The Treatment of Allergic Respiratory Disease During Pregnancy

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J Investig Allergol Clin Immunol 2016; Vol. 26(1): 1-7 doi: 10.18176/jiaci.0001

Abstract

Pregnancy may be complicated by new-onset or preexisting asthma and allergic rhinitis. This article reviews the recognition and management of asthma and allergic rhinitis during pregnancy, paying close attention to the general principles of allergy and use of asthma medication during pregnancy. Both allergic rhinitis and asthma can adversely affect both maternal quality of life and, in the case of maternal asthma, perinatal outcomes. Optimal management is thus important for both mother and baby. This article reviews the safety of asthma and allergy medications commonly used during pregnancy.

Key words: Pregnancy. Asthma. Treatment. Inhaled corticosteroids. Bronchodilators. B-agonists. Leukotriene modifiers. Oral corticosteroids.

Resumen

El embarazo puede complicarse por una nueva presentación de un asma y rinitis alérgica preexistentes. En este artículo se revisa el reconocimiento y manejo del asma y la rinitis alérgica durante el embarazo, con atención especial a los principios generales del tratamiento de la alergia y el asma durante esta situación. Ambas patologías pueden afectar de forma adversa a la calidad de vida de la madre y al periodo perinatal. El manejo óptimo de esta situación es muy importante tanto para la madre como para el hijo. Este artículo revisa la seguridad del tratamiento habitualmente utilizado durante el embarazo del asma bronquial.

Palabras clave: Embarazo. Asma. Tratamiento. Corticoides inhalados. Broncodilatadores. Agonistas beta. Modificadores de leucotrienos. Corticoides orales.

Clinical Vignette

A 20-year-old pregnant woman (G1P0, estimated gestation 8 weeks) with a history of allergic rhinitis and asthma came to the clinic. This was her first visit and she presented with multiple complaints. One month previously, she had rescued a stray cat and began to experience increased runny nose, sneezing, stuffiness, and watery eyes. Since before becoming pregnant, she had been using fluticasone nasal spray, which provided some relief from her symptoms, although she expressed concerns about its safety during pregnancy. The patient also complained of dyspnea, wheezing, and nighttime awakenings caused by cough and was concerned about restarting her asthma medications. At the time of her visit, she was using an inhaled short-acting β-agonist 3-4 times a day. She was recently prescribed an inhaled corticosteroid but has been reluctant to use it because of its possible adverse effects on her unborn baby. Despite having a history of asthma since childhood, she has never been hospitalized for asthma but did need a short course of oral corticosteroids about a year ago. Her asthma symptoms are triggered by cleaning her house, upper respiratory infections, and being around tobacco smoke. The patient is a nonsmoker with 1 cat at home and has never been evaluated for allergies. She has no history of food allergies or eczema.

On physical examination the patient had scattered end-expiratory wheeze and boggy, pale, inferior turbinates bilaterally. Spirometry revealed an FEV₁ of 77% of predicted, which increased to 90% after administration of inhaled albuterol. In vitro allergy testing demonstrated a specific IgE level of >100 kU_A/L for dust mite and cat dander. Treatment included education regarding the interrelationships between asthma and pregnancy, environmental control information, confirmation of correct inhaler technique, discussion of the benefits and risks of treating asthma during pregnancy, continuation of fluticasone nasal spray, and initiation of inhaled budesonide.

Allergic Rhinitis

Allergic rhinitis is usually preexisting, although it may develop or be recognized for the first time during pregnancy. Patients with allergic rhinitis often report prominent sneezing. nasal pruritus, and rhinorrhea, and some have concomitant ocular itching and irritation. Common triggers for allergic rhinitis include dust mites, animal dander, molds, and pollens. Allergen avoidance is an important part of the treatment of allergic rhinitis. If skin testing was not performed in the past, then it should be deferred until after delivery. During pregnancy, the benefits of skin tests with allergens need to be weighed against the small, finite risks of iatrogenic anaphylaxis induced by these procedures. Although skin testing is more sensitive for the diagnosis of sensitivities to inhaled allergens, in vitro tests for allergen-specific IgE are widely available and may provide valuable information during pregnancy (see below) without the risk of systemic reactions.

