

Update in the Treatment of Asthma During Pregnancy

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Abstract

Asthma is the most common potentially serious medical problem to complicate pregnancy. Recent reports suggest that 7 of every 100 pregnant women suffer from asthma during pregnancy. Asthmatic women have been shown to be at an increased risk of complications during pregnancy. This may be secondary to inadequately controlled asthma or perhaps the result of the effects of certain asthma medications taken during pregnancy. The choice to use a specific medication during pregnancy is based on available human and animal data. Much of the information currently available regarding the safety of various asthma medications during pregnancy comes from several large cohort studies. This article reviews the specific aspects of pharmacological therapy during pregnancy as provided in the recommendations of the joint ad hoc committee of the American College of Allergy Asthma and Immunology and the American College of Obstetricians and Gynecologists. This article presents practical strategies for the management of asthma in our pregnant patients.

Index Entries

Asthma; pregnancy; birth weight; medications; corticosteroids.

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Introduction

Asthma is the most common potentially serious medical problem to complicate pregnancy. Recent reports suggest that 7 of every 100 pregnant women suffer from asthma during their pregnancy (1).

Studies have shown that pregnant asthmatic women have an increased risk of adverse perinatal outcomes (2,3) but that controlled asthma is associated with reduced risks (4). This article reviews the specific aspects of pharmacological therapy during pregnancy.

The two main goals of asthma management during pregnancy are to optimize maternal and fetal health. By preventing acute episodes and maximizing maternal lung function, one should prevent asthma symptoms as well as maternal hypoxia, which could lead to adverse effects on fetal development.

Risks of Uncontrolled Asthma

Numerous studies have suggested that maternal asthma may increase the risks of perinatal mortality, preeclampsia, low birth weight and/or preterm birth (2). Although some of the past data have been conflicting in this area, the largest and most recent population-based cohort study confirms all of the above findings (3). Several studies have suggested that more severe asthma confers the greatest risk (2,3). Definitive clinical trials to evaluate the risk of controlled vs uncontrolled asthma would be unethical because they would involve assigning patients to an "uncontrolled" status.

Several observations do support the hypothesis that uncontrolled asthma increases perinatal risks and better controlled asthma reduces these risks. Because severe acute maternal asthma has been associated with maternal mortality, fetal mortality, or both (2), it is assumed that preventing asthma from becoming that acutely and severely uncontrolled would prevent such mortality. Three studies show 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) (2,4). Finally, several studies in which the asthma was prospectively managed by specialists during pregnancy do not show an increase in adverse fetal outcomes compared to control pregnancies (2). These observations suggest that any possible risk of asthma medications must be balanced against the risk of uncontrolled asthma, particularly regarding perinatal mortality and intrauterine growth. This information also supports the recommendation that optimal asthma control must be a primary goal of gestational asthma therapy.

Studying Medications During Pregnancy

The choice to use a specific medication during pregnancy is based on available human and animal data. Human studies exist in the form of case reports, cohort studies, and case control studies (5,6). The gold standard for medical human experimental studies is the randomized clinical trial. This type of study generally is not feasible to evaluate the safety of medications during pregnancy, partly because it would require a subset of pregnant women to be exposed to a medication that they did not need. Although case control and cohort studies may suggest an association, they do not in themselves prove causation. These studies generally must be considered to suggest hypotheses requiring independent confirmation. Nonetheless, when effective alternatives are available, it seems advisable to avoid drugs implicated as producing adverse effects in cohort or case control studies. Reassuring cohort studies often are limited by sample size considerations.

Animal teratology experiments can also be useful in evaluating human drug risks. Animal studies are designed to maximize the response of the system to potential toxic effects of the test agent by using large doses (7). There are no known human developmental toxicants that have not been identified in this manner (7).

Table 1
Food and Drug Administration Pregnancy Categories^a

Category risk	Animal studies	Human data	Benefit may outweigh
A	Negative ^b	Studies ^c negative	Yes
B	Negative	Studies not done	Yes
B	Positive ^d	Studies negative	Yes
C	Positive	Studies not done	Yes
C	Not done	Studies not done	Yes
D	Positive or negative	Studies or reports positive	Yes
X ^e	Positive	Studies or reports positive	No

^a Reprinted from ref. 40 with permission.

^b No teratogenicity demonstrated.

^c "Adequate and well-controlled" studies in pregnant women.

^d Teratogenicity demonstrated.

^e Drug is contraindicated in pregnancy.

