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REVIEW

Asthma in pregnancy

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Abstract

Asthma affects approximately 8% of women during pregnancy. Pregnancy results in a variable course for asthma control, likely contributed to by physiological changes affecting the respiratory, immune, and hormonal systems. While asthma during pregnancy has been associated with an increased risk of maternal and fetal complications including malformations, available data also suggest that active asthma management and monitoring can decrease the risk of adverse outcomes. The diagnosis, disease classification, and goals for asthma management in the pregnant woman are the same as for nonpregnant patients. However, evidence shows that pregnant asthmatics are more likely to be undertreated, resulting in asthma exacerbations occurring in approximately one third and hospitalization in one tenth of patients. Pharmacotherapeutic management of asthma exacerbations in pregnant patients follows standard treatment guidelines. In contrast, the principles of asthma maintenance therapy are slightly modified in the pregnant patient. Patients and practitioners may avoid use of asthma medications due to concern for a risk of fetal complications and malformations. A variable amount of information is available regarding the risk of a given asthma medication to cause adverse fetal outcomes, and it is preferable to use an inhaled product. Nevertheless, based on available data, the majority of asthma medications are regarded as safe for use during pregnancy. And, any increased risk to either the mother or fetus from medication use appears to be small compared to that associated with poor asthma control.

Key words: Asthma; Pregnancy; Fetal outcomes; Maternal outcomes; Management of asthma; Pharmacotherapy

Core tip: This comprehensive review of the impact of asthma during pregnancy provides information regarding proposed pathophysiological alterations and fetal and maternal outcomes associated with asthma during pregnancy. In addition, we outline the treatment of acute exacerbations and the maintenance management of asthma throughout pregnancy, including specific information on the various classes of medication used to treat asthma.

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INTRODUCTION

Asthma is a common condition affecting approximately 8% of pregnant women[1]. Epidemiological evidence demonstrates that the course of asthma during pregnancy is variable and unpredictable, with approximately one-third of women experiencing an improvement, one-third experiencing a worsening, and one-third having no

changes in asthma symptoms[2,3]. It is also apparent that poor control of maternal asthma leads to increased risk of adverse maternal and fetal outcomes. Because of these risks and the unpredictable course of asthma symptoms, it is especially important to provide appropriate monitoring and management of the asthmatic patient throughout pregnancy. This review will discuss the physiologic changes associated with asthma during pregnancy, asthma control and its effect on pregnancy outcomes, and the management of asthma in pregnancy.

PHYSIOLOGICAL CHANGES AND ASTHMA IN PREGNANCY

The relationship between the changes in body physiology as pregnancy progresses and the physiological processes driving asthma symptoms is not well understood, but it is evident that the relationship is bidirectional and complex[3-5]. It is thought that changes including alterations in pulmonary physiology, maternal immune function and hormonal balance contribute to the unpredictable course of asthma during pregnancy.

Pulmonary changes

As pregnancy progresses, the uterus expands and causes elevation of the diaphragm by 4-5 centimeters, resulting in a decrease in lung functional residual capacity (FRC) of 10%-25%. However, the decrease in FRC does not typically result in significant changes to forced vital capacity, peak expiratory flow rate, or forced expiratory volume in 1 second (FEV1). Minute ventilation (VE) may be elevated as much as 50% by the third trimester of pregnancy as a result of progesterone-driven increases in tidal volume and respiratory rate[6]. Concomitantly, oxygen consumption can increase up to 35%[7]. Respiratory alkalosis occurs as a result of the increase in VE but is compensated for by increased renal excretion of bicarbonate. Typical arterial blood gas values in pregnancy are altered only slightly from the nonpregnant state, with a normal pH of 7.40-7.45 and pCO_2 of 28-32 mmHg[7-9].

Due to the pulmonary changes during pregnancy, dyspnea is common and manifests as shortness of breath with rest or mild exertion. The pulmonary changes are often magnified in an asthmatic patient, and may contribute to the perception of changing symptoms during pregnancy[6].

Immunologic changes

Physiological immunosuppression is characteristic of pregnancy and results in feto-maternal tolerance required for completion of a normal gestation[10]. Changes in immune characteristics during pregnancy include a shift in the helper T cell (Th1)/Th2 ratio toward a Th2-predominant immune state and an increase in regulatory T cells (Tregs) that work to suppress activation of effector T cells and natural killer cells. This immune deviation is thought to prevent Th1-induced fetal rejection as paternally originated antigens are expressed during development[10]. A number of immune-mediated disease states can be affected by this Th2-predominant shift during pregnancy. For example, rheumatoid arthritis is a Th1-mediated disease that goes into remission during pregnancy in the majority of patients[11]. Asthma, on the other hand, has traditionally been categorized as a Th2-predominant disease state, with allergic Th2-type inflammation leading to airway hyperresponsiveness in patients. Evidence suggests that the pregnancy-associated Th2 immunological shift leads to worsening of the Th2-driven manifestations of asthma[10,12,13].

Immune changes in pregnant asthmatic women have not been well elucidated but recent studies have helped to better characterize the interplay of immunologic processes associated with pregnancy and asthma. Results of several studies provide evidence that exaggerated Th2 responses in pregnant women with uncontrolled asthma contribute to worsening of maternal symptoms, as well as low birth weight in neonates[14,15]. In contrast, no differences in the Th1/Th2 ratio were observed between healthy pregnant women and pregnant women with well-controlled asthma, suggesting that pregnancy and asthma do not have additive effects in terms of Th2 prevalence if asthma is well-controlled with medication therapy[15,16].

The relative number of peripheral Treg cells has been found to be lower in asthmatic compared to healthy pregnant women. It is thought that a decrease in Treg cells results in decreased suppression of the effects of pro-inflammatory Th17 cells and may contribute both to worsening of symptoms as well as increased likelihood of poor fetal outcomes in asthmatic patients[16]. Increased numbers of pro-inflammatory Th17 cells, have been observed in pregnant asthmatic women, and are hypothesized to contribute to impaired intrauterine growth (Figure 1)[3]. Continued research is needed to further characterize the complex and bidirectional relationships between T-cell subpopulations and the immunologic processes of asthma, in order to understand their role and importance in asthma during pregnancy.

Another factor associated with immunological changes of pregnancy relates to women's changing susceptibility to respiratory pathogens. The pregnancy-associated decrease in cell-mediated immunity is also known to make pregnant women more susceptible to viral respiratory infections, a common precipitating factor in asthma exacerbations during pregnancy[17,18].