The mainstays of therapy for allergic rhinitis in nonpregnant patients are antihistamines and intranasal corticosteroids (Table 1). No important differences in efficacy or safety appear to exist between the various intranasal corticosteroid preparations. Thus, if a patient is well controlled with an intranasal corticosteroid, it would be reasonable to continue it during pregnancy. Some clinicians choose budesonide if starting intranasal corticosteroids for the first time during pregnancy, since they are classified as category B drugs based on reassuring data available for its use as an inhaled preparation [1].

Antihistamines are less effective than intranasal corticosteroids for the treatment of allergic rhinitis, particularly for the relief of nasal congestion and postnasal drip. Most pregnant women who require antihistamines for allergic rhinitis are best treated with a second-generation agent, because these drugs are less sedating and have fewer cholinergic side effects than first-generation agents.

Among second-generation antihistamines, loratadine (10 mg once daily) and cetirizine (10 mg once daily) may be considered the second-generation antihistamines of choice in pregnancy. There are reassuring human data for each of these drugs in a large number of pregnant patients [2].

First-generation agents are widely available and inexpensive, and can be useful as needed and/or before bed. Chlorpheniramine has been recommended as the firstgeneration antihistamine of choice during pregnancy [3]. Intranasal cromolyn sodium may be considered a first-line therapy for mild allergic rhinitis in pregnancy because of its excellent safety profile. Decongestants are vasoconstrictors that are available as both oral preparations and nasal sprays. Decongestant nasal sprays can be used very briefly (eg, ≤ 3 days) for temporary relief of severe nasal congestion, and reassuring

Table 1. Safety of Commo	nly Used Medications for the Treatment of Rhinitis During	Pregnancy

Drug Class	Drug/FDA Class	Adverse Perinatal Outcome
Oral	Azelastine/C	No human data, animal studies show increase in teratogenicity,
Antihistamines		skeletal abnormalities, and fetal death in high doses
	Cetirizine/B	No increase in congenital malformations
	Chlorpheniramine	No increase in congenital malformations
	Dexchlorpheniramine/B	No increase in congenital malformations
	Fexofenadine/C	This active metabolite of terfenadine has been associated with dose-related weight gain in animal studies
	Diphenhydramine	No increase in congenital malformations; risk of withdrawal syndrome
	Hydroxyzine	No increase in congenital malformations; risk of withdrawal syndrome
	Loratadine/B	No increase in congenital malformations, low birth weight, or small size
		for gestational age
Decongestants	Oxymetazoline	No increase in congenital malformations; possible uteroplacental
	DI 11'	insufficiency with higher doses
	Phenylephrine	Associated with club foot, eye/ear malformations
	Phenylpropanolamine	Increase in total and specific congenital malformations in one study, association with gastroschisis and VSD in case-control studies
	Pseudoephedrine	Association with gastroschisis, hemifacial microsomia and small intestinal atresia in some case-control studies
Intranasal	Azelastine	No controlled studies;
Antihistamines	Olopatadine	No controlled data; animal studies reassuring
Intranasal	Budesonide/B	Substantial reassuring data for inhaled corticosteroids. Risk of increased
Corticosteroids	Fluticasone/C	malformations with high doses, but may be confounded by severity.
	Triamcinolone/C	Most data for budesonide.
	Mometasone/C	

Adapted from Schatz M, Zeiger RS, Falkoff R, Chambers C, Macy E, Mellon MH. Asthma and allergic diseases during pregnancy. In: Middleton' s Allergy: Principles and Practice, 8th edition. Adkinson, NF, Yunginger, JW, Busse, WW, et al (Eds), Mosby, St. Louis, MO, 2014, p. 951-69.