Negative data in animal studies for a developmental toxicant indicate a low potential for human developmental toxicity. However, positive animal data is less useful, because it is often not possible to know whether species differences, clinically irrelevant high doses used, or maternal toxicity was responsible for the adverse effects in the offspring (7).

The current pregnancy category system (i.e., the A, B, C, D, X system) adopted in 1979 by the Food and Drug Administration (FDA) is used in official labeling for drug products (Table 1). This system was developed as a guide for drug selection during pregnancy. Some problems associated with this form of labeling include the lack of "adequate and controlled" data on drug effects in humans, resulting in an emphasis on animal data, and an inability to interpret the "C" category clinically. This category system also fails to take into account drug efficacy, route of exposure, and potential pharmacokinetic or pharmacodynamic changes during pregnancy. For a drug to be labeled as a category A, "adequate and controlled" studies must demonstrate safety in both animals and humans (8). No asthma or allergy medication labeled to date meets the requirements for category A. Drugs in categories B and C are almost always placed in these categories based on findings in animal studies alone because human data is not avail-

able or adequate. The FDA has elevated the classification of budesonide to a category B drug based on reassuring data from the population-based Swedish Medical Birth Registry (9).

Evidence for the Safety of Specific Asthma Medications During Pregnancy

Much of the information currently available regarding the safety of various asthma medications during pregnancy comes from several large cohort studies. These include the Swedish Medical Birth Registry, the Collaborative Perinatal Project (CPP), and the Michigan Medicaid Database (9–11). These studies have provided information regarding the incidence of congenital malformations in those infants whose mothers were exposed to asthma medications during pregnancy compared to infants of unexposed women. A smaller cohort from the Kaiser-Permanente Prospective Study of Asthma During Pregnancy was evaluated for outcomes other than congenital malformations, including preeclampsia, preterm birth, and low birth weight (12). Most recently, a group of over 400 asthmatic women were enrolled in the Registry for Allergic and Asthmatic Pregnant Patients (RAAPP) of the American College of Allergy Asthma and Immunology (ACAAI) and the American

Table 2
ACAAI-ACOG Recommendations for the Pharmacological
Step Therapy of Chronic Asthma During Pregnancy^a

Category	Step therapy
Mild intermittent Mild persistent	Inhaled β_2 -agonists as needed (for all categories) ^b Inhaled cromolyn Substitute inhaled corticosteroids ^c if above not adequate
Moderate persistent	Inhaled corticosteroids ^c Continue inhaled salmeterol in patients who have shown a very good response prior to pregnancy Add oral theophylline and/or inhaled salmeterol for patients inadequately controlled by medium-dose inhaled corticosteroids
Severe persistent	Above + oral corticosteroids (burst for active symptoms, alternate-day or daily if necessary)

^aBased on the recommendations of the National Asthma Education Program Report of the Working Group on Asthma During Pregnancy (14), updated to incorporate newer information (15).

^bMost published human data using albuterol, metaproterenol, or terbutaline.

^cBeclomethasone or budesonide if inhaled corticosteroids are initiated during pregnancy; continuation of other inhaled corticosteroid if patient was well controlled by it prior to pregnancy; consider budesonide if patient requires high-dose inhaled corticosteroids for adequate control.

Academy of Allergy Asthma and Immunology by the allergists managing their asthma. These women were evaluated for potential effects of specific inhaled steroids during pregnancy on the incidence of small for gestational age (SGA) infants and mean birth weight (13).

Recommendations for Management

In 1993, the National Asthma Education Program published the report of the Working Group on Asthma and Pregnancy (14). These recommendations for the pharmacological step therapy of chronic asthma during pregnancy were updated in 2000 by a joint ad hoc committee of the ACAAI and the American College of Obstetricians and Gynecologists (ACOG) (15) (Table 2). The gestational safety data on specific drug classes and their recommended use during pregnancy are presented in the next section.

Short-Acting β -Agonists

β -Agonist use was reported in over 600 subjects in the Kaiser-Permanente Prospective Study of Asthma During Pregnancy (12). 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 (11). These studies found no association between the use of β -agonists in pregnant subjects and an increased risk of congenital malformations or other adverse pregnancy outcomes.

β -Agonists are recommended as rescue therapy for all asthmatics, as well as in the management of acute asthma episodes. Although no recommendations regarding a specific inhaled β -agonist were made in the consensus recommendations, albuterol is the only short-acting β -agonist currently available as a metered dose inhaler for which there are published human data during pregnancy.

