

Interrelationships between asthma and pregnancy: A literature review

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Pregnancy can affect the course of asthma, and asthma can affect pregnancy outcomes. Asthma course may improve, worsen, or remain unchanged during pregnancy. The mechanisms involved have not been defined, and the course in an individual woman is largely unpredictable. Therefore pregnant women with asthma must be followed up particularly closely so that any change in course can be matched by an appropriate change in therapy. The data also suggest that asthma is associated with increased frequencies of adverse pregnancy outcomes. The mechanisms of this are not totally clear either, but some data support the hypothesis that improved pregnancy outcomes are associated with well-controlled disease. The risk of using medications to control asthma during pregnancy appears to be much less than the risk of adverse outcomes related to severe uncontrolled asthma. (*J Allergy Clin Immunol* 1999;103:S330-6.)

In an examination of the interrelationships between asthma and pregnancy, both the effect of the pregnancy on asthma and the effect of the asthma on pregnancy must be considered. Fourteen studies have asked the question, "How does the course of asthma change during pregnancy?"¹ The sample sizes in these studies varied from very tiny ($n = 16$) to not very big ($n = 366$), and the variation in terms of results was equally great. Anywhere from 0% to 69% of patients experienced improvement, 0% to 44% of patients experienced worsening of symptoms, and 6% to 100% of patients remained the same. Two main sources of variation were the way in which asthma course was assessed and the severity of asthma within the populations, because some data suggest that the more severe the asthma, the more likely it is to worsen during pregnancy.²

The commonly quoted generalization is that during pregnancy, about one third of women with asthma experience improvement, one third experience worsening of symptoms, and one third remain the same. Juniper and Newhouse¹ assessed the 14 studies by meta-analysis, and their conclusions are in agreement with this distribution. Therefore we can assume that this is a good generalization, although it may still be population-dependent.

One question in particular for researchers is: What is the mechanism of these changes? Asthma is an extremely variable disease. Maybe this has nothing to do with pregnancy, but the variability during pregnancy is

because the disease itself has a variable natural history. To shed light on this possibility, patients who were 6 weeks post partum were asked to evaluate their asthma course during pregnancy (better, worse, same) in comparison with what they would have expected at that time of year if they were not pregnant.³ Then, 3 months after delivery, the patients were asked to evaluate their asthma course in the 3 months post partum (better, worse, same) in comparison with the severity of asthma during pregnancy. Basically, the data showed that most patients (73%) whose asthma changes course during pregnancy revert to their pre-pregnancy status in the 3 months after delivery.³ This supports the concept that the change in asthma course during pregnancy is in fact pregnancy-specific.

What might be the mechanism or mechanisms of the variation in asthma course during pregnancy? A number of physiologic changes occur during pregnancy, which could worsen or improve asthma (Table I), but it is not clear which, if any, are actually important in determining asthma course during pregnancy. It may be that the algebraic sum of the positive and negative changes determines the asthma course in an individual pregnant patient. I would like to make 2 points regarding these mechanistic considerations. First, this is a "fertile" area for research. Second, *clinically*, the mechanisms of the changes are not really important. The only clinically meaningful message is that the course of asthma can change during pregnancy, so pregnant women with asthma need to be followed up more closely, and their pharmacotherapy should be adjusted as required.

Other important clinical observations have been made regarding the course of asthma during pregnancy. First, as mentioned before, severe asthma is more likely than milder asthma to worsen during pregnancy.^{2,4} Exacerbations appear to be most frequent between weeks 24 and 36.^{2,3} The fewest symptoms tend to occur after week 37, and fortunately, exacerbations during delivery are unusual. Finally, the change in course of asthma tends to be consistent from one pregnancy to the next.³ Let us look at some of the actual data supporting these generalizations.

