

EXPERT OPINION

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Safety of therapeutic options for treating asthma in pregnancy

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Introduction: Pregnancy may be complicated by new onset or preexisting asthma. Asthma is one of the most common potentially serious medical problems to complicate pregnancy, and it may adversely affect both maternal quality of life and perinatal outcomes. Optimal management of asthma during pregnancy is thus important for both mother and baby.

Areas covered: This article reviews the recognition and management of asthma during pregnancy, paying close attention to the general principles of asthma medication use during pregnancy. Further, the article reviews the safety of asthma medications commonly used during pregnancy. In this article, the most pertinent recent publications are reported. Electronic databases, such as PUBMED, were searched for terms pregnan* or perinat* or obstet* and asthma or wheeze and treatment.

Expert opinion: Because pregnant women are generally excluded from clinical trials, there is a lack of adequate safety information for most medications taken during pregnancy. One of the most important requirements for the future is the availability of further safety information for asthma medications used during pregnancy that can also account for asthma control.

Keywords: asthma, bronchodilators, inhaled corticosteroids, leukotriene modifiers, oral corticosteroids, pregnancy, treatment

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1. Introduction

Asthma is one of the most common potentially serious medical problems to complicate pregnancy and may adversely affect both maternal quality of life and perinatal outcomes. Optimal management of asthma during pregnancy is thus important for both mother and baby. This article reviews the safety of asthma medications commonly used during pregnancy.

Recent US national surveys report that the prevalence of asthma during pregnancy is about 8.8% [1]. This is supported by a recent study from the UK, which demonstrated that the prevalence of asthma during pregnancy was about 8.3% between 2000 and 2008 [2].

It has been shown that the course of asthma may worsen, improve or remain unchanged during pregnancy, and the overall data suggest that these various courses occur with approximately equal frequencies. This conclusion was reinforced by several studies using measures of asthma severity such as symptoms, pulmonary function and medication use [3]. Asthma appears more likely to become more severe or to worsen during pregnancy in women with more severe asthma before becoming pregnant [4].

Asthma exacerbations during pregnancy have been shown to occur at a rate of up to 6% from a UK database study of 12,828 pregnant women with asthma [2,5]. Risk factors for asthma exacerbations include: increasing asthma severity, nonadherence to medications, viral respiratory infections and possibly fetal sex [5].

One of the largest controlled studies that evaluated the outcomes of pregnancy recently described 26,586 women identified as having asthma in the Swedish

Article highlights.

- Asthma may worsen, improve or remain unchanged during pregnancy.
- Although data have been conflicting, the largest and most recent studies have suggested that maternal asthma increases the risk of adverse perinatal outcomes.
- Several observations support the hypothesis that uncontrolled asthma increases perinatal risks, whereas controlled asthma reduces these risks.
- There is a lack of adequate safety information for most medications taken during pregnancy as well as new medications, biologics and sublingual immunotherapy.
- Although more safety information is needed, the safety of currently available asthma medications has been reassuring.

This box summarizes key points contained in the article.

Medical Birth Registry [6]. Significantly increased rates of preeclampsia (adjusted odd ratio [AOR] = 1.15; 95% CI: 1.06 – 1.24), caesarean section (AOR = 1.29; 95% CI: 1.23 – 1.34), small for gestational age (SGA) (AOR = 1.23 95% CI: 1.13 – 1.33) and low birth weight infants (AOR = 1.32 95% CI: 1.20 – 1.45), were found in pregnancies of asthmatic versus control women. The risks appeared to be greater in patients with more severe asthma, which was confirmed in a more recent Swedish Birth Registry report. A recent meta-analysis, derived from a substantial body of literature spanning several decades and including very large numbers of pregnant women (over 1,000,000 for low birth weight and over 250,000 for preterm labor), indicated that pregnant women with asthma were at a significantly increased risk of a range of adverse perinatal outcomes including low birth weight, SGA, preterm labor and delivery and preeclampsia [7] as well as other adverse neonatal and maternal outcomes.

Mechanisms postulated to explain the increased perinatal risks in pregnant asthmatic women demonstrated in these studies included: i) hypoxia and other physiologic consequences of poorly controlled asthma; ii) medications used to treat asthma; and iii) pathogenic or demographic factors associated with asthma but not actually caused by the disease or its treatment, such as abnormal placental function.

