

Treatment of asthma during pregnancy and perinatal outcomes

Jennifer Altamura Namazy and Michael Schatz

Purpose of review

Asthma is the most common, potentially serious medical problem to complicate pregnancy. Women with asthma have been shown to be at increased risk of complications during pregnancy. Managing asthma during pregnancy is unique because the effect of both the illness and the treatment on the developing fetus as well as the patient must be considered. This review summarizes the recent studies addressing the effects of asthma or asthma medications on perinatal outcomes, including the 2004 Asthma and Pregnancy Working Group of the National Asthma Education and Prevention Program.

Recent findings

This review summarizes the recent studies addressing the effect of asthma or asthma medications on perinatal outcomes.

Summary

The prevalence of asthma in pregnant women appears to be increasing. Recent evidence supports that pregnant women with moderate to severe asthma may have an increased risk of adverse perinatal outcomes. The goal of asthma management during pregnancy is to optimize maternal and fetal health.

Keywords

asthma, corticosteroids, medications, pregnancy

Introduction

Asthma is the most common, potentially serious medical problem to complicate pregnancy. Studies have shown that pregnant women with asthma have an increased risk of adverse perinatal outcomes [1,2], while controlled asthma is associated with reduced risks [3].

Managing asthma during pregnancy is unique because the effect of both the illness and the treatment on the developing fetus as well as the patient must be considered.

The two main goals of asthma management during pregnancy are to optimize maternal and fetal health. In this review we will summarize recently published articles which have provided more insight into the relationship between asthma severity and perinatal outcomes and the possible mechanisms involved. We will also address the concern regarding the use of asthma medications during pregnancy, especially inhaled corticosteroids.

Prevalence of asthma during pregnancy is increasing

Previous estimates of asthma prevalence reported that between 4% and 7% of women suffer from asthma during pregnancy [1–5]. Recently, Kwon *et al.* [6] reviewed US national health surveys spanning 1997–2001. They found that asthma affected between 3.7% and 8.4% of pregnant women in the US. There was a twofold increase in the prevalence of asthma (2.9–5.8%) between 1976–80 and 1988–94. This study supports initial prevalence estimates but also suggests that they may, in fact, be conservative.

Perinatal outcomes in pregnant women with asthma

Controlled studies that have evaluated outcomes of pregnancy in women with asthma compared with those without the condition have suggested that maternal asthma may increase the risk of perinatal mortality, pre-eclampsia, low birth weight infants, and preterm births [7–11]. Linton and Peterson [8] also observed that asthma was a risk factor for cesarean delivery in one age group (25–29 years).

In a recent nested case–control study by Sorensen *et al.* [9], the authors tried to determine the extent to which maternal asthma is associated with an increased risk of preterm labor and delivery. The study included women

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Kaiser-Permanente Medical Center, San Diego, California, USA

Correspondence to Jennifer Altamura Namazy, 7060 Clairemont Mesa Blvd, San Diego, CA 92111, USA
Tel: +1 858 573 9213; e-mail: janamazy@yahoo.com

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who delivered prior to the completion of 37 weeks' gestation in a cohort population of 3253 pregnant women. In women with asthma there was a twofold increased risk of preterm delivery compared with women who had no history of the condition (OR = 2.03; 95% CI 1.01–4.09).

The observations that maternal asthma may increase the risk of perinatal complications is confirmed by one of the largest studies to date [10], which described the outcomes of pregnancy in 36 985 women identified as having asthma in either the Swedish Medical Birth Registry or the Swedish Hospital Discharge Registry. These outcomes were compared with the total of 1.32 million births that occurred in the Swedish population during the years of the study (1984–95). Pregnancies in women with asthma were significantly more likely to be complicated by preeclampsia, perinatal mortality, preterm birth, and low birth weight (but not congenital malformations). The study also suggests that patients with more severe asthma are at greater risk.

Mechanisms postulated to explain the possible increased perinatal risks of previous studies have included hypoxia and other physiologic consequences of poorly controlled asthma; medications used to treat asthma; and pathogenic or demographic factors associated with asthma but actually not caused by the disease or its treatment.

