choosing a medication if the mother wishes to nurse her infant. As described above, the safety profile of the medications to treat potentially aggravating conditions of asthma should also be taken into account (Table 4).

β_2 agonists

β_2 agonists have a pivotal role in the treatment of asthma and are the most effective bronchodilators. Through activation of the β_2 adrenergic receptors these agents may prevent the development and reverse the bronchoconstriction caused by an asthma exacerbation. Short-acting β_2 agonists

(SABAs) (e.g. albuterol, salbutamol) are prescribed for quick relief of symptoms. SABAs are regarded as safe and there is no evidence of any associations with congenital anomalies, low birth weight, IUGR or increased rates of poor maternal or perinatal outcomes [Schatz *et al.* 1988b; Guy *et al.* 2004]. Long-acting β_2 agonists (LABAs) (e.g. formoterol, salmeterol) are used as maintenance therapy in patients with moderate to severe asthma in combination with ICS. Long-term safety has not been established for LABAs, therefore these medications should only be prescribed as a 'step-up' therapy during pregnancy if asthma control cannot be achieved using medium-dose ICS in addition to SABAs, which is a slight variation from nonpregnant step-up therapy (Table 2). The US Food and Drug Administration (FDA) has classified both SABAs and LABAs as category C.

Inhaled corticosteroids

Corticosteroids are the mainstay therapy for uncontrolled asthma. They possess anti-inflammatory properties that are necessary to control and prevent asthma exacerbations. ICS are part of the step-guided therapy for asthma and are the initial step in the controller therapy for patients who have symptoms despite the use of SABAs (Table 2). There are several formulations of ICS approved by the FDA (Table 3). With the exception of budesonide (category B), all other ICS are classified as category C.

Several studies have evaluated the effectiveness and adverse effects of ICS during pregnancy. The use of ICS has been shown to decrease readmissions to the hospital for asthma [Wendel *et al.* 1996]. A study of 504 prospectively followed pregnant women with asthma demonstrated that patients who were treated with ICS had a decreased risk for asthma exacerbations [Stenius-Aarniala *et al.* 1996]. In addition, this study showed no increased rate of anomalies or other adverse events after treatment with ICS. There has been concern regarding an association between exposure to corticosteroids during pregnancy and IUGR. Namazy and colleagues specifically studied this association and demonstrated no relation between ICS and IUGR or other birth defects [Namazy *et al.* 2004]. Perhaps the most reassuring data come from two large studies obtained from the Swedish Medical Birth Register evaluating the use of budesonide. The first study included 2014 exposures during early pregnancy and showed no evidence of teratogenic effects of budesonide

Table 3. Medications used for asthma.

Medication	Category	Lactation profile
ICS		
Beclomethasone	C	Unknown
Budesonide	B	Unknown
Ciclesonide	C	Unknown
Fluticasone	C	Unknown
Mometasone	C	Unknown
Ipratropium bromide	B	Unknown
LABA		
Formoterol	C	Unknown
Salmeterol	C	Unknown
Leukotriene inhibitors		
Montelukast	B	Unknown
Zafirlukast	B	Possibly unsafe
Zileuton	C	Probably safe
Mast-cell stabilizers		
Nedocromil	B	Unknown
Cromolyn	B	Unknown
Omalizumab	B	Unknown
Systemic corticosteroids		
Dexamethasone	C	Probably safe
Hydrocortisone	C	Probably safe
Methylprednisolone	C	Probably safe
Prednisone	C	Probably safe
SABA		
Albuterol	C	Probably safe
Levalbuterol	C	Unknown
Metaproterenol	C	Unknown
Pirbuterol	C	Unknown
Terbutaline	C	Probably safe
Theophylline	C	Probably safe
FDA categories: category B, animal studies show no risk or adverse fetal effects, but controlled human first trimester studies do not avail or confirm adverse effects, no evidence of second or third trimester risk, fetal harm is possible but unlikely; category C, animal studies show adverse fetal effects(s) but no controlled human studies have been done, maternal <i>versus</i> fetal risk should be weighed. Lactation profile: unknown, inadequate literature is available to evaluate the risk and caution is advised; probably safe, limited information in animals and humans demonstrate no risk or there is minimal risk of adverse effects to infants, caution is advised; possibly unsafe, available animal or human data demonstrates potential or actual adverse effects to infants, consider alternatives and maternal versus fetal risk should be weighed. FDA has proposed that both pregnancy and lactation subsections of labeling include a risk summary and clinical considerations to support patient care decisions and counseling. The proposed regulations will eliminate the current pregnancy categories A, B, C, D, and X (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm) FDA, US Food and Drug Administration; ICS, inhaled corticosteroids; LABA, long-acting β_2 agonist; SABA, short-acting β_2 agonist.		