Long-Acting β -Agonists

According to current guidelines for the treatment of asthma in nonpregnant women, long-acting β -agonists are considered add-on therapy for those patients who are not well controlled on inhaled corticosteroids alone (16). However, animal studies have not been reassuring, and few human data exist regard-

Table 3
Pharmacological Management of Acute Asthma During Pregnancy

1. β_2 -agonist bronchodilator (*see text*)
 - Up to three doses in the first 60–90 min
 - Every 1–2 h thereafter until adequate response
2. Nebulized ipratropium
3. Intravenous methylprednisolone (with initial therapy in patients on regular corticosteroids and for those with poor response during the first hour of treatment)
 - 1 mg/kg every 6–8 h
 - Taper as patient improves
4. Consider intravenous aminophylline (generally only if patient requires hospitalization)
 - 6 mg/kg loading dose
 - 0.5 mg/kg/h initial maintenance dose
 - Adjust rate to keep theophylline level between 8 and 12 $\mu\text{g/mL}$
5. Consider 0.25 mg subcutaneous terbutaline or magnesium sulfate if the patient does not respond to the above therapy

ing the safety of salmeterol or formoterol during pregnancy (17,18).

The consensus recommendations (15) have suggested that benefit–risk considerations may favor the continuation of salmeterol during pregnancy in those women with moderate or severe asthma who have demonstrated a very good therapeutic response prior to becoming pregnant. In addition, long-acting β -agonists should be considered as add-on therapy in patients not controlled by inhaled steroids. Although human gestational data are limited, the existing data are somewhat more reassuring for salmeterol than for formoterol (17,18).

Nebulized Ipratropium

Recent data have demonstrated that the bronchodilatory effect of ipratropium is additive to that of inhaled β -agonists in the management of acute asthma (19–21). Although there are no available human data, animal studies are reassuring (22). Therefore, nebulized ipratropium can be considered in women presenting with acute asthma who do not improve substantially with the first inhaled β -agonist treatment (Table 3) (23).

Theophylline

Several studies have evaluated the risk of congenital malformations in those mothers

using theophylline during pregnancy. No significant increased risk was reported in any of the studies, which included a total of 1861 pregnant women exposed to theophylline (10–12). Other perinatal outcomes have also been evaluated. One study demonstrated no increased risk of fetal deaths in infants of 410 exposed mothers (24). Theophylline exposure was not independently associated with an increased risk of preeclampsia, preterm birth, or low birth weight infants in 429 subjects from the Kaiser study after adjusting for confounders (12).

According to current recommendations (15), theophylline may be used as add-on therapy in addition to inhaled corticosteroid medication in those pregnant patients with moderate persistent asthma not controlled by inhaled steroids alone.

Cromolyn

No increased risk of congenital malformations has been reported in a total of 730 pregnant women exposed to cromolyn in several studies (11,12,25). In addition, cromolyn data have been reassuring for other perinatal complications, such as prematurity and low birth weight (12,25). The other inhaled nonsteroidal anti-inflammatory drug mentioned in the recent consensus recommendations, nedocromil, is no longer available in the United States.

Cromolyn is not as effective as inhaled steroids in the management of persistent asthma (16). However, the consensus guidelines suggest that considering its safety record, cromolyn could be continued during pregnancy in adequately controlled patients with mild persistent asthma.

Inhaled Corticosteroids

Inhaled steroids are recommended as the mainstay of controller therapy for all patients with persistent asthma (16). Concern has been raised regarding a possible adverse effect of inhaled steroids on intrauterine growth because (a) oral steroid use has been associated with reduced birth weight (26) and (b) inhaled steroids have been reported to reduce the growth rate in children at least during the first year of exposure (27). Therefore, in addition to data for congenital malformations, data for intrauterine growth retardation are important.

Regarding congenital malformations, data have been extensive for budesonide ($n = 2534$) (28) but more limited for beclomethasone ($n = 577$) (11,12,29) and absent for other inhaled steroids. In the Swedish Medical Birth Registry, 3.6% of 2534 infants of mothers exposed to budesonide manifested congenital malformations, which was the same as in the total Swedish infant population observed over the same time period (28). In addition, the sample size was large enough to evaluate oral clefts and congenital cardiac defects, which were not increased in infants of exposed mothers (30).

Studies that have sought a relationship between inhaled steroid use during pregnancy and intrauterine growth include a study of 45 pregnancies in 40 women who used inhaled beclomethasone during pregnancy (29). This study suggested a possible association with an increased incidence of low-birth-weight infants (14%), but no comparison group was included and prednisone was required in more than 80% of the pregnancies.