One study attempted to distinguish whether asthma, asthma symptoms, or asthma therapy influence pregnancy outcomes (specifically, preterm delivery and intrauterine growth restriction). Bracken *et al.* [11] recruited a group of 873 pregnant women with asthma who were classified by symptom severity and medication use (intermittent, mild persistent, moderate persistent, or severe persistent). About 50% of the study population were classified as 'intermittent asthmatics' (no asthma symptoms or treatment during their pregnancy). Increasing severity and symptoms were associated with fetal growth restriction. No specific medication type was observed to lead to an increased risk of fetal growth restriction. An increased risk of preterm delivery was associated with greater medication use, specifically, theophylline and oral corticosteroids.

These data suggest that poor asthma control, by causing acute or chronic maternal hypoxia, may be the most remedial responsible factor for impaired fetal growth and supports the important generalization that adequate asthma control during pregnancy is important in improving maternal fetal outcome. These data also raise the question regarding adverse effects of asthma medication during pregnancy, at least regarding preterm birth (see below).

Uncontrolled asthma increases perinatal risk

Several observations do support the hypothesis that uncontrolled asthma increases perinatal risks while controlled asthma reduces these risks. For example, studies have shown that better controlled asthma (defined by lack of acute episodes or higher maternal pulmonary function) lead to improved intrauterine growth (measured by birth weight or ponderal indices) [7,12].

In one of the first studies to determine pregnancy outcomes stratified by asthma severity (as reported by the National Asthma Education Program [1]), Dombrowski *et al.* [13•] conducted a multicenter, prospective, observational cohort study involving 16 centers between 1994 and 1999. Of all the outcomes explored (including preterm delivery, gestational diabetes, preeclampsia, preterm labor, chorioamnionitis, oligohydramnios, cesarean delivery, low birth weight, small for gestational age, and congenital malformations), only cesarean delivery rates were increased in the group with moderate to severe asthma. This may be due to the fact that study participants underwent asthma severity classification upon enrollment and were followed by physicians familiar with asthma treatment guidelines, which may have led to more optimal asthma control and fewer observed complications.

In a separate study of the same cohort of patients, Schatz *et al.* [14] reported the effects of pregnancy on asthma and related asthma morbidity to asthma severity. They observed that asthma morbidity (hospitalizations, unscheduled office visits or emergency department visits, oral corticosteroid use) correlated closely with asthma classification applied to the patients at entry; that is, those patients with mild asthma experienced fewer hospitalizations, unscheduled visits, oral corticosteroid courses and total exacerbations than those with moderate to severe asthma. An interesting finding was that about 30% of patients whose asthma was classified as mild at entry 'switched' categories during pregnancy to the moderate or severe groups. One of the most important conclusions to be drawn from this study is that pregnant patients, even with mild or well controlled asthma, need to be closely monitored with pulmonary function testing during pregnancy.

Most recently, using this same stratification process of asthma severity used in the above studies, Triche *et al.* [15•] examined the association of various aspects of asthma status, including diagnosis, overall severity, symptom severity, and treatment, on risk of preeclampsia. A total of 1708 pregnant women were included, of whom 656 had an asthma diagnosis. Of the 656 women with diagnosed asthma, 568 had symptoms during pregnancy, whereas 353 of 1052 women without an asthma diagnosis also experienced symptoms. Neither overall asthma

severity nor having a diagnosis of asthma was associated with an increased risk of preeclampsia in these women. However, having active asthma symptoms through pregnancy was associated with preeclampsia. Women using theophylline were at increased risk for preeclampsia, but no association was observed with other asthma medications. One of the greatest limitations of this study was that it relied solely on self-reported data. Women were not only responsible for reporting a diagnosis of asthma, but also any symptoms or medications used during pregnancy.