Hormonal changes

As a pregnancy progresses, concentrations of circulating maternal hormones increase to varying degrees. As such, inter-individual variations in hormonal changes could contribute to the unpredictable course seen in maternal asthma. Pregnancy is associated with an increase in serum free cortisol, a hormone with endogenous anti-inflammatory activity which can improve asthma[19]. Evidence also suggests that levels of sex steroids including estrogen and progesterone can affect asthma symptoms. Changes

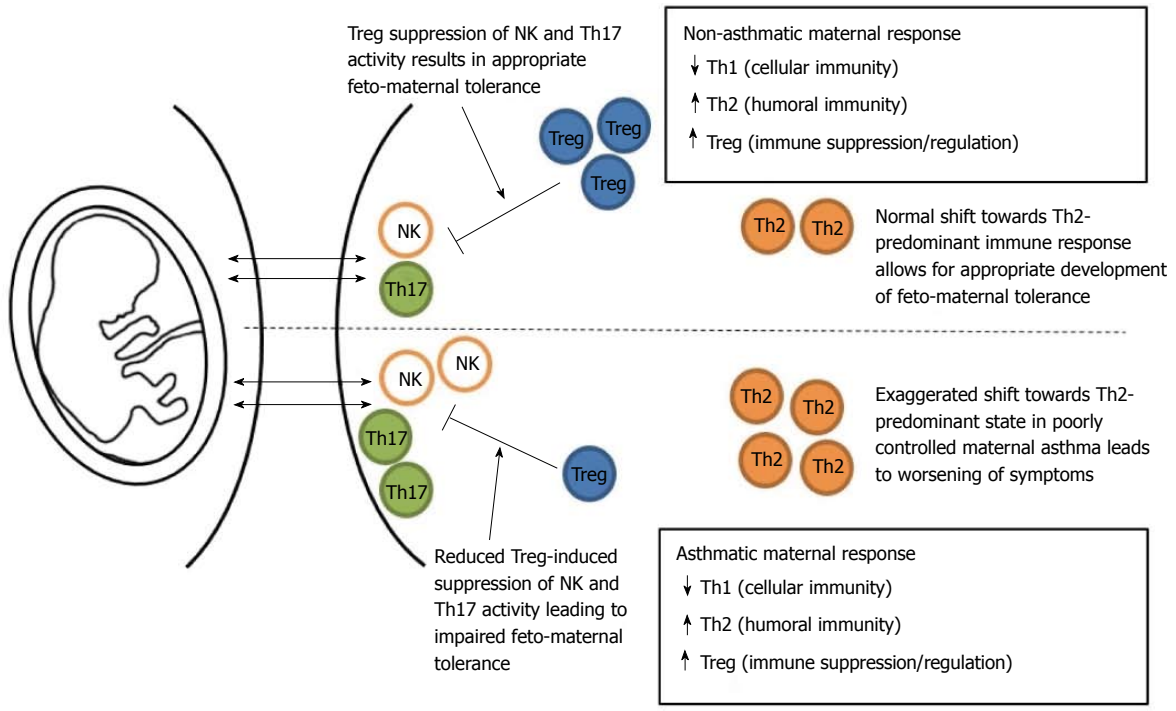

Figure 1 Immunology of Asthma in pregnancy. NK: Natural killer; Treg: Regulatory T cells.

in asthma symptoms are known to occur throughout the menstrual cycle, with up to 40% of females experiencing premenstrual asthma worsening during the follicular phase when progesterone and estrogen levels are normally low[20-23].

Estrogen levels have been shown to be correlated with the quantity of peripheral Tregs, suggesting an interrelationship between the hormonal and immunological effects of pregnancy. Arruvito *et al*[24] observed a strong correlation between increasing estradiol levels in fertile women and the percentage of Tregs found in the total number of $CD4^+$ T lymphocytes. An elevation of estrogen during the third trimester has been associated with increased bronchial mucus production and airway edema, thereby increasing symptoms of asthma[6,25]. Increased progesterone levels during pregnancy can result in a multitude of effects as a potent smooth muscle relaxant. While smooth muscle relaxation in the lungs would likely improve asthma symptoms, relaxation of the smooth muscle controlling the esophageal sphincter could result in increased gastroesophageal reflux, a condition known to exacerbate the symptoms of asthma[26].

Additionally, serum progesterone levels have been shown to exert effects on the regulation of β2-adrenoreceptors in female asthmatics, which could in turn effect changes in asthma symptoms and medication response. In a study of seven asthmatic females receiving exogenous progesterone during the follicular phase of their menstrual cycle, a significant decrease in lymphocyte β2-adrenoreceptors was determined when compared to baseline, with a trend towards decreased responsiveness to exogenously administered isoproterenol. Results of this study suggest that downregulation of β2-adrenoreceptors in response to increases in serum progesterone may result in loss of responsiveness to both endogenous catecholamines and exogenously administered beta-agonists[27].

Available evidence also suggests there may be inherent differences in the course of asthma during pregnancy based on fetal sex, with a worsening of maternal asthma more likely in the presence of a female fetus[28-31]. In a study of pregnant women with asthma, there was a significantly increased dose requirement of inhaled corticosteroid (ICS) and a significant rise in circulating monocytes that progressed throughout the pregnancy in women with a female compared to those carrying a male fetus[29]. It has been proposed that factors such as differences in hormone or protein production between male and female fetuses account for the variability in maternal asthma severity and treatment response, although currently there is no specific evidence to support this hypothesis.

ASTHMA CONTROL AND PREGNANCY OUTCOMES

Maternal outcomes

Compared to pregnant women without asthma, asthma during pregnancy is consistently associated with higher rates of preeclampsia, pregnancy-induced hypertension, transient hypertension of pregnancy, gestational diabetes, placenta previa or placental abruption, premature labor or delivery, cesarean section and postpartum hemorrhage[32-37]. Results from a recent retrospective cohort study conducted in the United States from 2002-2008 of obstetric complications among women with asthma (n = 17044) compared to women without asthma (n =

206468) found asthma was associated with increased rates of preeclampsia [adjusted odds ratio (aOR = 1.14; 95%CI: 1.06-1.22), superimposed hypertension (aOR 1.34; 95%CI: 1.15-1.56), placenta previa (aOR = 1.30; 95%CI: 1.08-1.56), placental abruption (aOR = 1.22; 95%CI: 1.09-1.36), preterm premature rupture of membranes (aOR = 1.18; 95%CI: 1.07-1.30), gestational diabetes (aOR = 1.11; 95%CI: 1.03-1.19), maternal hemorrhage (aOR = 1.09; 95%CI: 1.03-1.16), breech presentation (aOR = 1.13; 95%CI: 1.05-1.22), prelabor cesarean delivery (aOR = 1.16; 95%CI: 1.09-1.23) and maternal intensive care unit admission (aOR = 1.34; 95%CI: 1.04-1.72)[38]. Blais *et al*[39] reported women with asthma have a higher rate of spontaneous abortion (OR = 1.41; 95%CI: 1.33-1.49) but a lower rate of induced abortion (OR = 0.92; 0.88-0.97); neither finding was influenced by baseline asthma severity. Actively managing asthma during pregnancy has resulted in reducing risks of certain maternal outcomes to non-significant levels such as preterm delivery and low birth weight but without effect on pre-eclampsia[40].