In a cohort of over 13,000 pregnancies in asthmatic women, almost one-third of the women had uncontrolled asthma and up to 5% had severe asthma [8]. This study utilized information gathered from three databases, one of which included prescribed medications. Uncontrolled asthma was defined in this study as the use of more than 10 doses of short acting beta agonist per week and emergency department visit for asthma, hospital admission, or a filled prescription for an oral corticosteroid over a 12 month period.

Several prospective studies [9-17] have shown that the pregnant asthmatic with mild-to-moderate but actively managed asthma can have excellent maternal and fetal outcomes. In contrast, suboptimal control of asthma or more severe asthma

during pregnancy may be associated with increased maternal or fetal risks [15,18,19].

2. Asthma management

The ultimate goal of asthma therapy in pregnancy is maintaining adequate oxygenation of the fetus and preventing hypoxic episodes in the mother. The management of asthma can be summarized in four categories: assessment and monitoring, education of patients, control of factors contributing to severity and pharmacological therapy (Table 1) [20].

The first step is assessment of severity (in patients not already on controller medications) or assessment of control (in patients already on controller medications). Severity is assessed in untreated patients based on the frequency of daytime and nighttime symptoms, rescue therapy use, activity limitation and pulmonary function (ideally spirometry, minimally peak flow rate) Based on this severity assessment, controller therapy is initiated (Table 2). Patients should be monitored monthly for asthma control and, if not responding adequately to treatment, the patients should have their level of treatment adjusted.

A 2011 double-blind, parallel-group, controlled study by Powell *et al.* tested the measurement of fractional exhaled nitric oxide (FeNO) to guide management of pregnant asthmatics. FeNO concentration was used to adjust the dose of inhaled corticosteroids (ICS) (budesonide), and the asthma control questionnaire (ACQ) was used to adjust inhaled long-acting β -agonist (LABA) therapy (formoterol). The cut-off for dose increase was FeNO 16 ppb and ACQ > 1.5, respectively. The primary outcome was total asthma exacerbations. The authors found that the exacerbation rate was lower in the group using FeNO to adjust asthma therapies during pregnancy (0.288 exacerbations per pregnancy) compared with the control group (0.615 exacerbations per pregnancy) [21]. SABA use was significantly less in the FeNO group. Overall, 68% of women in the FeNO group were being treated with ICS at the end of the study compared with 42% in the control group. The mean daily inhaled corticosteroid dose was lower in the FeNO group than in the control group. More women received LABAs in the FeNO group than in the control group. Further studies will be necessary to confirm the generalizability of these findings.

3. Pharmacological therapy

Asthma medications generally are divided into long-term controller medications and rescue therapy. Long-term controller medications are used for maintenance therapy to prevent asthma manifestations and include ICS, cromolyn, LABAs, leukotriene receptor antagonists (LTRA), theophylline and omalizumab. Rescue therapy, most commonly with inhaled SABAs, provides immediate relief of symptoms. Oral corticosteroids can either be used as a form of rescue therapy or as chronic therapy for severe persistent asthma.

Table 1. Steps of asthma therapy during pregnancy*.

Step	Preferred controller medication	Alternative controller medication
1	None	–
2	Low-dose ICS	LTRA, theophylline
3	Medium-dose ICS	Low-dose ICS + either LABA, LTRA or theophylline
4	Medium-dose ICS + LABA	Medium-dose ICS + LTRA or theophylline
5	High-dose ICS + LABA	Omalizumab [‡]
6	High-dose ICS + LABA + oral prednisone	Omalizumab [‡]

*Data modified with permission from [59].

[‡]For patients with allergic asthma (FDA category B with ongoing safety studies).

ICS: Inhaled corticosteroids; LABAs: Long-acting β -agonists; LTRA: Leukotriene-receptor antagonists.

Table 2. Safety of oral corticosteroids during pregnancy.