Efficacy and safety of inhaled corticosteroids during pregnancy

As mentioned above, another possible explanation for increased perinatal complications in the infants of mothers with asthma is maternal medication. Concern has been raised regarding a possible adverse effect of inhaled steroids on intrauterine growth because not only has oral steroid use been associated with reduced birth weight [16], but also inhaled steroids have been reported to reduce the growth rate in children, at least during the first year of exposure [17].

Much of the information available regarding the safety of various asthma medications comes from large cohort studies such as the Swedish Medical Birth Registry. This study provided information regarding the incidence of congenital malformations in those infants whose mothers were exposed to inhaled budesonide during pregnancy compared with infants of unexposed women. However, the effect of inhaled corticosteroids on the rate of preterm births, cesarean births, birth weight and length was still unknown. Three studies published in the last 2 years have shed more light on these concerns [18,19^{••},20[•]].

The first, by Norjavaara and Gerhardsson de Verdier [18], searched for an association between inhaled budesonide use during pregnancy and adverse perinatal outcomes. Data included information from 2968 pregnant women enrolled in the Swedish Medical Birth Registry who reported the use of inhaled budesonide. These women gave birth to infants of normal gestational age, birth weight, and length with no increased risk of stillbirths or multiple births.

Schatz *et al.* [19^{••}] evaluated the relationship between a variety of asthma medications and adverse perinatal outcomes. This cohort included over 2000 women from 16 centers of the National Institute of Child Health and Human Developmental Maternal Fetal Medicine Units Network. No significant relationships were found between adverse perinatal outcomes and the use of inhaled β -agonists, inhaled corticosteroids, theophylline, or cromolyn-nedocromil. There was an observed

increased risk of preterm and low birth weight infants associated with oral corticosteroid use. These findings are consistent with previous studies, but it remains to be determined whether oral corticosteroids directly cause these outcomes, or rather, serve as a marker for asthma uncontrolled enough to cause prematurity.

Most recently, pregnant women with asthma treated with inhaled steroids were enrolled in the Registry for Allergic and Asthmatic Pregnant Patients of the American College of Allergy Asthma and Immunology and the American Academy of Allergy Asthma and Immunology by the allergists managing their asthma. Namazy *et al.* [20[•]] described the incidence of small for gestational age infants, an important measure of intrauterine growth retardation, in the offspring of 396 exposed mothers enrolled into the Registry. Beclomethasone was the most commonly used inhaled steroid, and 20.2% of patients used more than one specific inhaled steroid during pregnancy. The incidence of small for gestational age infants was 7.1% (95% CI 5.0–10.1%) compared with the expected incidence of 10%. There was no significant relationship identified between specific inhaled steroid use or the dose of inhaled steroid used and the incidence of small for gestational age infants or mean birth weight.

In summary, the data provided by these studies suggest that the currently available inhaled steroids used at clinically relevant doses do not impair intrauterine growth. These data suggest that inhaled steroids should be used when indicated for the management of persistent asthma during pregnancy. This is supported by a prospective, double-blind, double placebo-controlled randomized clinical trial recently published by Dombrowski *et al.* [21[•]]. This type of study is generally not feasible to evaluate the safety of medications during pregnancy. However, the authors succeeded in comparing the efficacy of inhaled beclomethasone dipropionate with oral theophylline for the prevention of asthma exacerbations during pregnancy. The results demonstrated that there was no significant difference in the proportion of asthma exacerbations among the 194 women in the beclomethasone cohort versus the 191 in the theophylline cohort. Women in the theophylline cohort had an increased proportion of study visits with forced expiratory volume in 1 s (FEV1) less than 80% predicted, and a greater proportion discontinued study medications because of side effects. Compared with beclomethasone dipropionate, theophylline has the disadvantage of requiring serum level monitoring and has more frequent side effects. While studies are needed to investigate the efficacy of newer inhaled corticosteroids during pregnancy, this study does support previous guidelines that inhaled corticosteroids are the therapy of choice for persistent asthma during pregnancy.