Fetal outcomes

Fetal complications associated with maternal asthma include premature delivery (< 37 wk), small for gestational age (SGA, defined as < 10% percentile for matched age), low birth weight (LBW, defined as < 2500 gm), intrauterine growth restriction, mortality, and congenital malformations. Asthma during pregnancy has been associated with increased rates of neonatal sepsis and hospitalization in some studies but results are inconsistent[33,41,42]. Clifton *et al*[30] completed a meta-analysis of literature describing perinatal outcomes in women with asthma. The meta-analysis included data from 11 prospective and 15 retrospective cohort studies with total subject populations exceeding 1500000. Subgroup analysis was conducted to compare outcomes of prospective *vs* retrospective studies, as well as outcomes of studies with active asthma management as compared to those without active asthma management. Maternal asthma without active management was associated with increased rates of preterm delivery [risk ratio (RR) = 1.41; 95%CI: 1.22-1.61], pre-eclampsia (RR = 1.54; 95%CI: 1.32-1.81), LBW (RR = 1.46; 95%CI: 1.22-1.75), and SGA (RR = 1.22; 95%CI: 1.14-1.31). Studies in the meta-analysis that included active asthma management reduced the relative risk of preterm labor and delivery to non-significant levels[40].

Maternal asthma is associated with increased risk of fetal malformations but the magnitude of the risk appears to be only slightly greater than risk associated in non-asthmatic pregnant women. Tata *et al*[43] performed a case-controlled study using 5124 fetal cases of major congenital malformations compared with over 30000 matched controls. Results indicated the malformation risk due to maternal asthma was marginally greater (aOR = 1.10; 95%CI: 1.01 to 1.20) than that in controls and that the risk could be modified by asthma therapy in the year before and during pregnancy[44]. Additionally, a meta-analysis and systematic review of maternal asthma and its influence on fetal outcomes was recently conducted by Murphy and colleagues. When compared to control groups consisting of pregnant women without asthma, maternal asthma was associated with a significantly increased RR for neonatal sepsis (RR = 2.27; 95%CI: 1.12-4.58), hospitalization (RR = 1.50; 95%CI: 1.03-2.20) and perinatal mortality (RR = 1.25; 95%CI: 1.05-1.50). Investigators also found an overall increased risk of congenital malformations (RR = 1.11; 95%CI: 1.02-1.21) but the increased risk was only significant in the subcategory of retrospective cohort studies that did not include active asthma management[44].

MANAGEMENT OF ASTHMA IN PREGNANCY

The goals of therapy and principles of management of asthma in pregnant women are similar to those for non-pregnant women[9]. However, pregnant women are more likely to be undertreated by physicians for a given level of asthma severity[45,46]. Evidence has also shown that pregnant asthma patients often avoid medications they believe are potentially harmful to the fetus. Rocklin *et al*[36] tracked the prescription claims data in a cohort of 112171 pregnant women who were enrolled in the Tennessee Medicaid program. Subjects significantly decreased ($P \leqslant 0.0005$) their use of asthma medications during the 5th-13th weeks of pregnancy. Utilization rates during the first trimester declined by 23% for ICS prescriptions, 13% for short-acting B2-agonists (SABA) prescriptions and 54% for rescue corticosteroid prescriptions[47].

It is known that critical fetal organ development occurs predominately during the first trimester, and available data suggest that first trimester asthma exacerbations in the mother lead to higher rates of malformation in the offspring. Infants born to mothers with a first trimester asthma exacerbation, compared to those without, were more likely to suffer at least one malformation affecting 9.2% of infants (aOR = 1.48 with 95%CI: 1.04-2.09) and a major malformation affecting 6.0% of infants (aOR = 1.32 with 95%CI: 0.86-2.04)[48]. Such evidence highlights the need for careful management of maintenance therapy in pregnant asthmatics, and suggests the value of a multidisciplinary approach to assessment and treatment of asthma to promote appropriate therapy and medication adherence.

Diagnosis and classification of asthma

The diagnosis of asthma in a pregnant patient is the same as in the nonpregnant population, ideally with confirmation by spirometry showing at least partially reversible obstruction of the airways. If a pregnant patient presents with symptoms of new-onset asthma without spirometric confirmation of diagnosis, they should be treated with appropriate asthma therapy only after other diagnoses are excluded. Differential diagnoses associated with new-

onset dyspnea during pregnancy include physiologic dyspnea of pregnancy, pulmonary embolism, amniotic fluid embolism, pneumonia or bronchitis, GERD, and/or vocal cord dysfunction[49,50]. It should be noted that testing of bronchial hyperresponsiveness with methacholine challenge is contraindicated during pregnancy due to a lack of safety data[49].

Evidence clearly shows that the course of asthma is unpredictable as the pregnancy progresses[17,51]. While baseline asthma severity, the frequency of asthma exacerbations, and the level of asthma control in prior pregnancies have been used as predictors for asthma outcomes during pregnancy, monitoring and assessment of patients with all levels of asthma severity is important. In a study of 1739 women, patients' asthma severity was classified at the onset of pregnancy based on standard criteria including FEV1, symptoms and rescue inhaler use. It was found that 13%, 16%, and 52% of women classified as having mild, moderate, and severe asthma, respectively, suffered at least one asthma exacerbation during pregnancy, suggesting a correlation between baseline asthma severity and the risk of an exacerbation during pregnancy. However, results of the study also demonstrated that 30% of patients initially classified with mild asthma progressed to moderate or severe disease throughout the course of pregnancy, while 23% of patients categorized as having baseline moderate or severe asthma improved to the mild disease category[51]. Results of this study and other studies (Table 1) illustrate the unpredictable nature of asthma in pregnancy and emphasize the ongoing need for monitoring of asthma symptoms regardless of initial asthma severity. Generally, a patient's asthma course and severity will revert to their pre-pregnancy status approximately 90 d postpartum[52].

Acute asthma exacerbation management

Most women with asthma complete their pregnancy without incident. But data also indicate 20%-36% of patients will experience an asthma exacerbation, 9%-11% will require hospitalization and some will need ICU management and rarely (< 1%), intubation[9,38,51]. Exacerbations during pregnancy most commonly occur during the 25th-36th week of pregnancy with fewer episodes occurring during labor and the peripartum period[53-55]. In addition, evidence suggests that pregnant black women with asthma are more likely to experience and require medical care for exacerbations[9].