Joan and Paul Gluck² divided patients according to whether their asthma was mild, moderate, or severe and then examined the course of asthma during pregnancy for each group. The course of most patients with mild asthma did not change at all, but as severity increased, the proportion of patients whose asthma worsened increased as well. These data suggest that baseline asthma severity does determine what happens to the course of asthma during pregnancy. It does not mean that some patients

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0091-6749/99 \$8.00 + 0 1/0/95695

with very severe asthma cannot experience improvement or that some patients with very mild asthma cannot experience worsening of symptoms. However, statistically, the more severe the patient's asthma, the more likely it is that the asthma will worsen further with pregnancy.

The same investigators² looked at the time during pregnancy when asthma was most frequently exacerbated. The frequency of exacerbations reached a peak around the sixth month. In a study by Schatz et al³ patients who experienced worsening of asthma during pregnancy had the most severe symptoms between the 24th and 36th weeks. The data from this study also showed that total symptoms and more severe symptoms decreased significantly during the last 4 weeks of pregnancy to a level below that seen at any other time during pregnancy. Even patients who had overall worsening of asthma during pregnancy experienced statistically significant improvement during their last month of pregnancy. A more recent Finnish study⁵ examined the time during pregnancy when patients experienced acute asthma exacerbations and determined the peak to be a bit earlier than prior data, that is, between 17 and 24 weeks. However, the Finnish data also support the observation that the last month of pregnancy is the one in which patients are least likely to manifest asthma exacerbations. These 3 studies do not agree absolutely, but they do all suggest that the first trimester and the last month of pregnancy appear to be relatively free of exacerbations.

Schatz et al³ evaluated exacerbations during labor and delivery in prospectively treated pregnant patients with asthma. Data from the first 366 patients³ showed that approximately 90% had no asthma symptoms whatsoever during labor and delivery. Of those who did, half required no immediate treatment, and only 2 patients required anything more than inhaled bronchodilators. The total population included nearly 900 asthmatic pregnant women, and the percentages have remained the same. Of course, this does not mean that asthma cannot be exacerbated during labor and delivery. However, such exacerbations are probably most likely to occur if the patient's asthma is not adequately controlled before labor and delivery or if she acquires an infection.

Multiple pregnancies tend to affect asthma similarly in an individual patient. Schatz et al³ followed up 34 patients during each of 2 pregnancies and compared the change in the course of each patient's asthma that occurred in one pregnancy with the change that occurred in the other. A statistically significant number ($P < .02$) of patients (about two thirds) reacted the same during one pregnancy as they did in the other, with regard to the course of their asthma.

The other important issue we need to address is: What do we know about how asthma affects pregnancy? Studies that have compared important outcomes of pregnancy in asthmatic women with those outcomes in nonasthmatic women are summarized in Table II. Of 12 studies that assessed preeclampsia, 6 documented a twofold to threefold increased incidence in asthmatic women. Of 8 studies that evaluated perinatal mortality rates, 2 showed an

TABLE I. Potential mechanisms of the change in asthma course during pregnancy*

Factors that may improve asthma

Progesterone-mediated bronchodilation
Estrogen or progesterone-mediated potentiation of β -adrenergic bronchodilation
Decreased plasma histamine-mediated bronchoconstriction (caused by increased circulating histaminase)
Pulmonary effects of increased serum free cortisol
Glucocorticoid-mediated increased β -adrenergic responsiveness
Prostaglandin E-mediated bronchodilation
Prostaglandin I₂-mediated bronchial stabilization
Atrial natriuretic factor-induced bronchodilation
Increased half-life or decreased protein-binding of endogenous or exogenous bronchodilators

Factors that may worsen asthma

Pulmonary refractoriness to cortisol effects because of competitive binding to glucocorticosteroid receptors by progesterone, aldosterone, or deoxycorticosterone
Prostaglandin F_{2 α} -mediated bronchoconstriction
Decreased functional residual capacity with resultant airway closure during tidal breathing and altered ventilation-perfusion ratios
Increased placental major basic protein reaching the lungs
Increased viral or bacterial respiratory tract infection-triggered asthma
Increased gastroesophageal reflux-induced asthma
Increased stress