Cohort			Case-control		
Study design	Ref.	OR (95% CI)*	Study design	Ref.	OR (95% CI)*
Preeclampsia	[24]	2.0 (1.1 – 3.6)	Cleft lip +/- palate	[60]	5.9 (1.7 – 20.3)
LBW	[24]	1.8 (1.1 – 2.9)	Cleft lip +/- palate	[61]	6.6 (1.4 – 29.8)
Preterm delivery	[16]	3.37(1.66 – 6.86)	Cleft lip +/- palate	[62]	4.3 (1.1 – 17.2)
Congenital malformations	[48]	1.45 (0.81 – 2.60)	Cleft lip +/- palate	[63]	2.59 (1.18 – 5.67)
			Cleft lip +/- palate	[49]	1.3 (0.6 – 2.8)

*Data taken from [64].

LBW: Low birth weight; OR: Odds ratio.

In a large US claims database cohort of 575,632 deliveries identified between 2001 and 2007, 9.7% ($n = 55,914$) of women were dispensed asthma medications during pregnancy. The overall prevalence of controller-only medication, rescue-only medication and combined controller and rescue medication was 0.6, 6.7 and 2.4%, respectively [22]. In a smaller UK cohort of deliveries, 14,141 (10.9%) were pregnancies resulting in which the mother had received a prescription for an asthma medication around the time of pregnancy. Of these, 68.4% received prescriptions for rescue medications and 41.2% received prescriptions for controller medications, specifically ICS [2]. Table 3 reviews the safety of commonly used asthma medications during pregnancy.

3.1 Inhaled corticosteroids

ICS are the mainstay of controller therapy during pregnancy. Many studies have shown no increased perinatal risks (including preeclampsia, preterm birth, low birth weight and congenital malformations) associated with gestational use of ICS [16,23–28]. A recent study of over 4000 women who used ICS during pregnancy found no increased risk of perinatal mortality associated with gestational ICS use [29].

Several large studies support the lack of association of ICS use with total or specific malformations [28,30–35]. One study [33] has suggested a possible relationship between high-dose ICS and total malformations, but confounding by severity is an alternative explanation, based on the relationships between exacerbations and congenital malformations demonstrated by the same group [19]. Another recent study associated the use

of > 125 mcg/day (fluticasone equivalent) with a nonsignificant trend of increased risk of low birth weight, preterm delivery and SGA [34] but confounding by severity may explain this trend as well. A recent meta-analysis of cohort studies found no significant increased risk of congenital malformations, stillbirth or cesarean section in pregnant asthmatics who used ICS during pregnancy compared to those who did not [35,36]. Because budesonide has been the specific ICS with the largest amount of published human gestational safety data, it is considered the preferred ICS for asthma treatment during pregnancy. However, existing data do not suggest that the other ICS preparations are unsafe. A recent study did not demonstrate any differences in the incidences of low birth weight, preterm birth or SGA in the pregnancies of women treated with inhaled budesonide ($n = 608$) compared to women treated with inhaled fluticasone ($n = 3190$) during pregnancy [37]. A systematic review of the literature regarding beclomethasone, the most common ICS used during pregnancy prior to 2000, was recently performed and did not show evidence of increased risk of adverse outcomes in pregnant asthmatics [38]. Therefore, ICS other than budesonide may be continued in patients who were well controlled by these agents prior to pregnancy, especially if it is thought that changing formulations may jeopardize asthma control.

3.2 Inhaled SABAs

Inhaled SABAs are the preferred rescue therapy for asthma during pregnancy. Inhaled albuterol is the first-choice SABA for pregnant women because it has been studied most

Table 3. Safety of commonly used medications for the treatment of asthma during pregnancy.

Drug category	Specific drug (FDA category)	Perinatal outcome
Inhaled bronchodilators Short-acting bronchodilators	Albuterol (C)	Reassuring human data; some associations with specific malformations but may be by chance or confounding by severity
Long-acting bronchodilators	Formoterol (C) Salmeterol (C)	Small amount of human data has been reassuring
Theophylline		No increase in congenital malformations; toxicity may be an issue
Systemic corticosteroids		Associated with oral clefts, low birth weight, preterm birth, preeclampsia and intrauterine growth retardation. Some of these effects may be confounding by severity
Inhaled corticosteroids	Budesonide-B Beclomethasone-C Fluticasone-C Mometasone-C Triamcinolone -C	Substantial reassuring data. Risk of increased malformations with high dose but may be confounding by severity. Most data are for budesonide
Leukotriene receptor antagonist	Montelukast-B Zafirlukast-B	Moderate amount of reassuring data
5-LO inhibitor Anti-IgE	Zileuton-C Omalizumab-B	Animal studies not reassuring; no human data Increased risk of low birth weight and preterm birth but may be confounding by severity

Adapted with permission from [65].