In the Emergency Department (ED), the pregnant asthmatic patient should receive a thorough physical examination, spirometry or peak flow meter assessment and arterial blood gas evaluation. Assessment of maternal oxygen saturation *via* pulse oximetry should be conducted to ensure oxygen saturation is maintained at or above 95%. Spirometry or peak flow meter results can be compared to the patient's baseline measurements or their predicted personal best. Arterial blood gas results usually demonstrate a compensated respiratory alkalosis common to pregnancy. As such, an otherwise normal value for arterial pCO_2 (pCO_2 of 40 mmHg) in some cases may signal relative hypercapnia and could be an indicator of respiratory fatigue in the pregnant patient[5].

The health status of the fetus must also be ascertained. Specific recommendations for fetal assessment are determined by the stage of pregnancy but a biophysical profile that combines ultrasound and a non-stress test is routine. These tests are used to measure amniotic fluid volume and fetal heart rate, muscle tone, breathing episodes and gross movements[9,56].

Recommended initial medical treatment for an acute asthma exacerbation in a pregnant woman presenting to the ED follows standard treatment guidelines. In addition to oxygen supplementation, inhaled albuterol every 20 min up to three doses in the first hour is recommended. If the exacerbation is severe, 500 μg of inhaled ipratropium bromide can supplement albuterol administrations. Oral or intravenous corticosteroids are recommended for individuals with inadequate response to bronchodilator therapy, for individuals who have required multiple short courses of steroids throughout their pregnancy or for those receiving systemic corticosteroids at time of presentation to the ED[5,9]. If the pregnant patient responds favorably to the bronchodilators and/or corticosteroids, generally within 4 h of presentation to the ED, she may be discharged. On discharge from the ED, a short 5-10 d course of oral prednisone given at 40-80 mg as a single or divided daily doses is recommended to prevent asthma relapses[5,9].

Alternatively, hospitalization is recommended if a maternal oxygenation saturation of 95% or greater cannot be maintained on room air after appropriate medication administration, if FEV1 or PEF measurements are persistently less than 70% despite therapy, or if fetal distress is evident. Subcutaneous or intravenous terbutaline can be utilized on a case-by-case basis if inhaled SABA have been maximized whereas systemic epinephrine should be avoided[9]. Life threatening asthma episodes are characterized by significant maternal hypoxemia (PaO_2 < 60 mmHg), hypercapnia ($PaCO_2$ > 40), respiratory acidosis, maternal respiratory fatigue and/or fetal distress. Intubation and mechanical ventilation can be required in these life-threatening circumstances and on rare occasion, delivery of the newborn by cesarean section is indicated[9,56].

Maintenance therapy

Due to the increased risk of adverse pregnancy outcomes associated with poor asthma control, optimal management of maternal asthma through optimization of maintenance therapy becomes especially important. Although evidence exists to support the safety of most major classes of medications used for asthma management during pregnancy, patients and providers often remain apprehensive about the use of any drug therapy. Unfortunately, the consequence of decreasing or discontinuing asthma medications during pregnancy is an increase in the likelihood of poor asthma control and its associated risks to both mother and fetus. Recent research has high-

Table 1 Pregnancy associated asthma morbidity by severity classification

	Mild asthma *n* (%)		Moderate asthma *n* (%)		Severe asthma *n* (%)	
	Schatz *et al*[51] (*n* = 873)	Murphy *et al*[55] (*n* = 63)	Schatz *et al*[51] (*n* = 814)	Murphy *et al*[55] (*n* = 34)	Schatz *et al*[51] (*n* = 52)	Murphy *et al*[55] (*n* = 49)
Asthma Exacerbation	110 (12.6)	5 (8)	209 (25.7)[b]	16 (47)	27 (51.9)[d]	32 (65)
Unscheduled physician or ED presentation	99 (11.3)	4 (6.3)	157 (19.3)[b]	14 (41)	19 (36.5)[b]	20 (41)
Oral corticosteroid use	19 (2.2)	0 (0)	71 (8.7)[b]	4 (11.8)	20 (38.5)[b]	19 (38.8)
Hospitalization	20 (2.3)	2 (3.2)	55 (6.8)[b]	1 (2.9)	14 (26.9)[b]	9 (18.4)

[b]$P < 0.0001$, [d]$P < 0.001$ *vs* preceding severity group (moderate to mild; severe to moderate). ED: Emergency Department.

lighted the importance of a multidisciplinary approach to patient education and management of maternal asthma by involving physicians, pharmacists, midwives and others associated with perinatal care, in order to ensure appropriate treatment and promote patient adherence[57,58].

Regular visits to evaluate asthma control are recommended throughout pregnancy in all patients regardless of disease severity. If there is any indication that maternal asthma symptoms are worsening, more frequent monitoring would be indicated. Disease evaluations should include objective assessment of lung function with the use of spirometry or peak flow meter, as well as assessment of symptoms using a validated questionnaire such as the Asthma Control Test or Asthma Control Questionnaire (ACQ)[59,60]. More recent research from a double-blind, parallel-group, controlled trial focused on the use of the fraction of exhaled nitric oxide (FeNO) as a marker of airway inflammation in asthma during pregnancy. Results showed a 50% reduction in asthma exacerbations using a treatment algorithm guided by FeNO compared to that guided by symptom assessment[60]. These early results are encouraging but the use of FeNO is not yet widely available, and its use has yet to be included in guidelines as a standard of care.

As in nonpregnant patients, the pharmacological treatment of asthma should be implemented in a stepwise fashion using current guidelines, with "step-up" therapy indicated if the patient is not adequately controlled with current therapy. Prior to medication regimen changes, issues such as poor medication adherence, improper inhaler technique, and other conditions associated with worsening dyspnea including pneumonia, pulmonary embolism or amniotic embolism, should be assessed[5,50].

There are, however, several exceptions to current asthma treatment guidelines in pregnant women. First, when a step-up in controller medication is indicated, an ICS should be initially trialed in preference to a combination ICS/long-acting bronchodilator (LABA) product due to the safety concerns associated with LABAs that will be discussed below (Table 2). Second, current asthma guidelines recommend step-down therapy to be considered in non-pregnant patients who are well controlled on a regimen for a minimum of three months[50]. In contrast, maintenance therapy should not be altered or escalated during pregnancy in asthmatics who are well controlled since fetal risks associated with the loss of disease control outweigh the benefits associated with a reduction in maintenance therapy[59,61].

Education

Patient education is an important component of appropriate management in any patient with asthma. Several studies have highlighted the importance of asthma education during pregnancy, using strategies to provide information to patients about the disease and its treatment, as well as improving medication adherence[55,57]. One recent study by Lim and colleagues showed that 70% of surveyed women were unaware of the risks associated with poor asthma control, while 32% discontinued or changed medications during pregnancy without discussing the changes with a healthcare professional[57]. Asthma education can directly address these issues and promote improved outcomes.

