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# The safety of asthma medications during pregnancy: an update for clinicians

Jennifer A. Namazy and Michael Schatz

**Abstract:** Pregnancy may be complicated by new onset or preexisting asthma. This article reviews the recognition and management of asthma during pregnancy, as well as general principles of asthma medication use during pregnancy.

**Keywords:** asthma, pregnancy, rhinitis

## Introduction

Asthma is one of the most common potentially serious medical problems to complicate pregnancy, and asthma 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 management of asthma during pregnancy and the safety of asthma medications.

Recent US national surveys, between 2000 and 2003, report that the prevalence of asthma during pregnancy is about 8.8% [Kwon *et al.* 2006]. 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 [Charlton *et al.* 2013]. 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 [Schatz *et al.* 2003]. Asthma also appears to be more likely to be more severe or to worsen during pregnancy in women with more severe asthma before becoming pregnant [Belanger *et al.* 2010].

One of the largest controlled studies that have evaluated outcomes of pregnancy described 36,985 women identified as having asthma in the Swedish Medical Birth Registry. These outcomes were compared with the total of 1.32 million births that occurred during the years of the study

(1984–1995). Significantly increased rates of preeclampsia [odds ratio (OR) 1.15], perinatal mortality (OR 1.21), preterm births (OR 1.15) and low birth weight infants (OR 1.21), but not congenital malformations (OR 1.05), were found in pregnancies of patients with asthma *versus* control women [Kallen *et al.* 2000]. The risks appeared to be greater in patients with more severe asthma, which was confirmed in a more recent Swedish Birth Registry report [Kallen and Otterblad Olausson, 2007a]. 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), indicates that pregnant women with asthma are at a significantly increased risk for a range of adverse perinatal outcomes, including low birth weight, small for gestational age, preterm labor and delivery, and preeclampsia [Murphy *et al.* 2011], as well as other neonatal and maternal outcomes.

Mechanisms postulated to explain the possible increased perinatal risks in pregnant women with asthma demonstrated in 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 not actually caused by the disease or its treatment, such as abnormal placental function.

Several prospective studies [Triche *et al.* 2004; Jana *et al.* 1995; Stenius-Aarniala *et al.* 1988, 1996; Minerbi-Codish *et al.* 1998; Mahrshahi

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*et al.* 2003; Dombrowski *et al.* 2004; Bracken *et al.* 2003; Schatz *et al.* 1995] have shown that the pregnant woman with asthma of mild to moderate severity 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 risk [Dombrowski *et al.* 2004; Firoozi *et al.* 2010; Blais and Forget, 2008].

### Asthma management

The ultimate goal of asthma therapy in pregnancy is maintaining adequate oxygenation of the fetus, 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 pharmacologic therapy [National Asthma Education and Prevention Program 2007]

The first step is assessment of severity (inpatients 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) (Table 2). Based on this severity assessment, controller therapy is initiated. Patients should be monitored monthly for asthma control (Table 3) and, if not responding adequately to treatment, should have their level of treatment adjusted (Table 4). A 2011 double-blind, parallel-group, controlled study by Powell and colleagues tested the measurement of fractional exhaled nitric oxide (FeNO) to guide the management of pregnant women with asthma. 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 [Powell *et al.* 2011]. Further studies will be necessary to confirm the generalizability of these findings.

### Pharmacologic 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 inhaled corticosteroids (ICS), cromolyn, long-acting  $\beta$  agonists (LABAs), leukotriene receptor antagonists (LTRAs),

**Table 1.** Adverse maternal and fetal outcomes reported to be increased in pregnancies of women with asthma.

|                           |
|---------------------------|
| Gestational diabetes      |
| Cesarean section          |
| Neonatal death            |
| Low birth weight          |
| Preterm birth             |
| Small for gestational age |
| Congenital anomalies      |

theophylline and omalizumab. Rescue therapy, most commonly inhaled short-acting  $\beta$  agonists (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.