human data have been published on the use of intranasal oxymetazoline during pregnancy [4,5]. However, patients should be warned about dependence with prolonged use of decongestant nasal sprays. Oral decongestants are probably best avoided altogether during the first trimester because of a possible increased risk of a rare birth defect, gastroschisis [6]. A possible association between pseudoephedrine and gastroschisis (baseline incidence of 1 in 10 000 births) was first raised in a case-control study [7]. However, in a later prospective study of over 2000 women who had reported use of oral decongestants during pregnancy, no increased risks of teratogenic effects were detected in the group using oral decongestants, which included pseudoephedrine [8]. A recent study found that women who took oral decongestants during the second or third trimester were less likely to experience preterm delivery than nonexposed women [9]. However, more research is needed to support this relationship. Pseudoephedrine is the oral decongestant of choice in the second and third trimesters in women without hypertension [1]. Phenylephrine should probably be avoided in pregnancy because of less reassuring data regarding safety and uncertain efficacy. For example, phenylephrine has been shown to be no better than placebo in relieving nasal congestion in nonpregnant adults with seasonal allergic rhinitis [10].

Saline irrigation is another option for women who experience rhinitis from allergies. One study reported that intranasal lavage with hypertonic saline significantly reduced the need for daily antihistamines and appeared to be a safe and effective option [11].

Asthma

Asthma is suspected based on the presence of typical symptoms such as wheezing, chest tightness, cough, and associated shortness of breath. The diagnosis is ideally confirmed by the demonstration of reversible airway obstruction, which most commonly takes the form of an increase in forced expiratory volume in 1 second (FEV₁) by $\geq 12\%$ and at least 200 mL after an inhaled short-acting bronchodilator. In nonpregnant patients with normal pulmonary function, asthma can be confirmed by means of methacholine challenge testing. However, this type of testing is not recommended in pregnant patients. Recent studies suggest that elevated fraction of exhaled nitric oxide (FeNO) can be used to monitor asthma in pregnant women, as in nonpregnant patients [12]. Thus, an elevated FeNO would likely support the diagnosis of asthma in pregnant patients. If FeNO is normal or unavailable, therapeutic trials of asthma therapy, such as 2-4 weeks of regular inhaled corticosteroids, may be used during pregnancy in patients with possible but unconfirmed asthma.

Assessment

Once the diagnosis of asthma is confirmed, the next step is to assess severity (in patients not already on controller therapy) or assessment of control (in patients already on controller therapy). Both severity and control are assessed based on frequency of symptoms, rescue therapy, nighttime awakenings, degree of interference with normal activity, exacerbations, and pulmonary function. Patients with intermittent asthma have short episodes and use rescue therapy ≤ 2 times per week, experience nocturnal symptoms ≤ 2 times a month, and have normal pulmonary function between episodes. Patients with more frequent symptoms or those who require daily asthma medications are considered to have persistent asthma.

Hyaluronic acid, which is a marker of systemic inflammation, was recently evaluated as a screening tool for asthma control during pregnancy [30]. The authors showed that hyaluronic acid values could discriminate between patients with a total Asthma Control Test score >20 (controlled patients) and patients with a score <20 (uncontrolled patients) (AUC, 0.78; 95%CI, 0.65-0.92). Further studies are needed to confirm the clinical utility of this measurement. A recent double-blind, parallel-group, controlled study by Powell et al [14] tested the measurement of FeNO to guide management of pregnant asthmatics. The primary outcome was total number of asthma exacerbations. The authors found that the exacerbation rate was lower in the group using FeNO to adjust asthma therapies.

Treatment

The medical management of asthma in pregnant asthmatic patients is not unlike that of nonpregnant asthmatic patients. Therapy is divided into long-term control medications and rescue therapy (Table 2). Long-term control medications are used for maintenance therapy to prevent asthma manifestations and include inhaled corticosteroids, cromolyn, long-acting β-agonists, leukotriene receptor antagonists, and theophylline. Controller therapy should be increased in steps (Table 3) until adequate control is achieved. Rescue therapy, most commonly inhaled short-acting β-agonists, provides immediate relief of symptoms. Oral corticosteroids can be used either as a form of rescue therapy or as chronic therapy for severe persistent asthma.