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increased incidence in the pregnancies of asthmatic women, again about a doubling. When preterm births were examined, 3 of 12 showed an increase in asthmatic women. That increase ranged from 1½-fold to almost 30-fold when patients with steroid-dependent asthma were compared with nonasthmatic women.¹³ Of 11 studies that assessed low birth weight, there was an increased incidence of low birth weight in infants of asthmatic mothers in 4 studies, again ranging from about a 33% increase to a 17-fold increase in patients treated with steroids.¹³ Finally, only 1 of the 9 studies^{10,11,13,16-21} that examined congenital malformations showed an increase in infants of patients with asthma compared with control subjects. In that study²¹ the increase was quite modest (6.4% vs 4.9%, odds ratio = 1.37) but statistically significant (95% CI, 1.12-1.68) because of the large sample size (Table II). Other adverse outcomes reported to be increased in the pregnancies of asthmatic versus nonasthmatic women have included: hyperemesis gravidarum,⁸ antepartum hemorrhage,^{8,19,21} placenta previa,²¹ preterm labor,^{13,15,22} preterm premature rupture of membranes,¹³ induced labor,⁸ cesarean section,^{11,13,21} small for gestational age infants,²¹ transient tachypnea of the newborn,^{23,24} neonatal hypoxia,⁸ neonatal hyperbilirubinemia,^{16,19} and postpartum bleeding.¹⁹

Asthma may therefore increase the risk of adverse pregnancy outcomes. The important question is: What is the mechanism? Unless we understand the mechanism,

we obviously cannot intervene. Three hypotheses have emerged: (1) poor asthma control, (2) asthma medication, or (3) other factors. Let us review the data that support or refute these hypotheses.

First, we must remember that asthma *control* and asthma *severity* are not the same thing. One can have severe asthma that is well controlled or one can have severe asthma that is poorly controlled. On the other hand, one can have moderate asthma that is not well controlled. Control and severity are not the same, but the literature is unclear on the distinction in most studies.

A number of conditions associated with poorly controlled asthma might adversely affect pregnancy. Maternal hypoxia associated with severe asthma may directly cause fetal hypoxia.²⁵ In addition, other conditions associated with uncontrolled asthma, including hypertension, hypocapnia, alkalosis, and dehydration, may also adversely affect fetal oxygenation by reducing uteroplacental blood flow.²⁵

Clearly, uncontrolled asthma could be a problem for the fetus during pregnancy. The clinical data supporting this statement are derived from a number of studies. The first study to suggest that severe asthma adversely affects gestational outcomes was the Collaborative Perinatal Project in 1970.⁷ This study showed an approximate doubling of perinatal mortality rate in patients with asthma compared with control subjects. Moreover, 16 patients who had "severe asthma" (which we assume was severe *uncontrolled* asthma) manifested particularly complicated pregnancies: 2 abortions, 3 fetal deaths, 1 neonatal death, and 3 of 11 live births with low birth weight.

Studying the effect of asthma *control* on the outcome of pregnancy prospectively and experimentally would entail randomly assigning pregnant women with asthma of uniform severity to either a "well-controlled" or a "poorly controlled" group. Such a study would clearly be unethical. Thus the best we can do is to examine pregnancy outcomes in studies in which the asthma appeared to be managed by asthma specialists,^{6,10,16-18,20} compared with studies in which the asthma was apparently managed by nonspecialists (Table III). Asthma management by specialists versus nonspecialists does not reduce the occurrence of preeclampsia. This suggests that the increased incidence of preeclampsia may be associated with medication used to treat asthma or with common pathogenetic factors (see below), rather than associated with disease control. However, patients treated by asthma specialists do appear to manifest a lower likelihood of other complications (perinatal mortality, preterm birth, and low birth weight). Indirectly at least, this supports the concept that better asthma control improves pregnancy outcomes.