[Kallen *et al.* 1999]. The second study evaluated 2968 pregnant women with asthma and determined no clinically relevant effects on pregnancy outcomes [Norjavaara and De Verdier, 2003]. The results of these studies suggest that budesonide is safe for both mother and fetus during pregnancy. If another ICS was previously prescribed before

conception it should not be changed, but if there is an indication to start an ICS (i.e. worsening asthma control), then budesonide is probably the therapy of choice. ICS are often prescribed in a formulation combined with LABAs. Because ICS have a relatively safer profile than LABAs, it is advocated to use low- or medium-dose ICS before

Table 4. Medications used in the treatment of potentially aggravating conditions of asthma.

Condition	Medication	Category	Lactation profile
GERD	H2 blockers		
	Cimetidine	B	Probably safe
	Famotidine	B	Probably safe
	Nizatidine	B	Probably safe
	Ranitidine	B	Probably safe
	PPIs		
	Omeprazole	C	Unknown
	Esomeprazole	B	Unknown
	Lanzoprazole	B	Unknown
Allergic rhinitis	Pantoprazole	B	Unknown
	Cetirizine	B	Unknown
	Levocetirizine	B	Unknown
	Loratadine	B	Probably safe
	Desloratidine	C	Unknown
	Fexofenadine	C	Probably safe

FDA categories: category B, animal studies show no risk or adverse fetal effects, but controlled human first trimester studies do not avail or confirm adverse effects, no evidence of second or third trimester risk, fetal harm is possible but unlikely; category C, animal studies show adverse fetal effects(s) but no controlled human studies have been done, maternal *versus* fetal risk should be weighed. Lactation profile: unknown, inadequate literature is available to evaluate the risk and caution is advised; probably safe, limited information in animals and humans demonstrate no risk or there is minimal risk of adverse effects to infants, caution is advised; possibly unsafe, available animal or human data demonstrate potential or actual adverse effects to infants, consider alternatives and maternal *versus* fetal risk should be weighed. FDA has proposed that both pregnancy and lactation subsections of labeling include a risk summary and clinical considerations to support patient care decisions and counseling. The proposed regulations will eliminate the current pregnancy categories A, B, C, D, and X.

FDA, US Food and Drug Administration; GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor.

a LABA is added to the therapeutic regimen when following the step-guided approach during pregnancy (Table 2) [Tamási *et al.* 2011; Schatz and Dombrowski, 2009].

Systemic corticosteroids

Systemic corticosteroids are typically used for acute exacerbations or when asthma control is not achieved using other medications. Oral corticosteroids are associated with more adverse effects compared with ICS. The use of oral corticosteroids has been associated with higher risk for preeclampsia, gestational diabetes, and the need for caesarian delivery [Schatz *et al.* 1997; Alexander *et al.* 1998; Perlow *et al.* 1992]. In addition, there have been conflicting reports regarding the risk for cleft lip (with or without palate malformations) after exposure to systemic corticosteroids [Czeizel and Rockenbauer, 1997; Rodriguez-Pinilla and Martínez-Frías, 1998].