Table 2. Steps in Asthma Therapy During Pregnancy^a

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 ^b
6	High-dose ICS + LABA + oral prednisone	Omalizumab ^b

Abbreviations: ICS, inhaled corticosteroids; LABA, long-acting beta agonists; LTRA, leukotriene-receptor antagonist. ^aData modified from Schatz M, Dombrowski M. N Engl J Med.

2009;360:1862-9.

 $^{\mathrm{b}}\mbox{For patients}$ with allergic asthma (FDA category B with ongoing safety studies)

Drug category	Specific Drug/FDA Pregnancy Category	Perinatal Outcome
Inhaled bronchodilators Short-acting bronchodilators	Albuterol/C	Reassuring human data; some associations with specific malformations, but may be chance or confounding by severity
Long-acting bronchodilators	Formoterol/C Salmeterol/C	Few reported human data have 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 restriction. Some of these effects may be confounded 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 findings may be confounded by severity. Most data for budesonide
Leukotriene receptor antagonist	Montelukast/B Zafirlukast/B	Moderate amount of reassuring data
5-LO Inhibitor	Zileuton/C	Animal studies not reassuring; no human data
Anti-IgE	Omalizumab/B	Increased risk of low birth weight and preterm birth, but findings may be confounded by severity

 Table 3. Safety of Commonly Used Medications for the Treatment of Asthma During Pregnancy

Adapted from Schatz M, Zeiger RS, Falkoff R, Chambers C, Macy E, Mellon MH. Asthma and allergic diseases during pregnancy. In: Middleton's Allergy: Principles and Practice, 8th edition, Adkinson NF, Bochner BS, Burks AW, et al (Eds), Mosby, St. Louis, MO 2014, pp. 951-69.

Inhaled Corticosteroids

Inhaled corticosteroids 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 inhaled corticosteroids [15-21]. A recent study of over 4000 women who used inhaled corticosteroids during pregnancy found no increased associated risk of perinatal mortality [22]. Several large studies support the lack of association between inhaled corticosteroid use and total or specific malformations [28-31,27,39,41,42]. One study [23] has suggested a relationship between high-dose inhaled corticosteroids and total number of malformations, although this finding could result from confounding by severity, based on the relationships between exacerbations and congenital malformations demonstrated by the same group [24]. In their recent population-based, multicenter, case-control study Lin et al [6] found a positive association between maternal use of inhaled corticosteroids (fluticasone being the most commonly reported drug) and anorectal atresia (aOR, 2.12; 95%CI, 1.09-4.12); however, this finding was not robust enough to alter recommendations on inhaled corticosteroids during pregnancy.

Given that most published human gestational safety data are available for budesonide, this drug is considered the preferred inhaled corticosteroid for the treatment of asthma during pregnancy, although that is not to say that the other inhaled corticosteroid preparations are unsafe. Therefore, inhaled corticosteroids other than budesonide may be continued in patients who were well controlled by these agents prior to pregnancy, especially if switching drugs could jeopardize control of asthma. Doses of inhaled corticosteroids are categorized as low, medium, and high.

Inhaled **B**-Agonists

Inhaled short-acting beta-agonists are the rescue therapy of choice for asthma during pregnancy. Inhaled albuterol is the first-choice short-acting *B*-agonist for pregnant women because it is the most extensively studied [15], although other agents may be used if uniquely helpful or well tolerated. In one case-control study, the use of bronchodilators during pregnancy was associated with an increased risk of gastroschisis among infants (OR, 2.1; 95%CI, 1.2-3.6) [6]. The results of a cohort study involving 4558 women revealed an increased risk of cardiac defects in the infants of mothers exposed to bronchodilators during pregnancy (OR, 1.4; 95%CI, 1.1-1.7) [25]. Another case control study also supported this association (OR, 2.20; 95%CI, 1.05-4.61) [26]. Data from a more recent population-based, multicenter, casecontrol study showed a positive association between maternal use of inhaled bronchodilators (albuterol being the most commonly reported specific drug) and isolated esophageal atresia (aOR, 2.39; 95%CI, 1.23-4.66) and omphalocele (aOR, 4.13; 95%CI, 1.43-11.95) for users of both inhaled bronchodilators and inhaled corticosteroids. However, these observations may be the result of confounding. Asthma exacerbations may be associated with increased use of bronchodilators and congenital malformations. In addition, factors such as obesity or lower socioeconomic status may be associated with more severe asthma requiring more bronchodilators and congenital malformations. In general, patients should use up to 2 treatments of inhaled albuterol (2-6 puffs) or nebulized albuterol at 20-minute intervals for most mild to moderate symptoms; higher doses can be used for severe exacerbations.