### 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 ICS [Schatz *et al.* 1997, 2004; Norjavaara and de Verdier, 2003; Bracken *et al.* 2003; Martel *et al.* 2005; Kallen *et al.* 1999; Bakhireva *et al.* 2005]. A recent study of over 4000 women who used ICS during pregnancy found no increased risk of perinatal mortality associated with gestational ICS use [Breton *et al.* 2010]. Several large studies support the lack of association of ICS use with total or specific malformations [Kallen and Otterblad Olausson, 2007b; Hyiid and Mølgaard-Nielsen, 2011; Blais *et al.* 2007]. One study [Blais *et al.* 2009] suggested a relationship between high-dose ICS and total malformations, but confounding by severity is a possible explanation, based on the relationships between exacerbations and congenital malformations demonstrated by the same group [Blais and Forget, 2008]. Another recent study associated use of more than 125  $\mu\text{g/day}$  (fluticasone equivalent) with a nonsignificant trend of increased risk of low birth weight, preterm delivery, and small for gestational age [Cossette *et al.* 2013].

A recent meta-analysis of cohort studies found no significant increased risk of congenital malformations, stillbirth or cesarean section in pregnant women with asthma who used ICS during pregnancy *versus* those who did not [Murphy *et al.* 2013; Wang *et al.* 2014].

**Table 2.** Classification of asthma severity in pregnant patients.

| Asthma severity     | Symptom frequency                        | Nighttime awakening         | Interference with normal activity | FEV <sub>1</sub> or peak flow (predicted percentage of personal best) |
|---------------------|------------------------------------------|-----------------------------|-----------------------------------|-----------------------------------------------------------------------|
| Intermittent        | 2 days per week or less                  | Twice per month or less     | None                              | More than 80%                                                         |
| Mild persistent     | More than 2 days per week, but not daily | More than twice per month   | Minor limitation                  | More than 80%                                                         |
| Moderate persistent | Daily symptoms                           | More than once per week     | Some limitation                   | 60–80%                                                                |
| Severe persistent   | Throughout the day                       | Four times per week or more | Extremely limited                 | Less than 60%                                                         |

Data from Dombrowski *et al.* (2008).  
FEV<sub>1</sub>, forced expiratory volume in the first second of expiration.

**Table 3.** Assessment of asthma control in pregnant women.

| Variable                                                                  | Well controlled asthma    | Asthma not well controlled | Very poorly controlled asthma |
|---------------------------------------------------------------------------|---------------------------|----------------------------|-------------------------------|
| Frequency of symptoms                                                     | ≤2 days/week              | >2 days/week               | Throughout the day            |
| Frequency of nighttime awakening                                          | ≤2 times/month            | 1–3 times/week             | ≥4 times/week                 |
| Interference with normal activity                                         | None                      | Some                       | Extreme                       |
| Use of short-acting $\beta$ agonist for symptoms control                  | ≤2 days/week              | >2 days/week               | Several times/day             |
| FEV <sub>1</sub> or peak flow (% of the predicted or personal best value) | >80                       | 60–80                      | < 60                          |
| Exacerbation requiring use of systemic corticosteroid (no.)               | 0–1 in the past 12 months | ≥2 in the past 12 months   | ≥2 in the past 12 months      |

Data from Schatz and Dombrowski (2009).  
FEV<sub>1</sub>, forced expiratory volume in the first second of expiration.

**Table 4.** 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 from Schatz and Dombrowski (2009).  
\*For patients with allergic asthma (US Food and Drug Administration category B with ongoing safety studies).  
ICS, inhaled corticosteroid; LABA, long-acting  $\beta$  agonist; LTRA, leukotriene-receptor antagonist.

Because it has the most published human gestational safety data, budesonide is considered the preferred ICS for asthma during pregnancy. However, existing data do not suggest that the other ICS preparations are unsafe. Therefore, ICS other than budesonide may be continued in patients whose asthma was well controlled by these agents prior to pregnancy, especially if it is

thought that changing formulations may jeopardize asthma control. Doses of ICS are categorized as low, medium, and high (Table 5).