Despite the risks identified with the use of systemic corticosteroids during pregnancy, these are

likely to be still lower than the actual risks of uncontrolled or poorly controlled asthma. Because the systemic corticosteroids are usually reserved for uncontrolled or severe asthma, the adverse effects seen in patients exposed to systemic corticosteroids might be a consequence of the uncontrolled asthma itself and not an effect of the therapy used to treat it. Therefore, the main focus of the clinician treating acute asthma or severe asthma during pregnancy is to achieve asthma control as readily as possible using all available therapy, including systemic corticosteroids. All patients who receive systemic corticosteroids should be closely monitored for gestational diabetes.

Ipratropium bromide

Ipratropium bromide can be used as a short-acting bronchodilator during an asthma exacerbation. It blocks muscarinic acetylcholine receptors in the bronchial smooth muscle causing bronchodilation. The FDA has categorized ipratropium bromide as a class B medication, but studies

are lacking regarding its safety and efficacy during pregnancy, and therefore it cannot be considered as first-line therapy.

Leukotriene antagonists

Leukotrienes are important signaling molecules in the pathways of allergic inflammation and have a central role in the pathophysiology of asthma. LTAs may affect these pathways by two mechanisms. Inhibition of the enzyme 5-lipoxygenase (e.g. zileuton) decreases the production of leukotrienes. Antagonism of the cysteinyl-leukotriene receptor (e.g. montelukast, zafirlukast) limits the biological activity of leukotrienes. Several studies have shown that the use of LTAs in patients with asthma results in a reduction in exacerbations and improvement in lung function and quality of life [Knorr *et al.* 1998; Malmstrom *et al.* 1999; Reiss *et al.* 1998].

A study evaluating the safety of LTA use during pregnancy did not find any association with a specific pattern of major structural anomalies or adverse perinatal outcomes [Bakhireva *et al.* 2007]. This study is limited by its sample size and should be interpreted with caution. Therefore, with the exception of zileuton (category C), the FDA classifies the LTAs as category B medications during pregnancy (Table 3). If a LTA is to be used, montelukast may be the therapy of choice among these medications due to its safer lactation profile.

Theophylline

Theophylline has been used for the treatment of asthma over the past seven decades. The exact mechanism of action has not been fully elucidated, but it appears to act by improving the function of the respiratory muscles and as weak a bronchodilator through nonselective inhibition of phosphodiesterases and antagonism of adenosine receptors [Barnes, 2003]. Theophylline has been shown to improve asthma control and can reduce the corticosteroid requirements [Evans *et al.* 1997; Markham and Faulds, 1998]. Serum drug levels have to be monitored regularly to ensure safety and reduce side effects. Levels of 10 µg/ml are generally considered therapeutic, and levels above 20 µg/ml are associated with higher incidence of toxicity and side effects [Barnes, 2003].

Theophylline has been used extensively during pregnancy and is classified as a category C medication

with probably a safe profile for lactation (Table 3). Drugs levels should be monitored more frequently because of the changes in the volume of distribution during pregnancy and because of a reduced clearance of up to 35% in the third trimester [Tan and Thomson, 2000]. The effectiveness and safety of theophylline during pregnancy has been compared with other agents. Dombrowski and colleagues performed a prospective, double-blind, double placebo-controlled randomized clinical trial of 385 pregnant women with moderate asthma comparing inhaled beclomethasone with oral theophylline [Dombrowski *et al.* 2004]. This study showed that both medications resulted in similar rates of exacerbations and similar obstetrical and perinatal outcomes. Despite these results, because of its side effects (e.g. nausea, vomiting, headache, gastric hypersecretion, hypertension, insomnia), interaction with other medications, and need for frequent drug-level monitoring, theophylline might not be well tolerated during pregnancy and is not a preferred agent during this period [Gardner and Doyle, 2004].