Other medications commonly used during pregnancy: beta-agonists

β -agonist use was reported in over 600 patients in the Kaiser-Permanente prospective study of asthma during pregnancy [22]. The most commonly used β -agonists in that study were metaproterenol ($n = 309$), terbutaline ($n = 316$), and albuterol ($n = 129$). In the Michigan Medicaid Study, albuterol ($n = 1090$) was the most commonly used β -agonist [23]. These studies found no association between the use of β -agonists in pregnant women and an increased risk of congenital malformations or other adverse pregnancy outcomes.

Short-acting β -agonists are recommended as rescue therapy for all asthma patients, as well as in the management of acute asthma episodes. Albuterol is the only short-acting β -agonist currently available as a metered dose inhaler for which there are published human data during pregnancy.

Regarding long-acting β -agonists, animal studies have not been reassuring, and few human data exist on the safety of salmeterol or formoterol during pregnancy [24,25]. However, benefit–risk considerations may favor salmeterol’s use during pregnancy in those women whose asthma is not controlled by medium-dose inhaled steroids [26^{••}]. Although human gestational data are limited [24,25], salmeterol may be preferred because of longer availability in this country [26^{••}].

Nebulized ipratropium

Recent data have demonstrated that the bronchodilatory effect of ipratropium may be additive to that of inhaled β -agonists in the management of acute asthma [27–29]. Although there are no available human data, animal studies are reassuring [30]. Therefore, nebulized ipratropium can be considered in women presenting with acute asthma who do not improve substantially with the first inhaled β -agonist treatment [31].

Theophylline

Several studies have evaluated the risk of congenital malformations in infants of mothers using theophylline during pregnancy. No significant increased risk was reported in any of the studies [22,23]. Other perinatal outcomes have also been evaluated. As noted above, Triche *et al.* [15[•]] and Bracken *et al.* [11] found an association between maternal theophylline use and preterm birth (Bracken) and preeclampsia (Triche), but the number of mothers exposed to theophylline in their cohort was small ($n = 15$). One study demonstrated no increased risk of fetal deaths in infants of 410 exposed mothers [32]. Theophylline exposure was not independently associated with an increased risk of preeclampsia, preterm birth, or low birth weight infants in 429 women from the Kaiser study after adjusting for confounders

[22]. Theophylline may be used as alternative add-on therapy in addition to inhaled corticosteroid medication in those pregnant patients with moderate persistent asthma not controlled by inhaled steroids alone [26^{••}].

Cromolyn

Outcomes in infants of cromolyn-treated mothers have been evaluated in three studies [22,23,33]. The Kaiser study [22] reported no increased risks of any adverse perinatal outcomes in pregnancies or infants of 243 mothers who received cromolyn. The Michigan Medicaid study reported a relative risk of total congenital malformations of 0.9 in infants of 191 exposed mothers [23]. Finally, Wilson [33] reported an incidence of 1.4% congenital malformation in 296 full-term infants of cromolyn-treated mothers. Cromolyn may be used safely as an alternative to inhaled corticosteroids for those patients with mild persistent symptoms.

Leukotriene modifiers

Newer medications currently used in asthma management include the leukotriene modifier drugs (zileuton, zafirlukast, and montelukast). However, there are no published human data regarding the use of these medications during pregnancy. Animal studies have been reassuring for montelukast and zafirlukast but nonreassuring for zileuton.

While leukotriene modifier drugs have been shown to be effective in the management of mild–moderate persistent asthma in nonpregnant women, until reassuring gestational human data are available, current recommendations suggest consideration of zafirlukast or montelukast only as alternative therapy in patients with asthma who have shown a uniquely favorable response prior to becoming pregnant [26^{••}]. However, zileuton cannot be recommended for use at this time based on the available animal data.

Conclusion

Over the past few years, much has been learned that is relevant to the management of asthma in pregnancy. While the studies reviewed here provide more insight into the treatment of asthma during pregnancy, there are still more questions to be answered. Hopefully, these new data addressing the safety of contemporary asthma medications during pregnancy will be a helpful resource in the treatment of pregnant patients with asthma.

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