5-LO: 5-lipoxygenase.

extensively [23], although other agents may be used if uniquely helpful or well tolerated.

A series of case-control studies using data from the National Birth Defects Prevention Study from 1997 to 2005 have reported the use of bronchodilators during pregnancy to be associated with an increased risk of selected specific congenital defects: gastroschisis (odds ratio [OR] = 2.1; 95% CI: 1.2 – 3.6) [39], cardiac defects (OR = 2.20; 95% CI: 1.05 – 4.61) [39,40], esophageal atresia (OR = 2.39; 95% CI: 1.23 – 4.66), omphalocele (OR = 4.13; 95% CI: 1.43 – 11.95) [41] and cleft lip (OR = 1.77; 95% CI: 1.08 – 2.88) [42]. Another case-control study by Munsie *et al.* compared asthma medication use in pregnancy among mothers of 2711 infants born with orofacial clefts and 6482 infants born without malformations. There was a statistically significant association between bronchodilator use and cleft lip (adjusted OR = 1.77; 95% CI: 1.08 – 2.88). However, as noted above, these observations may be a result of uncontrolled confounding by indication. Asthma exacerbations may be associated with both increased use of bronchodilators and congenital malformations. In addition, factors such as obesity or lower household socioeconomic status may be associated with both more severe asthma requiring more bronchodilators and congenital malformations.

In a meta-analysis of cohort studies from 1975 to 2012, there appeared to be no increased risk of congenital malformations, caesarean section or postpartum hemorrhage in pregnant asthmatics who used inhaled bronchodilators during pregnancy [35,36]. However, these data were from a small number of studies for caesarean section (n = 3), postpartum

hemorrhage (n = 2) and congenital malformations (n = 3). There was a significantly decreased risk of gestational diabetes among users of bronchodilators compared to non-users (relative risk [RR] = 0.64; 95% CI: 0.57 – 0.72) in two studies.

3.3 Inhaled LABAs

The use of LABAs is the preferred add-on controller therapy for asthma during pregnancy. This therapy should be added on when patients' symptoms are not controlled with the use of medium-dose ICS. Because LABAs and SABAs have similar pharmacology and toxicology, LABAs are expected to have a safety profile during pregnancy similar to that of albuterol. Two LABAs are available: salmeterol and formoterol. Limited observational data exist on their use during pregnancy. Cossette *et al.* observed no statistically significant differences between salmeterol (n = 385) and formoterol (n = 162) use during pregnancy in regard to low birth weight, preterm or SGA infants [37].

A possible association between LABA and an increased risk of severe and even fatal asthma exacerbations has been observed in non-pregnant patients. As a result, LABAs are no longer recommended as monotherapy for the treatment of asthma and are available in fixed combination preparations with ICS. Expert panels suggest that the benefits of the use of LABA appear to outweigh the risks as long as they are used concurrently with ICS [43].

3.4 Leukotriene modifiers

Leukotrienes are 5-lipoxygenase-derived inflammatory mediators involved in allergic diseases such as asthma and allergic

rhinitis. It has been shown that 5-lipoxygenase product formation in stimulated blood of pregnant women is significantly higher than in non-pregnant females. Interestingly, granulocytes from non-pregnant women produced more leukotrienes when resuspended in plasma of pregnant women, suggesting possible stimulatory effects of plasma during pregnancy [44].

Both zafirlukast and montelukast are selective-LTRAs indicated for the maintenance treatment of asthma. Both are pregnancy category B; however, data on the use of LTRA during human pregnancy are limited. One study of 180 montelukast-exposed pregnancies found no increase in baseline rate of major congenital malformations [45]. In a recent retrospective insurance claims cohort analysis of > 50,000 pregnancies, with a focus on evaluating the risk of limb reduction defects, three cohorts were compared: those prescribed montelukast anytime in pregnancy ($n = 1535$), those prescribed ICS anytime in pregnancy ($n = 3918$) and a reference group of non-asthmatic women ($n = 38,828$). Congenital malformations in the montelukast cohort were reported at a rate similar to the other two cohorts [46]. Zileuton, a 5-lipoxygenase inhibitor, is generally avoided during pregnancy based on nonreassuring animal studies.