Mast-cell stabilizers

Nedocromil sodium and cromolyn sodium are mast-cell stabilizers that prevent the release of histamine and other inflammatory mediators of the allergic response [Leung *et al.* 1988]. They are effective as controller therapies for asthma [Blumenthal *et al.* 1988; Edwards and Stevens, 1993]. Only a few studies have evaluated fetal anomalies associated with cromolyn, but because of their small sample size and other confounding variables, it is not clear if the adverse events reported were due to the other medications or poorly controlled asthma. In addition, these medications have limited systemic effects due to their poor absorption, making it less likely for adverse fetal effects [Lim *et al.* 2011]. Serious adverse effects have not been reported. Therefore, mast-cell stabilizers are considered safe during pregnancy and are labeled as category B by the FDA. Owing to the availability of newer more effective therapies, these medications are now used less often, but they may still have a role in patients who do not tolerate other classes of medications or in those who develop exercise-induced bronchoconstriction [Spooner *et al.* 2003].

Omalizumab

Omalizumab is a recombinant DNA-derived monoclonal antibody that selectively binds to

human immunoglobulin E (IgE). This prevents the interaction of IgE with the high-affinity receptors in basophils and mast cells, preventing their activation. This therapy is indicated for patients with moderate to severe asthma who have an elevated level of IgE, positive testing for perennial allergens, and whose condition cannot be controlled with medium- to high-dose ICS and a LABA. Several studies have shown the therapeutic efficacy and safety of omalizumab, and demonstrated a reduced rate in clinically significant asthma exacerbations, systemic requirements of corticosteroids, emergency visits, and overall symptoms [Busse *et al.* 2001; Holgate *et al.* 2004; Humbert *et al.* 2005].

The FDA has classified omalizumab as category B, but there is limited clinical experience with the use of this medication during pregnancy (Table 3). The Xolair (Genentech, Inc., South San Francisco, CA, USA) Pregnancy Registry (EXPECT study) is an observational study of the safety of omalizumab during pregnancy in women with asthma. This ongoing study was created to evaluate outcomes in at least 250 pregnant women and their infants exposed to omalizumab 8 weeks prior to conception or at any time during pregnancy. Upon review of preliminary data from 170 pregnancies with an average exposure to omalizumab of 7.7 months, an external advisory committee continues to see no apparent increase in prevalence of major birth anomalies [Namazy *et al.* 2012]. These preliminary findings are encouraging, but the study needs to be completed to reach its final conclusions. In addition to safety there are other considerations regarding omalizumab. Because omalizumab is dosed depending on patient weight, it is unclear how to adequately adjust the dosing as weight increases during pregnancy and how this may affect the control of asthma. Furthermore, it remains unclear if pregnant women with asthma will have the same clinical benefit as nonpregnant women with asthma. It is uncertain whether omalizumab should be initiated during pregnancy, but if the patient was already using it to achieve asthma control, then it should be continued. Future studies will help clarify these questions, but centers with experience with omalizumab are encouraged to enroll pregnant patients treated with omalizumab in ongoing trials.

Conclusion

Asthma remains a common condition during pregnancy and has a significant impact on maternal and perinatal outcomes. Asthma control has

been shown to be the most effective strategy to prevent complications during pregnancy. Pregnant women with asthma should be considered high risk and followed closely by their obstetricians and asthma specialists. Asthma control should be achieved using a step-guided therapy approach. Clinicians should encourage pregnant women with asthma to avoid asthma triggers, use a proper inhaler technique, comply with controller medications, and seek early consultation when symptoms develop. Despite relatively limited information regarding the maternal and fetal effects of the medications used to treat asthma, these are generally considered safe. As with all therapy, the risk *versus* benefit ratio should be weighed carefully; however, optimal asthma therapy has been correlated with better fetal and maternal outcomes.

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Conflict of interest statement

The authors declare that there are no conflicts of interest.

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