Four subsequent studies did not suggest a relationship between inhaled steroids and

reduced intrauterine growth. The first was a small study in which patients using inhaled triamcinolone acetonide ($n = 15$) or beclomethasone ($n = 14$) did not deliver infants with lower mean birth weight than infants of mothers receiving theophylline without inhaled steroids ($n = 25$) (31).

The second study was a larger study of 149 patients receiving inhaled steroids for asthma during pregnancy, 137 of whom used beclomethasone (12). In this study, women receiving inhaled steroids (with or without oral steroids) were significantly more likely to deliver low-birth-weight (<2500 g) infants than mothers not receiving inhaled steroids, but this relationship disappeared when adjusted for race, weight gain during pregnancy, oral steroids, and mean forced expiratory volume in 1 s (FEV₁).

The third study, a large cohort study of infants of mothers exposed to budesonide ($n = 2968$) in the Swedish Medical Birth Registry, was recently described (32). In this study, gestational age, birth weight, and length of infants of exposed mothers were comparable to the entire Swedish infant population, although low birth weight (<2500 g) and birth weight for gestational age were not specifically reported.

Finally, Namazy et al. (13) described the incidence of SGA infants, an important measure of intrauterine growth retardation, in the offspring of 396 exposed mothers enrolled by their allergist in the Registry for Allergic and Asthmatic Pregnant Patients. Beclomethasone was the most commonly used inhaled steroid, and 20.2% of patients used more than one specific inhaled steroid during pregnancy. The distribution of birth weight for gestational age percentiles for the study population was similar to that of the referent population. The incidence of SGA infants was 7.1% (95% confidence interval [CI] 5.0–10.1%) compared to the expected incidence of 10%. There was no significant relationship identified between specific inhaled steroid use and the incidence of SGA infants or mean birth weight. Although there was a trend toward increasing incidence

of SGA infants with increasing doses of inhaled steroid, this was not statistically significant. There was also no significant linear relationship demonstrated between total doses of inhaled steroid and 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.

The consensus recommendations for the management of chronic asthma during pregnancy suggested the use of beclomethasone or budesonide if inhaled steroids were initiated during pregnancy. The consensus statement also suggested that other inhaled corticosteroids could be continued if the patient was well controlled on one of these medications prior to pregnancy. The recent strongly reassuring human data for budesonide and elevation of its FDA pregnancy class to category B based on these data have suggested to some observers that pending additional data, budesonide should be considered the inhaled steroid of choice during pregnancy.

Systemic Corticosteroids

Data regarding the use of systemic corticosteroids during pregnancy have not been totally reassuring. Park-Wyllie et al. (33) published a meta-analysis of six cohort studies evaluating the relationship between corticosteroid use during pregnancy and congenital malformations and four case control studies evaluating the potential relationship between systemic corticosteroid use during pregnancy and oral clefts. They found that although there was no definite increased risk of total congenital malformations, there was a statistically significant increased risk of oral clefts in infants of corticosteroid-treated mothers (summary OR = 3.35; 95% CI 1.97, 5.69).

Several other adverse outcomes have been reported in association with systemic corticost-

eroid use during pregnancy. In one study of nonasthmatic patients, the birth weight of infants of 119 mothers receiving 10 mg of prednisone throughout pregnancy was significantly lower than the birth weight of 67 control infants (26). Perlow et al. (34) reported increased incidences of preterm birth and low birth weight in infants of 31 steroid-dependent asthmatic mothers compared to 50 asthmatic mothers requiring nonsteroid medications and 130 nonasthmatic controls. However, an effect of steroids could not be differentiated from an effect of severe and possibly poorly controlled asthma in this study. Finally, two studies have suggested a relationship between oral steroid use during pregnancy and preeclampsia (12,35). In the Kaiser-Permanente Prospective Study of Asthma During Pregnancy (12), there were 130 women exposed to oral corticosteroids during pregnancy. The authors found that corticosteroid use was independently associated with an increased risk of preeclampsia (OR = 2.0, $p = 0.027$), even after adjusting for other potential confounders.

It must be stressed that the potential risks of oral corticosteroid use during pregnancy must be balanced against the risks to both the mother and infant of poorly managed severe disease, which include maternal and/or fetal mortality. Because of this, the joint committee of the ACAAI/ACOG continued to recommend the use of oral corticosteroids when indicated in the treatment of severe asthma (15).

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. Unpublished data from the Merck Pregnancy Registry described 200 patients prospectively enrolled between 1998 and 2002 who were exposed to montelukast during pregnancy. Of these, 38 were nondelivered, 52 were lost to follow-up, and 110 reports were com-

plete and contained outcomes of pregnancy. Thus far, there have been 2 spontaneous and 2 elective abortions and 107 live births (one set of twins). The rates of congenital malformations, preterm births, and low birth weight are 2.8%, 10.1%, and 4.4%, respectively, within expected values for the general population. Animal studies have been reassuring for montelukast and zafirlukast but nonreassuring for zileuton.