3.5 Cromolyn and theophylline

Based on the superiority of ICS over cromolyn and theophylline in the prevention of asthma symptoms, cromolyn and theophylline are considered alternative, but not preferred, treatments for mild persistent asthma. Theophylline is also an alternative, but not a preferred, add-on treatment for moderate-to-severe persistent asthma. Reassuring data on the use of cromolyn and theophylline in pregnant women have been published [43]. A prospective, double-blind, double placebo-controlled randomized clinical trial of pregnant women with moderate asthma using inhaled beclomethasone dipropionate versus theophylline was performed. There was no significant difference in the proportion of asthma exacerbations among the 194 women in the beclomethasone cohort (18%) versus the 191 in theophylline cohort (20.4%, $RR = 0.9$; 95% CI: 0.6 – 1.3). There were no significant differences in maternal or perinatal outcomes [47]. Theophylline use is also limited by its many adverse side effects and potential drug interactions resulting in possible toxicity. Serum levels should be monitored during pregnancy and maintained between 5 and 12 mcg/ml. Cromolyn is now only available in the USA as a nebulizer solution.

3.6 Oral corticosteroids

Some patients with severe asthma may require regular oral corticosteroids use to achieve adequate asthma control. Oral corticosteroids are also typically part of the discharge regimen after an acute asthma episode. Oral corticosteroid use has been associated with an increased risk of preterm birth [16,23] and low birth weight infants [23] in 185 exposed women. An increased risk of orofacial clefts was reported in a meta-

analysis of case-control studies [48] but was not supported by a small cohort study by the same authors. The increased risk was also not confirmed in a recent large cohort study [32]. In addition, the US National Birth Defects Prevention case-control study, which had demonstrated an increased risk of oral clefts in data from 1997 to 2002 recently published an analysis of data from 2003 to 2009 and found no evidence of a link between oral clefts and corticosteroids [49]. Much of the data on cleft lip/cleft palate (Table 3) came from studies in which little information was provided for the indication of treatment. A meta-analysis of cohort studies between 1975 and 2012 found that pregnant asthmatic women who used oral corticosteroids during pregnancy had an increased risk of preterm delivery (< 37 completed weeks gestation) ($RR = 1.51$; 95% CI: 1.15, 1.98) and low birth weight infants ($RR = 1.41$; 95% CI: 1.04, 1.93) [50].

As each of these potential risks of adverse pregnancy outcomes with oral corticosteroid use would likely be outweighed by the potential risks of a severe asthma exacerbation, which include maternal or fetal mortality, oral corticosteroids are recommended when indicated for the management of severe asthma during pregnancy [43].

3.7 Omalizumab

One of the treatment options for the moderate-to-severe persistent allergic asthmatic is omalizumab. It is a recombinant DNA-derived humanized IgG1k mAb that specifically binds to free human IgE in the blood. It currently has an FDA category B classification based on reassuring animal studies and the expected limited placental passage in the first trimester due to the size of the molecule. A single-arm observational study of 156 pregnant asthmatic women exposed to omalizumab within 8 weeks prior to conception or at any time during pregnancy reported no increased risk of congenital malformations or low birth weight. The rates of prematurity (< 37 weeks gestation) and SGA were not unlike those seen in other studies of severe pregnant asthmatics [51]. This is an ongoing registry with a target goal of enrolling 250 asthmatic women treated with omalizumab during pregnancy.

4. Asthma education and adherence

There are additional factors that may contribute to the clinical course of asthma during pregnancy and are related to the optimal use of medications. Adherence to therapy can change during pregnancy with a corresponding change in asthma control. Most commonly observed is decreased adherence as a result of a mother's concerns about the safety of medications for the fetus. One study found that women with asthma significantly decreased their asthma medication use from 5 to 13 weeks of pregnancy. During the first trimester, there was a 23% decline in ICS prescriptions, a 13% decline in SABA prescriptions and a 54% decline in rescue oral corticosteroid prescriptions [52]. Lim *et al.* [53] tried to elucidate the

reasons for nonadherence in this particular population of patients. Data were obtained from interviews with pregnant asthmatic subjects. Concerns about medication use, specifically glucocorticosteroids, overshadowed the potential risk of uncontrolled asthma. Similarly, in another study, women perceived there was a 42% teratogenic risk with oral corticosteroids, 12% teratogenic risk with ICS and 5% teratogenic risk with SABA [54].