Key education topics for patients should include general information about asthma, potential complications and their relationship to pregnancy, proper use of inhaler devices, appropriate self-monitoring, adherence to medications, and optimal control of environmental factors. A written asthma action plan should be established to assist patients with self-monitoring and treatment in response to asthma control based on symptoms and/or peak flow monitoring. The plan should be developed in coordination with a healthcare provider and communicated to all those involved in the treatment of the patient. Patients should receive follow-up education and assessment of medication adherence and inhaler technique at every visit. The use of regular education and monitoring through a multidisciplinary team approach has been shown to significantly decrease ACQ scores when compared to groups receiving usual asthma care without education[50,57-59].

Nonpharmacologic measures and immunizations

Nonpharmacologic approaches can improve asthma symptoms while decreasing the use of "as needed" medication, thereby minimizing any associated maternal or fetal risk. The identification and avoidance or removal of indoor and outdoor environmental asthma "triggers" may greatly reduce the risk of asthma exacerbation. Common triggers including mold, dust, animal dander, cockroaches, pollens, and perfumes are often impossible to avoid completely but minimization of exposure is a treatment goal. Furthermore, smoking cessation and/or avoidance

Table 2 Stepwise approach to asthma therapy in pregnant and nonpregnant patients[49,60,62]

	Step	Preferred therapy in nonpregnant patients	Preferred therapy in pregnant patients	Alternative therapy in pregnant patients
Intermittent asthma	1	SABA, as needed[1]	SABA, as needed[1]	N/A
Persistent asthma	2	Low-dose ICS	Low-dose ICS	LTRA
	3	Low-dose ICS + LABA, or medium-dose ICS	Medium-dose ICS	LTRA
	4	Medium-dose ICS +LABA	Low-dose ICS + LABA	Medium-dose ICS, or high-dose ICS, or low-dose ICS + LABA + LTRA
	5	High-dose ICS + LABA	Medium-dose ICS +LABA, or high-dose ICS + LABA	LTRA + theophylline
	6	High-dose ICS + LABA + oral corticosteroid	High-dose ICS + LABA + oral corticosteroids	Omalizumab

[1]SABA should be included as quick-acting rescue medication to be used as needed in all patients. SABA: Short-acting beta-agonist; LABA: Long-acting beta-agonist; ICS: Inhaled corticosteroid.

of secondhand smoke always should be incorporated to treatment plans of pregnant asthmatic patients[50,62].

Immunization against influenza is strongly recommended in both pregnant and postpartum patients with asthma, as influenza is more likely to cause severe illness in these populations, leading to serious disease exacerbations that pose risk to maternal and fetal wellbeing. Pregnant women should receive an inactivated influenza vaccine by injection while postpartum women who are breastfeeding may receive either the live or attenuated vaccine given *via* the intranasal route or by injection. Recommendations regarding administration of pneumococcal vaccine in asthmatic patients vary between countries, and some controversy regarding the effectiveness of pneumococcal vaccination in asthma exists. Although no evidence of maternal or fetal harm has been demonstrated following administration of the pneumococcal vaccine (PPSV23) during pregnancy, providers should make every effort to vaccinate women with asthma prior to pregnancy. Pneumococcal vaccine is not, however, contraindicated in breastfeeding[63-65].

Management of comorbid conditions

While the use of allergen immunotherapy is known to be effective for improving asthma symptoms in patients with allergies, anaphylaxis is the greatest risk accompanying allergen injections in the asthmatic patient and has the potential to result in maternal and/or fetal death. The risk is especially high earlier in the course of immunotherapy when allergen doses are being increased. Consideration of the benefits and risks of allergen immunotherapy generally favors continuation of the treatment if a patient has reached a maintenance or near-maintenance dose without adverse reactions prior to a pregnancy. However, initiation of allergen immunotherapy during pregnancy is not recommended[50].

As in nonpregnant patients, rhinitis and gastroesophageal reflux may lead to exacerbation of asthma symptoms during pregnancy. Management of these comorbid conditions should be considered an integral part of patient care because pregnancy can result in physiological alterations that lead to worsening of the conditions. Details of the management of these conditions during pregnancy are beyond the scope of this review; however, the interested reader is referred to references for further information[66-71].

ASTHMA MEDICATIONS USED DURING PREGNANCY

Data from three studies describing the association of congenital malformations with maternal asthma medication use have been recently published[44,72,73]. The National Birth Defects Prevention Study by Källén *et al*[73] included 2853 infants with one or more specific malformations compared to a control group of 6726 unaffected infants. Mothers of cases and controls were contacted by telephone and asked to describe their medication use beginning one month prior to and through their third month of pregnancy. Other potential risk factors such as tobacco and alcohol use, co-morbid chronic diseases and exposures at home and work were also solicited. Congenital malformations included esophageal atresia, small intestinal atresia, anorectal atresia, limb deficiencies, diaphragmatic hernia, omphalocele, or neural tube defects. Significant associations were determined for omphalocele with both bronchodilators (SABA and/or LABA use) and anti-inflammatory medication use (aOR = 4.13; 95%CI: 1.43-11.95), isolated anorectal atresia with anti-inflammatory use (aOR = 2.12; 95%CI: 1.09-4.12) and isolated esophageal atresia with bronchodilator use (aOR = 2.39; 95%CI: 1.23-4.66). No other positive associations with other birth defects were determined[72].

Cydulka *et al*[45] conducted a systematic review and meta-analysis of the literature concerning the association of maternal asthma disease management with the risk of congenital malformations. Data from 12 cohort studies (four prospective and eight retrospective studies) of women with asthma stratified according to disease severity, exacerbation history, corticosteroid use, or bronchodilator use were included in the analysis. In accordance with other studies, maternal asthma was associated with a significantly increased risk of malformations for the en-

tire group (RR = 1.11; 95%CI: 1.02-1.21) but no increase was observed in the subset of patients in the prospective studies with active asthma medication management. While the presence of asthma was associated with an overall increased risk of congenital malformations, significant associations were not found for any specific factors related to asthma including maternal asthma exacerbation history, bronchodilator use, or ICS use[44].

Mendola *et al*[38] used data from the Swedish Medical Birth Register for the period 1996-2011 to investigate the risk of congenital malformations in infants born to women who had received medications for asthma during early pregnancy. Maternal drug use information was obtained from midwife interview records of patients during the first perinatal care appointment that typically occurred during the 10th-12th wk of pregnancy. The data spanned a 15-year timeframe with over 1.5 million births, including those of 44772 (2.9%) patients who received asthma medications from at least one of the following medication classes: inhaled adrenergics (SABA and/or LABA), ICS, anticholinergics, anti-allergics, xanthines, and leukotriene receptor antagonists. Women receiving antiasthmatic medications were compared to women who did not receive a drug from the listed classes, with adjustments made for year of delivery, maternal age, parity, smoking, and BMI. Those receiving antiasthmatic drugs were further stratified into specific medication classes.