Although leukotriene modifier drugs have been shown to be effective in the management of mild-moderate persistent asthma in non-pregnant women, until published reassuring gestational human data are available, the joint ACAAI/ACOG committee recommendations suggest consideration of zafirlukast or montelukast only in patients with recalcitrant asthma who have shown a uniquely favorable response prior to becoming pregnant (15). However, zileuton cannot be recommended for use at this time based on the nonreassuring animal data.

Immunotherapy

Allergen immunotherapy often is effective for those patients in whom symptoms persist despite optimal environmental control and proper drug therapy. Two studies of 121 pregnancies in 90 women (36) and 109 pregnancies in 81 women (37) who received immunotherapy during pregnancy found no increased incidence of abortion, neonatal death, prematurity, toxemia, or congenital malformation compared to the general population.

Allergen immunotherapy can be carefully continued during pregnancy in patients who are deriving benefit, not experiencing systemic reactions, and receiving maintenance doses.

Benefit-risk considerations do not favor beginning immunotherapy during pregnancy for most patients because of the (a) undefined propensity for systemic reactions, (b) increased likelihood of systemic reactions during initiation of immunotherapy, (c) latency of immunotherapy effect, and (d) frequent difficulty in

predicting which asthmatic patients will benefit from immunotherapy.

Summary of Recommendations

Pregnant asthmatic patients may be considered in two general categories regarding pharmacological therapy; those already on a medication program when they become pregnant and those in whom therapy is initiated during pregnancy. In patients adequately controlled on inhaled steroids, cromolyn, theophylline, or long-acting β -agonists (especially salmeterol) when pregnancy is recognized, these medications should be continued. Zileuton would ideally be discontinued, and the leukotriene receptor antagonists (montelukast and zafirlukast) would be continued only if they appeared to be uniquely effective for potentially moderate-to-severe asthma. Patients who are oral steroid-dependent in spite of high doses of inhaled steroids and long-acting β -agonist therapy should be maintained on the lowest effective daily dose of prednisone.

In patients beginning therapy for persistent asthma during pregnancy, the authors would recommend budesonide at low-to-moderate doses. In patients uncontrolled by moderate-dose budesonide, either salmeterol or theophylline should be added. Although there are few published data for salmeterol and much more reassuring data for theophylline, the authors would generally favor salmeterol over theophylline because (a) it is an inhaled medication; (b) it is chemically related to albuterol, for which there are reassuring data; (c) in comparative studies, salmeterol is more effective than theophylline; and (d) in comparative studies, salmeterol has fewer side effects than theophylline. In patients chronically controlled by medium-dose budesonide and salmeterol, the authors would consider a trial of single inhaler high-dose fluticasone/salmeterol. Finally, in patients still chronically uncontrolled by such therapy, oral prednisone at the lowest effective daily dose is recommended.

Conclusions

Administering medications for the treatment of asthma during pregnancy can be a challenging process. Careful follow-up by a physician experienced in managing asthma is an essential part of optimizing gestational asthma management. Asthmatic women requiring controller therapy should be evaluated at least monthly. In addition to a careful physical examination, objective measurement of respiratory function, including spirometry, should be obtained at every visit. Those patients with more severe or labile asthma should be considered for home peak expiratory flow monitoring.

All pregnant patients should have facilitated access to their physician for increased symptoms. Above all, there should be open channels of communication between the patient, the physician managing the asthma, and the obstetrician.

The medical/legal implications of treating asthma during pregnancy must also be considered (38,39). Numerous steps have been recommended to reduce medicolegal jeopardy in managing gestational asthma (40).

1. Discuss with the patient that although relatively few medications of any kind have been "proven" harmful during pregnancy, no asthma/allergy medication can be considered to be "proven" absolutely safe.
2. Discuss with the patient the potential direct and indirect consequences of inadequately controlled asthma for the mother and the baby.
3. Discuss with the patient the concept that there are medications that appear safe enough that their use is preferable to the uncontrolled illness that would result if they were not used.
4. Discuss the alternative medication choices available for the patient's particular situation and the rationale for choosing among those alternatives.
5. A written informed consent document is not recommended. However, clearly

document in the chart that the discussion has taken place—that the benefits, risks, and alternatives of the specific pharmacological approach have been discussed with the patient and her informed consent to that approach has been obtained.

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