Physician reluctance to treat may also affect the severity of asthma during pregnancy. A recent study found that that < 40% of women who classified themselves as 'poorly controlled' reported use of a controller medication during pregnancy [55]. Another study identified 51 pregnant women and 500 non-pregnant women presenting to the emergency department with acute asthma. Although asthma severity appeared to be similar between the two groups based on peak flow rates, pregnant women were significantly less likely to be discharged on oral steroids (38 vs 64%) [56]. Presumably related to this undertreatment, pregnant women were three times more likely than non-pregnant women to report an ongoing exacerbation 2 weeks later.

Uninformed decisions by pregnant asthmatic patients or those managing their asthma may lead to exacerbations of asthma during pregnancy and to potentially adverse perinatal outcomes. Therefore, asthma education is a critical component in the management of the pregnant asthmatic, especially regarding the potential effects of uncontrolled asthma on the baby and the self-management strategies such as proper inhaler technique, adherence and appropriate responses to increased symptoms. A recent study by Lim *et al.* suggests that a multidisciplinary approach may be ideal in managing these patients [57]. The authors performed a randomized control trial wherein 60 pregnant asthmatics were randomized to either an intervention or regular care group and were followed prospectively during pregnancy. The primary outcome was asthma control as defined by the ACQ. The intervention group received a multidisciplinary, pharmacist-led intervention that included asthma education (review of medications and inhaler technique, trigger avoidance, smoking cessation), monitoring (home monitoring of lung function), feedback (assessment of asthma control and step up therapy as needed) and monthly follow up. The intervention group demonstrated a significant reduction in ACQ scores throughout pregnancy, indicating improved asthma control.

5. Conclusion

Asthma is a common medical problem that may worsen during pregnancy. In addition to affecting maternal quality of life, uncontrolled asthma may lead to adverse perinatal outcomes. Awareness of proper treatment options for asthma during pregnancy is important for clinicians who care for pregnant patients in order to optimize maternal and infant health. Although more safety information is needed,

appropriate use of currently available asthma medications has been associated with a high likelihood of an uncomplicated pregnancy and a healthy infant.

6. Expert opinion

Because pregnant women are generally excluded from clinical trials, there is a lack of adequate safety information for most medications taken during pregnancy as well as new medications, biologics and sublingual immunotherapy. Moreover, the existing observational data are often limited by the lack of information regarding asthma control as mentioned above. Similarly, more studies are needed with information about the effect of asthma severity and control on perinatal outcomes, in general and as a potential confounder in the medication data. There is also a lack of information on the mechanism of worsening of asthma during pregnancy that may have therapeutic implications.

It has been shown that pregnant women are at an increased risk for viral-induced respiratory infections. More research is needed on the prevention of viral-induced asthma exacerbations during pregnancy.

More clinical trials are needed for addressing the non-medication aspects of asthma management, including assessment and monitoring, self-management education and adherence.

One of the most important needs for the future is the availability of further safety information on asthma medications used during pregnancy that can also account for asthma control. The Vaccines and Medications in Pregnancy Surveillance System (VAMPSS) is a new nationwide post-marketing surveillance system established to comprehensively monitor the use and safety of vaccines and medications during pregnancy. The VAMPSS system provides a coordinated effort involving both prospective registry surveillance and case-control surveillance. One focus of VAMPSS is on asthma medications, and parameters of asthma control are also assessed in both arms of the VAMPSS system [58].

Another priority for future research is developing methods for overcoming barriers to asthma control during pregnancy. These barriers include cigarette smoking, clinician undertreatment, patient nonadherence and viral infections. Optimal smoking cessation strategies, clinician education, effective patient education and support and means of preventing viral infections or at least reducing their adverse effect on asthma should increase the likelihood of adequately controlled gestational asthma.

Declaration of interest

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