Results indicated the OR for bearing an infant with a major congenital malformation was 1.09 (95%CI: 1.03-1.15) for women receiving any antiasthmatic medication *vs* those with no exposure to asthma medications. Median cleft palate (but not cleft lip/palate) with an OR of 1.45 (95%CI: 1.06-1.98), cardiovascular defects with an OR of 1.13 (95%CI: 1.04-1.23), and pyloric stenosis with an OR of 1.42 (95%CI: 1.06-1.91) were determined to be significantly increased malformations in infants born to mothers who took asthma medications. Risk estimates for the associations of the number of different asthma medications taken by the mother with a major malformation were significant for use of medication from a single group 1.11 (95%CI: 1.04-1.19) and use of medications from three or more groups 1.18 (95%CI: 1.01-1.38). In regard to specific medication classes, significantly increased odds or risk ratio OR/RR were found for the use of SABA (OR/RR = 1.10; 95%CI: 1.04-1.10) and ICS (OR/RR = 1.08; 95%CI: 1.01-1.16). However, there was no examination of asthma severity and its potential links to fetal outcomes in this study. Furthermore, as with all of these recently published studies, increased congenital risks could not be linked to specific, individual medications within a given medication group[73].

β2-agonists

SABAs are effective bronchodilators for quick-acting relief of asthma symptoms and are generally considered safe for use during pregnancy and breastfeeding. While SABA use was associated with a small increased risk of congenital malformation in some of the large studies described above, most studies evaluating maternal SABA use during pregnancy have not shown significant increases in adverse maternal or fetal outcomes associated with drug use[6,74,75]. In other studies that did show significant increases in adverse events potentially correlated with SABA use during pregnancy, reference groups of healthy non-asthmatic women or mixed asthmatic plus non-asthmatic women were used, making it impossible to discern if observed adverse outcomes were attributable to medication use or the disease[73,74,76-80]. Results of a single population-based case-control study of 511 pregnant women with asthma demonstrated an increased risk of congenital malformations with fenoterol use, but no association with other SABA use[79]. Due to the preponderance of evidence supporting the safety of SABA use in pregnancy, the drugs should be used according to guidelines for the quick-relief of asthma symptoms.

There is limited data regarding the safety of LABAs during pregnancy. In a population-based retrospective cohort study of β-2 agonist use in pregnancy, Eltonsy and colleagues observed a nonsignificant trend for an increased risk of major congenital malformations in infants of women who used LABAs during the first trimester. In the same study, SABA use was not associated with any increased risk of malformations[74]. On further analysis of those using a LABA in the first trimester (*n* = 165), investigators found that while there was no significant increase in all major malformations (defined as malformations that were life-threatening, caused major cosmetic defects, or resulted in at least one hospitalization within the first year of life), there were significant increased risks for the subtype of major cardiac malformations (aOR = 2.38, 95%CI: 1.11-5.10), genital organ malformations (aOR = 6.84, 95%CI: 2.58-18.10) and major "other and unspecified congenital malformations" (aOR = 3.97, 95%CI: 1.29-12.20)[75]. The authors of the study offered explanations for the observed trend of adverse outcomes associated with LABA use beyond that of a true causal relationship. First, while the investigators attempted to correct for asthma severity in the analysis of the data, it was possible that there was residual confounding of results by asthma disease severity. Second, specific interactions between concurrent LABA and steroid use have been identified including effects on protein kinase A (PKA) and ligand-independent activation of glucocorticoid receptors[81]. Because LABAs were used concomitantly with ICS for asthma in this study, authors suggest that observed increases in fetal malformations might be due to an effect of LABA use on steroid function, leading to potentiation of steroid-associated adverse effects[75].

Other studies examining LABA use have not found significant association between LABA use and major fetal malformations, and evidence supporting differences in the safety profiles of individual LABAs is lacking[75,77,80-83]. A recent study by Cossette *et al*[84] failed to find any statistically significant differences in low birth weight or preterm birth for infants of mothers who had used sal-

meterol *vs* formoterol during pregnancy.

Due to a lack of robust evidence for the safety of LABA use in pregnancy, the medications should only be used if asthma control cannot be achieved using medium-dose steroids in addition to SABAs. As previously noted, this recommendation is a deviation from asthma guidelines for nonpregnant patients (Table 2). Maternal plasma concentrations of inhaled LABAs have been shown to be undetectable or minimal, however, and the use of the agents is not considered a contraindication to breastfeeding[85].

Inhaled and systemic corticosteroids

Due to potent and predictable anti-inflammatory effects, ICS form the foundation of maintenance therapy in patients with persistent asthma. As a drug class, ICS have generally been shown to decrease the risk of asthma exacerbations among pregnant women, with no increased rate in adverse maternal or fetal outcomes[86-88]. Systemic absorption of an ICS is typically very low, with data demonstrating very low to undetectable plasma concentrations of triamcinolone, fluticasone, ciclesonide and becolmethasone after inhalation[89]. Inhaled budesonide has approximately 39% bioavailability, but results of studies of inhaled budesonide in lactation demonstrated a negligible amount transferred to the breastfeeding infant[90]. Additionally, similar incidences of adverse pregnancy outcomes were observed in a randomized, controlled trial comparing the use of inhaled budesonide *vs* placebo in pregnant women with asthma[90]. Information from other studies of ICS use in asthmatic patients during pregnancy provide similar evidence indicating no significant increased risk for neonatal adverse events including oral clefts, cardiac defects, spina bifida and other congenital malformations beyond those expected in the general population[88,91-93].

Concerns regarding the safety of corticosteroids in pregnancy have been specifically addressed in a number of studies. Data from most studies support the safety of ICS use for asthma during pregnancy[55,76,88,93-96]. However, in a retrospective cohort study of 817 asthmatic women during pregnancy, Lim *et al*[97] found statistically significant increases in the rates of pregnancy-induced hypertension (OR = 1.7, 95%CI: 1.0-2.9) and neonatal hyperbilirubinemia (OR = 1.9, 95%CI: 1.1-3.4) associated with the use of ICS or oral corticosteroid as compared to those using no medication. It is important to note, however, that outcomes associated with oral and inhaled corticosteroids were combined in this analysis, rather than independently assessed. Additionally, the authors cite the inability to distinguish well-controlled from uncontrolled asthma as an important limitation to this study[96].

Comparative studies of various ICS and commonly used dosages are somewhat lacking. All ICS except budesonide are classified as pregnancy category C by the United States Federal Drug Administration (FDA). Budesonide was moved to category B based on evidence of its safety from Dombrowski *et al*[93]; however, no specific data exists to suggest that other ICS are less safe for use during pregnancy. The United States National Heart Lung and Blood Institute guidelines of 2008 state that budesonide is the preferred ICS during pregnancy, but states that other ICS may be continued[58,59]. More recent global guidelines do not distinguish a preferred ICS for treatment of asthma during pregnancy, consistent with evidence from studies that has not shown significant differences in adverse maternal or fetal outcomes between patients using an ICS with beclomethasone, budesonide or fluticasone during pregnancy[50,77,88].