#### *Inhaled $\beta$ agonists*

Inhaled SABAs are the preferred rescue therapy for asthma during pregnancy. Inhaled albuterol

**Table 5.** Comparative daily doses for inhaled corticosteroids.

| Corticosteroid     | Amount                | Low dose  | Medium dose          | High dose          |
|--------------------|-----------------------|-----------|----------------------|--------------------|
| Beclomethasone HFA | 40 µg per puff        | 2–6 puffs | More than 6–12 puffs | More than 12 puffs |
|                    | 80 µg per puff        | 1–3 puffs | More than 3–6 puffs  | More than 6 puffs  |
| Budesonide         | 90 µg per inhalation  | 2–6 puffs | More than 6–12 puffs | More than 12 puffs |
|                    | 180 µg per inhalation | 1–3 puffs | More than 3–6 puffs  | More than 6 puffs  |
| Ciclesonide        | 80 µg per actuation   | 2–4 puffs | More than 4–8 puffs  | More than 8 puffs  |
|                    | 160 µg per actuation  | 1–2 puffs | More than 2–4 puffs  | More than 4 puffs  |
| Flunisolide HFA    | 80 µg per puff        | 4 puffs   | More than 4–8 puffs  | More than 8 puffs  |
| Fluticasone HFA    | 44 µg per puff        | 2–6 puffs | –                    | –                  |
|                    | 110 µg per puff       | 2 puffs   | More than 2–4 puffs  | More than 4 puffs  |
|                    | 220 µg per puff       | 1 puff    | More than 1–2 puffs  | More than 2 puffs  |
| Fluticasone DPI    | 50 µg per inhalation  | 2–6 puffs | –                    | –                  |
|                    | 100 µg per inhalation | 1–3 puffs | More than 3–5 puffs  | More than 5 puffs  |
|                    | 250 µg per inhalation | 1 puff    | More than 1–2 puffs  | More than 2 puffs  |
| Mometasone         | 110 µg per actuation  | 2 puffs   | 3–4 puffs            | More than 4 puffs  |
|                    | 220 µg per actuation  | 1 puff    | 2 puffs              | More than 2 puffs  |

Data from EPR3 [Busse, 2005] and Kelly [2009] 43: 519.

\*Total daily puffs are usually divided into a twice-per-day regimen.

DPI, dry powder inhaler; HFA, hydrofluoroalkane.

is the first-choice SABA for pregnant women because it has been studied most extensively [Schatz *et al.* 2004], 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 infant gastroschisis [OR 2.1; 95% confidence interval (CI) 1.2–3.6] [Lin *et al.* 2008], cardiac defects (OR 2.20; 95% CI 1.05–4.61) [Lin *et al.* 2008, 2009], esophageal atresia (OR 2.39; 95% CI 1.23–4.66), omphalocele (OR 4.13; 95% CI 1.43–11.95) [Lin *et al.* 2009] and cleft lip (OR 1.77; 95% CI 1.08–2.88) [Lin *et al.* 2012]. However, this observation may be a result of confounding. 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 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 women with asthma who used inhaled bronchodilators during pregnancy [Murphy *et al.* 2013].

In general, patients should use up to two treatments of inhaled albuterol (two to six puffs) or nebulized albuterol at 20 min intervals for most mild to moderate symptoms; higher doses can be used for severe symptom exacerbations.

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. A possible association between LABAs and an increased risk of severe and even fatal asthma exacerbations has been observed in nonpregnant 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 LABAs appear to outweigh the risks as long as they are used concurrently with ICS [Busse, 2005].