Long-acting β -agonists are the preferred add-on controller therapy for asthma during pregnancy. This option should be

added on in patients whose symptoms are not controlled with medium-dose inhaled corticosteroids. Because long-acting and short-acting inhaled B-agonists have similar pharmacology and toxicology, long-acting B-agonists are expected to have a safety profile similar to that of albuterol. The 2 available long-acting B-agonist drugs are salmeterol and formoterol. A possible association between long-acting B-agonists and an increased risk of severe and even fatal asthma exacerbations has been observed in nonpregnant patients. As a result, long-acting B-agonists are no longer recommended as monotherapy for the treatment of asthma and are available in fixed-combination preparations with inhaled corticosteroids. Eltonsy et al [27] compared combination therapy based on long-acting B-agonists and inhaled corticosteroids with high-dose corticosteroids alone and found no significant differences in the rate of congenital malformations between the groups. Cossette et al [28] reported no difference in risk of low birth weight, preterm birth, or small for gestational age between salmeterol and formoterol. These data support the above recommendation to add on long-acting B-agonists for patients who are uncontrolled on medium dose inhaled corticosteroids and suggest that either formoterol or salmeterol could be used.

Leukotriene Modifiers

Both zafirlukast and montelukast are selective leukotriene receptor antagonists indicated for the maintenance treatment of asthma. Based on animal studies, both are pregnancy category B of the United States Food and Drug Administration; however, human data on the use of leukotriene receptor antagonists during pregnancy are more limited. One published study involving 96 patients supports their safety during pregnancy [29]. Another study of 180 montelukast-exposed pregnancies found no increase in the baseline rate of major congenital malformations [30]. Worldwide postmarketing surveillance of montelukast between 1997 and 2006 revealed 6 reports of limb reduction defects in live-born offspring of women taking montelukast during pregnancy. A subsequent retrospective insurance claims cohort study (approximately 12 million covered lives and more than 277 000 pregnancies with live births) revealed no events similar to the 6 postmarketing surveillance events of limb reduction defects among the 1535 infants born to mothers in the montelukast cohort [31]. Montelukast is available as a once-daily medication with doses varying based on age. For adults, the typical dose is 10 mg daily. Overall, fewer human data are available for montelukast than for inhaled corticosteroids, although gestational data for inhaled corticosteroids are generally reassuring. Therefore, montelukast is still considered second-line treatment for management of persistent asthma in pregnant women.

Oral corticosteroids

Some patients with severe asthma may require regular oral corticosteroids to achieve adequate asthma control. Oral corticosteroids are also typically part of the discharge regimen after an acute asthma episode. Doses are typically 40-60 mg in a single dose or 2 divided doses over 3-10 days. Oral corticosteroids were associated with an increased risk of preterm birth [15,18] and low birth weight in 52-185 exposed women [15]. An increased risk of orofacial clefts was reported in a meta-analysis of case-control studies [32], although this increased risk was not confirmed in a recent large cohort study [33]. Since these risks would be less likely 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 [1].

Omalizumab

Omalizumab can be used to treat moderate to severe persistent allergic asthma. This recombinant DNA-derived humanized IgG1k monoclonal antibody binds specifically to free human IgE in the blood. It is currently classed as Category B of the United States Food and Drug Administration based on reassuring animal studies and the limited placental passage expected in the first trimester owing to the size of the molecule. A single-arm observational study of 191 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 small size for gestational age were not unlike those seen in other studies of pregnant women with severe asthma [34]. This ongoing registry study aimed to enroll 250 asthmatic women treated with omalizumab during pregnancy.