Few studies contain information regarding dosage ranges for the ICS used, making it difficult to determine if any risk of fetal adverse effects is dose-related[98]. Investigators in several studies did detect trends towards increased rates of SGA infants and increased congenital malformations with increasing doses of ICS, but the differences did not reach statistical significance and authors could not rule out confounding of results due to asthma severity[98,99]. In summary, there is no compelling evidence to substantiate a correlation between the use of an ICS during pregnancy and an increased risk of adverse infant outcomes; currently, these agents should be used when necessary to maintain asthma control.

Systemic corticosteroids should be reserved for use in acute exacerbations for all asthma patients or in those patients unable to achieve disease control using other agents. In contrast to ICS, oral corticosteroids have been associated with a higher incidence of maternal adverse effects, including preeclampsia and gestational diabetes[94,96,100,101]. A meta-analysis and systematic literature review conducted by Murphy *et al*[44] could not rule out the possibility of increased malformation risk associated with maternal oral corticosteroid use during a critical period for fetal lip and palate closure. The suggestion is based on data from case control studies that have indicated cleft lip and or cleft palate may not only be associated with maternal asthma but also with exposure to first-trimester oral corticosteroids[101,102]. As with other asthma therapies, the benefits associated with gaining control of severe uncontrolled asthma symptoms often outweigh the risks of adverse events associated with systemic steroid use. Nevertheless, systemic corticosteroids should be used judiciously in pregnancy and patients should be closely monitored for adverse effects.

Leukotriene receptor antagonists

Leukotrienes are potent mediators in the signaling pathways of allergic inflammation and thus play a central role in the pathophysiology of asthma. Leukotriene antagonists (LTRAs) function to reduce inflammation through this pathway and can reduce asthma exacerbations and improve lung function in persistent asthma. Few studies have been conducted to analyze the effects of this medication class exclusively and large, well-designed studies of LTRA use in pregnancy are lacking.

Limited data from available studies have shown conflicting results regarding maternal and fetal adverse out-

comes associated with the use of LTRAs[103-108]. A study of 180 pregnant asthmatics examined the effects of montelukast exposure compared to two separate groups of pregnant women: 180 disease-matched controls using inhalers but with no exposure to LTRAs and 180 age-matched healthy controls with no known teratogen exposure. Investigators found that in asthmatic women who used montelukast during the first trimester of pregnancy, there were significantly increased rates of infant LBW, preterm delivery and fetal distress when compared to healthy non-asthmatic maternal controls. Although only 47.4% of pregnant women taking montelukast in the first trimester continued the medication throughout pregnancy, a subgroup analysis of these patients demonstrated no significant difference in rates of fetal distress or preterm delivery when compared to asthmatic controls. This finding suggested a protective effect of montelukast likely due to improved asthma control throughout pregnancy. Moreover, investigators found no significant differences in adverse effects in pregnant women with asthma exposed to LTRAs compared to disease-matched asthmatic maternal controls[108].

In contrast, a previously published study generated results that indicated a nonsignificant increase in the rate of malformations in 96 asthma patients who received a LTRA throughout pregnancy as compared to 122 pregnant asthmatics who received SABA monotherapy. Malformations were observed in 5.95% of LTRA compared to 3.9% of SABA users, respectively (P = 0.524). Notably, the study had important limitations in addition to a relatively small sample size. The women taking LTRAs also were exposed during pregnancy to other asthma medications including SABAs, ICS, and oral corticosteroids. Also, LTRA use was associated with an increased patient baseline asthma severity which was not adjusted for in this study, and could account for the increased rate of malformations[104]. Further studies are needed in order to determine the safety of LTRA agents during pregnancy and/or lactation, but available data suggest that if necessary, montelukast would be the preferred LTRA due to a greater amount of evidence supporting its safety and a safer lactation profile.

Theophylline

Theophylline is a drug with mild bronchial anti-inflammatory effects[105]. While it is not a preferred agent in the treatment of asthma due to prevalent adverse effects, drug-drug interactions and the need for monitoring of serum concentrations, theophylline may be beneficial in selected patients. In a prospective study, 153 women with asthma including 85 receiving theophylline were followed throughout the course of their pregnancy. Results of the study demonstrated a significantly reduced risk of preeclampsia in patients treated with compared to those not receiving theophylline. Investigators suggested that theophylline's ability to increase cAMP levels and thereby reduce vascular reactivity and platelet aggregation may result in the decreased incidence of preeclampsia[106].

A subsequent study compared theophylline with inhaled beclomethasone therapy in 398 pregnant females with mild or moderate persistent asthma. No significant differences in adverse obstetric outcomes including preeclampsia, preterm delivery and oligohydramnos were detected between patient groups. Additionally, there was no significant difference in the number of asthma exacerbations between the two groups, although there was a significant increase in the proportion of women with a FEV1 less than 80% of predicted among the theophylline group[107]. Available evidence suggests that use of theophylline in pregnancy is likely safe; the drug is currently classified as a category C medication by the United States FDA[85,108].

Mast-cell stabilizers

Mast-cell stabilizers prevent mast-cell release of histamine and other inflammatory mediators during allergic response. Although they are not commonly compared to other asthma medications, they are considered effective second-line agents for asthma control. Very few studies have evaluated the use of mast-cell stabilizers for asthma during pregnancy and major limitations of available studies include small patient sample size, concurrent use of other medications, and comparison of treatment groups to healthy, non-asthmatic controls. Nevertheless, cromolyns are considered safe for use during pregnancy due to limited systemic bioavailability, and could be an appropriate adjunctive therapy in some patients[86,109].

Omalizumab

Omalizumab is a recombinant monoclonal anti-IgE therapy that works by binding and neutralizing the effects of IgE in basophils and mast cells, thereby preventing downstream allergic inflammation. The biologic therapy is reserved for patients with moderate to severe persistent asthma who are unable to be controlled by medium- to high-dose ICS plus LABA therapy. As a relatively new therapy, evidence for safety of omalizumab use in pregnancy is very limited. Currently, the Xolair® Pregnancy Registry (EXPECT) is collecting data for an ongoing observational study designed to monitor outcomes in women exposed to omalizumab during the time period starting eight weeks prior to conception and continuing throughout the pregnancy. Of the 128 known outcomes from preliminary data in this registry, there were 119 live births, with 117 singletons and two pairs of twins for a total of 121 infants. Of these infants, 16% were premature (gestational age less than 37 wk) and 7% had a birth weight less than 2.5 kg. The rate of major birth defects was 4%, with observed defects including patent foramen ovale, cutaneous mastocytosis, hemangioma, hypospadias, and bilateral renal pelvis dilation[110]. It is important to note that this agent is typically reserved for patients with moderate to severe asthma, and thus, it is difficult for effects related to omalizumab use to be differentiated from effects due to disease severity. Currently, the United States FDA has classified this agent as pregnancy cat-