Some more direct data are also available. First, infants born to mothers hospitalized for treatment of asthma during pregnancy have lower birth weights than those born to mothers not requiring emergency therapy for gestational asthma. Greenberger and Patterson²⁶ compared birth weights in 8 infants of 7 mothers who were hospitalized for treatment of asthma during pregnancy with 41

infants of 40 mothers whose asthma did not require emergency therapy. Infants in the latter group manifested a significantly higher birth weight (3284 g) than infants in the former group (2764 g). A more recent, larger study from India¹⁸ described 15 infants of mothers hospitalized because of gestational asthma and 169 infants of 167 mothers who did not require emergency therapy. Again, a statistically significant difference was found between the mean birth weight of infants of hospitalized (2469 g) compared with nonhospitalized (2838 g) mothers. These data suggest that intrauterine growth may depend on the degree of asthma control.

Control of asthma, as measured by pulmonary function tests, also seems to affect the occurrence of intrauterine growth retardation as assessed by low ponderal indices. Schatz et al²⁷ obtained FEV₁ measurements by spirometry monthly in pregnant patients with asthma and calculated a mean FEV₁ for each patient. They then divided the population into 4 quartiles based on mean FEV₁ values and looked at the incidences of low ponderal indices in the various quartiles. They found that as patients moved into a higher pulmonary function quartile, the incidence of a low ponderal index significantly decreased ($P < .05$). These observations are also consistent with those of Mabie et al¹² who showed that intrauterine growth retardation was more common in infants of mothers with moderate or severe asthma versus those with mild asthma. All of these data support, but certainly do not prove, the concept that the better controlled (or perhaps the less severe) the asthma, the better the outcome in terms of intrauterine growth.

What about the effects of asthma medications on pregnancy? Human data exist for β -agonists, cromolyn, theophylline, inhaled corticosteroids, and oral corticosteroids. Data from a study by Schatz et al²⁸ and the Michigan Medicaid Study²⁹ support the safety of β -agonists, especially albuterol, metaproterenol, and terbutaline. Reassuring data regarding cromolyn have been presented in 2 studies.^{28,30}

An increased incidence of congenital malformations has not been reported with theophylline,^{28,29,31} but data regarding other complications have been conflicting. A study by Dombrowski et al⁹ suggested that patients who received theophylline actually experienced *less* preeclampsia when compared with asthmatic patients not receiving theophylline. However, a more recent study by Stenius-Aarniala et al¹⁶ reported that patients taking theophylline had an *increased* incidence of preeclampsia. The problem with those data is that the patients receiving theophylline were also more likely to have experienced severe episodes and more likely to have received steroids. The data in a larger number of patients²⁸ did not suggest any significant association between theophylline use and preeclampsia.

What about inhaled corticosteroids? Inhaled corticosteroids are being increasingly used to treat asthma in patients with persistent asthma, and they will be used increasingly in pregnant women with asthma as well. Moreover, 2 studies have suggested that pregnant women

TABLE II. Controlled studies evaluating outcome of pregnancy in asthmatic versus control women