#### *Leukotriene modifiers*

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 LTRAs during pregnancy are more limited. One study of 180 montelukast-exposed pregnancies found no increase in baseline rate of major congenital malformations [Sarkar *et al.* 2009]. In a recent retrospective insurance claims cohort analysis of more than 50,000 pregnancies, there were three cohorts: montelukast (1535), ICS (3918), and a reference group. Congenital malformations in the montelukast cohort were reported at a rate similar to the other two cohorts [Nelsen *et al.* 2012]. Montelukast is available as a once daily medication with doses variable based on age. For adults, the typical dose is 10 mg daily. Zileuton, a 5-lipoxygenase inhibitor, is generally avoided during pregnancy based on nonreassuring animal studies.

#### *Cromolyn and theophylline*

Based on the superiority of ICS over cromolyn and theophylline in the prevention of asthma symptoms, they are considered alternative treatments for mild persistent asthma. Theophylline is also an alternative, but not 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 [Busse, 2005]. 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 µg/ml. Cromolyn is now only available in the USA as a nebulizer solution.

#### *Oral corticosteroids*

Some patients with severe asthma may require regular oral corticosteroid use to achieve adequate asthma control. Oral corticosteroids are also typically part of the discharge regimen after an acute asthma episode. Doses are typically prednisone 40–60 mg in a single dose or two divided doses for 3–10 days. Oral corticosteroid use has been associated with an increased risk of preterm birth [Bracken *et al.* 2003; Schatz *et al.* 2004] and low birth weight infants [Schatz *et al.* 2004] in 52–185 exposed women. An increased risk of orofacial clefts was reported in a meta-analysis of case-control studies [Park-Wyllie *et al.* 2000], but this increased risk was not confirmed in a recent large cohort study [Hyiid and Mølgaard-Nielsen, 2011]. Since these risks would be less than 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 [Busse, 2005].

#### *Omalizumab*

One of the treatment options for the patient with moderate to severe persistent allergic asthma is omalizumab (Xolair, Genentech). It is a recombinant DNA-derived humanized immunoglobulin (Ig)-G1k monoclonal antibody that specifically binds to free human IgE in the blood. It currently has a US Food and Drug Administration category B classification based on reassuring animal studies. A single-arm observational study of 156 pregnant women with asthma 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 small for gestational age were not unlike those seen in other studies of pregnant women with severe asthma (Namazy *et al.* 2012). This is an ongoing registry with a target goal of enrolling 250 women with asthma treated with omalizumab during pregnancy.

#### *Asthma education and adherence*

There are additional factors that may contribute to the clinical course of asthma during pregnancy. Pregnancy may be a source of stress for many women, and this stress can aggravate asthma. One study found that increased anxiety regarding asthma control increased the odds of subsequent exacerbation (OR 1.05; 95% CI 1.01–1.08) [Powell *et al.* 2013]. 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 corticosteroid prescriptions [Enriquez, 2006]. Lim and colleagues tried to elucidate the reasons for non-adherence in this particular population of patients [Lim *et al.* 2012]. Data were obtained from interviews with pregnant women with asthma. 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 for oral corticosteroids, a 12% teratogenic risk for ICS, and a 5% teratogenic risk for SABAs [Powell *et al.* 2013].

Physician reluctance to treat may also affect the severity of asthma during pregnancy. A recent study found that less than 40% of women who classified themselves as having 'poorly controlled' asthma reported use of a controller medication during pregnancy [Louik *et al.* 2010]. Another study identified 51 pregnant women and 500 nonpregnant 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% *versus* 64%). Presumably related to this under treatment, pregnant women were three times more likely than nonpregnant women to report an ongoing exacerbation 2 weeks later [Cydulka *et al.* 1999; McCallister *et al.* 2011].

Uninformed decisions by pregnant women with asthma or those managing their asthma may lead to exacerbations of asthma during pregnancy and potentially adverse perinatal outcomes. Therefore, asthma education is a critical component in the management of the pregnant woman with asthma, 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 and colleagues suggests that a multidisciplinary approach may be ideal in managing these patients [Lim *et al.* 2014].

Smokers must be encouraged to discontinue smoking. All patients should try to avoid exposure to environmental tobacco smoke and other potential irritants as much as possible.

## 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.

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