Table 3 Asthma medications in pregnancy and lactation

Medication	United States FDA pregnancy category[1]	Australian Drug Evaluation Committee pregnancy category[2]	German pregnancy risk category[3]	Lactation[85]
Inhaled corticosteroids				
Beclomethasone	C	B3	Group 3	Unknown
Budesonide	B	A	Group 3	Unknown
Ciclesonide	C	B3	--	Unknown
Fluticasone	C	B3	Group 5	Unknown
Mometasone	C	B3	Group 5	Unknown
Short-acting β-agonists				
Albuterol	C	A	--	Likely safe
Levalbuterol	C	A	--	Unknown
Terbutaline	C	A	--	Likely safe
Long-acting β-agonists				
Formoterol	C	B3	Group 4	Unknown
Salmeterol	C	B3	Group 5	Unknown
Leukotriene inhibitors				
Montelukast	B	B1	Group 5	Likely safe
Zafirlukast	B	B1	--	Possibly unsafe
Zileuton	C	--	--	Likely safe
Mast-cell stabilizers				
Nedocromil	B	B1	Group 4	Unknown
Cromolyn	B	A	Group 1	Unknown
Systemic corticosteroids				
Dexamethasone	C	A	--	Likely safe
Methylprednisolone	C	A	Group 3	Likely safe
Prednisone	C	A	Group 3	Likely safe
Theophylline	C	A	--	Likely safe
Omalizumab	B	B1	Group 4	Unknown

[1]United States Federal Drug Association pregnancy categories[111]: Category A: Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters); Category B: Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women; Category C: Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks; Category D: There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks; Category X: Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits; [2]Australian Drug Evaluation Committee pregnancy categories[111]: Category A: Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed; Category B1: Drugs that have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage; Category B2: Drugs that have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage; Category B3: Drugs that have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans; Category C: Drugs that, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible; Category D: Drugs that have caused are suspected to have caused or may be expected to cause an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects; Category X: Drugs that have such a high risk of causing permanent damage to the fetus that they should not be used in pregnancy or when there is a possibility of pregnancy; [3]German pregnancy risk categories[113]: Group 1: Extensive human tests and animal studies have not shown the drug to be embryotoxic/teratogenic; Group 2: Extensive human tests of the drug have not shown the drug to be embryotoxic/teratogenic; Group 3: Extensive human tests of the drug have not shown the drug to be embryotoxic/teratogenic. However, the drug appears to be embryotoxic/teratogenic in animals; Group 4: No adequate and well-controlled studies of the drug's effects on humans are available. Animal studies have shown no embryotoxic/teratogenic effects; Group 5: No adequate and well-controlled studies of the drug's effects on humans are available; Group 6: No adequate and well-controlled studies of the drug's effects on humans are available. Animal studies have shown embryotoxic/teratogenic effects"; Group 7: There is a risk that the drug is embryotoxic/teratogenic in humans, at least in the first trimester; Group 8: There is a risk that the drug is toxic to fetuses throughout the second and third trimesters; Group 9: There is a risk that the drug causes prenatal complications or abnormalities; Group 10: There is a risk that the drug causes hormone specific action on the human fetus; Group 11: There is a known risk that the drug is a mutagen/carcinogen.

egory B based on evidence from animal studies (Table 2). Due to the small amount of human safety data, appropriate risk-benefit analysis should be undertaken before use in pregnancy.

DISCUSSION

Despite large amounts of data related to the influence of asthma and its treatment on maternal and fetal outcomes,

there are a number of limitations to these studies. Many early studies evaluating the influence of asthma control on maternal and fetal outcomes failed to assess, or poorly defined baseline asthma severity as well as the frequency, timing and severity of asthma exacerbations during pregnancy. However, data are available from other studies that have corrected for race, smoking status, age of mother, mean gestational age at enrollment, baseline asthma severity classification, severity of asthma exacerbations and other important covariates[33,35,42,111]. Based on existing information, it is clear that poor maternal asthma control has serious implications for both maternal and fetal health.

While congenital malformations are believed to be caused by a variety of factors associated with maternal asthma during pregnancy, establishing an association between maternal asthma effects and neonatal congenital malformations has also been challenging. Small sample sizes, varying study designs (case-control *vs* cohort), the timing of maternal study enrollment, a lack of correction for multiple testing and other confounders are routinely cited as key limitations[43,44,73]. Additionally, separating the impact of maternal asthma from effects caused by asthma medications on resultant fetal malformations is a daunting task. Given the low overall rate of congenital malformations in the general population (3%), a power analysis indicates that nearly 12000 women with asthma would be needed to detect a relatively small 15% increase for a major congenital malformation, given an alpha level of significance of 0.05 and a beta of 0.80[73]. Generally, data from large studies support a small increased risk of malformations from asthma medication use, although this risk is difficult to delineate from confounding factors including asthma severity, asthma control during pregnancy, fetal hypoxia at birth or simply chance[44,73,73]. Further studies that control for these confounding factors are required in order to truly separate the effects of disease *vs* the effects of medication use in pregnancy.

Although patients may express concerns regarding possible fetal adverse effects related to medication use, the majority of medications used for asthma maintenance therapy are regarded as safe (Table 3). In 2008, the United States FDA proposed the elimination of current pregnancy categories A, B, C, D, and X in favor of more detailed information for drug safety in pregnancy in lactation. The new format of pregnancy and lactation labeling aims to provide improved information for risk analysis and patient counseling on package inserts for all drugs. With its final version currently undergoing review and clearance, these changes are expected to improve the data available for the sometimes difficult clinical decision-making regarding the use of prescription drugs during pregnancy and lactation[112,113].

Most evidence indicates that improved maternal and fetal outcomes are correlated with improved asthma control with medications during pregnancy, suggesting the greatest adverse fetal risks are associated with poor asthma control[48]. Outcomes can be further improved through appropriate disease monitoring and management, patient education, and optimization of nonpharmacologic interventions to improve asthma control[50,57-59].

CONCLUSION

As a common condition in pregnancy, asthma can have a significant impact on both maternal and fetal health. Frequent monitoring and optimization of both pharmacological and nonpharmacological modalities are crucial to maintaining asthma control throughout pregnancy. Asthma management should also focus on education to promote patient understanding of the risks associated with uncontrolled asthma, avoidance of asthma triggers, proper inhaler technique and appropriate adherence to asthma therapy. Although some patients and providers will be concerned about the use of asthma medications during pregnancy, evidence shows the greatest risk of adverse maternal and perinatal outcomes is associated with uncontrolled asthma, and that the benefits of maintaining asthma control outweigh the risks associated with medication use.

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