Education and Adherence

Based on available data, control of maternal asthma is essential to reduce the risk of perinatal complications. It therefore comes as no surprise that pregnant women are hesitant about continuing asthma medications during pregnancy for fear of untoward effects on their unborn baby. One study found that women with asthma significantly decreased asthma medication from weeks 5 to 13 of pregnancy. During the first trimester, there was a 23% decline in inhaled corticosteroid prescriptions, a 13% decline in short-acting ß-agonist prescriptions, and a 54% decline in rescue corticosteroid prescriptions [35]. A more recent study found that about one-third of pregnant asthmatics discontinued asthma medications during pregnancy, often without consulting their physicians [36]. Lim et al [37] examined the reasons for nonadherence in this particular population of patients using data from interviews with pregnant asthmatic women. Concerns about medication, specifically corticosteroids, overshadowed the potential risk of uncontrolled asthma. Many women were happy to rely on their reliever therapy, and many decreased their preventive therapy without consulting their doctors. Interestingly, most participants complained about the lack of information available about asthma during pregnancy. Lack of support was also a common complaint. Many women felt that the information they were receiving from their pharmacists, nurses, and doctors was contradictory, leading them to make their own choices about medication management. As a result, many participants decreased or discontinued their asthma medications or withheld doses during pregnancy. According to the authors, it was clear from the interviews that women felt it would have

been helpful if asthma had been brought up more by their health care professionals, thus providing them with opportunities to pursue more reliable information.

It is disappointing that medical professionals can provide incorrect information. A recent study found that over a quarter of family physicians instructed their patients to decrease or discontinue asthma medication during pregnancy when asthma was well controlled by current therapy [38]. Cimbollek et al [39] surveyed 1000 physicians, almost half of whom were respiratory medicine specialists/allergy specialists and the other half were primary care physicians. Almost 30% of physicians did not perform spirometry in pregnant asthmatic patients, and only 64% reported that they followed asthma guidelines in the management of pregnant asthmatic patients [39].

Uninformed decisions by pregnant asthmatic patients 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 asthmatic patient. One successful approach was recently reported in the MAMMA trial [40]. Patients were randomized to a pharmacist-led intervention (self-management strategies such as proper inhaler technique, adherence support, monthly Asthma Control Questionnaire, FEV_1 , and action plans) or usual care. There was communication between the pharmacist, family physician, midwife, and patient. At the end of 6 months, there was a significant reduction in the Asthma Control Questionnaire score (improved asthma control) compared to the group that received usual care [40].

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.

Clinical Vignette (continued)

The relationship between allergic rhinitis and pregnancy was reviewed. It was explained that while uncontrolled allergic rhinitis would not likely lead to complications for mother or baby, it would likely affect the mother's quality of life. For example, uncontrolled allergic rhinitis has been associated with sleep disturbance. The patient was recommended to put the cat up for adoption and, in the interim, continue fluticasone nasal spray and add cetirizine or loratadine for breakthrough symptoms.

The relationship between asthma and pregnancy and the risk of untreated asthma was discussed with the patient. She was told that pregnant asthmatic patients have an increased risk of complications, including low birth weight, small size for gestational age, preterm labor and delivery, and preeclampsia during pregnancy, and that women with uncontrolled asthma have an even greater risk of these complications. On the basis of the frequency of her symptoms, she was told that her asthma was uncontrolled. She agreed to start inhaled budesonide (180 μ g, 2 puffs twice a day) and was instructed on technique. The patient's reluctance to use asthma medications for fear of potential adverse effects on the fetus was acknowledged, but she was told that the risks of uncontrolled asthma for both herself and her baby appear to be greater than the risks of using inhaled corticosteroids during pregnancy. She was invited to the clinic 1 month later to repeat pulmonary function testing and reassess control and adherence of the current treatment regimen. *Funding*

The authors declare that no funding was received for the present study.

Conflicts of Interest

Jennifer Namazy has consulting arrangements with Genentech. Michael Schatz has consulting arrangements with Amgen and Boston Scientific.

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