Study	Design/ setting	Sample size		Odds ratios (incidence in asthma/control) or Incidence %			
		Asthmatic	Control (matching)	Preeclampsia	Perinatal mortality	Low BW (<2500 g)	Preterm (<37 wk gestation)
Schaefer and Silverman ⁶	Retrospective; obstetric-pulmonary clinic	293	30,000	NR	NR	1.4	NR
Gordon et al ⁷	Prospective cohort; multicenter	277	30,861	NR	P, 1.8*	1.3	0.8
Bahna and Bjerkedal ⁸	Retrospective; medical birth registry (Norway)	381	125,423	2.2 [†]	F, 1.7; N, 2.3*; P, 1.8	1.9 [†]	1.5 [‡]
Dombrowski et al ⁹	Retrospective; antenatal clinic	153	116	1.3	NR	No diff mean BW	No diff mean gestational age
Stenius-Aarniala et al ¹⁰	Prospective; pulmonary medicine department	198	198 (age, parity)	3.2 [†]	P, 2.0	No diff mean BW	No diff mean gestational age
Lao and Huengsborg ¹¹	Retrospective; antenatal clinic	87	87 (age, parity)	2.3% (control NR)	P, 2.3% in asthmatic group (control NR)	9.4 [‡]	3.1
Mabie et al ¹²	Retrospective; antenatal clinic	200	22,651	0.9	P, 0.2	NR	0.9
Perlow et al ¹³	Case control; antenatal clinic	81 total; 31 receiving steroids (S); 50 not rec S (NS)	130	S, 4.0; NS, 0.9	NR	S, 17.0 [†] ; NS, 3.4	S, 29.9 [†] ; NS, 4.0*
Lehrer et al ¹⁴	Retrospective; perinatal database	136	23,979 (statistical control for confounders)	2.5 [†]	NR	NR	NR
Doucette and Bracken ¹⁵	Prospective; secondary analysis; antenatal clinic	32	3850 (statistical control for confounders)	NR	NR	0.7	1.8 (2.3 preterm labor)
Stenius-Aarniala et al ¹⁶	Prospective; pulmonary medicine department	504 total; 212 rec theophylline (T); 292 not rec T (NT)	237 (age, parity)	2.4T [‡] 1.7 NT	0 T; 0.4 NT	NR	1.4 T; 1.0 NT
Schatz et al ¹⁷	Prospective inception cohort; allergy clinic	486	486 (age, smoking, parity, year of delivery)	1.3	2.0	1.6	1.7
Jana et al ¹⁸	Retrospective; obstetrical/medical disorder clinic	182	364 (age, parity)	NR	0.3	1.0	1.2
Alexander et al ¹⁹	Retrospective; perinatal database (Nova Scotia)	817 [No med (N) = 375; β -agonist only (B) = 303; Steroids (S) =	13,709 (statistical control for confounders)	N, 1.3; B, 1.0; S, 1.7*	NR	N, 0.9; B, 1.4; S, 1.0	N, 1.0; B, 1.0; S, 1.4

Continued

BW, Birth weight; NR, not reported; P, perinatal mortality; F, fetal mortality; N, neonatal mortality.

* $P < .05$ between groups.

[†] $P < .001$ between groups.

[‡] $P < .01$ between groups.

TABLE II. CONT. Controlled studies evaluating outcome of pregnancy in asthmatic versus control women

Study	Design/ setting	Sample size		Odds ratios (incidence in asthma/control) or Incidence %			
		Asthmatic	Control (matching)	Preeclampsia	Perinatal mortality	Low BW (<2500 g)	Preterm (<37 wk gestation)
Minerbi-Codish et al ²⁰	Prospective; pulmonary medicine department	139] 101	77 (age, ethnicity)	$P > .05$ (specific OR NR)	NR	$P > .05$ (specific OR NR)	$P > .05$ (specific OR NR)
Demissie et al ²¹	Retrospective; linked birth certificate/ maternal and newborn hospital claims data	2289	9156 (statistical control for confounders)	2.18*	NR	1.32*	1.36*

TABLE III. Incidence of adverse perinatal outcomes in studies in which asthma was managed by asthma specialists versus non-asthma specialists

Outcome	Number of studies with increased incidences in patients with asthma/total studies	
	Asthma managed by specialists	Other
Preeclampsia	2/4	4/8
Perinatal mortality	0/4	2/4
Preterm births	0/4	3/8
Low-birth-weight infants	0/4	4/8

with asthma treated with inhaled steroids experience fewer acute asthmatic exacerbations than those not treated with inhaled corticosteroids.^{5,32} Stenius-Aarniala et al⁵ evaluated 504 pregnant asthmatic patients, 47 (9.3%) of whom experienced acute exacerbations. However, the 257 patients treated with inhaled beclomethasone or budesonide from the start of pregnancy had only a 4% incidence of acute exacerbations, whereas 17% of the 177 patients not initially treated with inhaled steroids experienced acute episodes ($P < .0001$). Wendel et al³² evaluated 84 subjects with non-steroid-dependent asthma who presented with 105 asthma exacerbations, 65 of which required hospitalization. Hospitalized patients were randomly assigned, on discharge, to 1 of the following 2 regimens: (1) albuterol and an oral steroid taper (31 patients) and (2) albuterol, an oral steroid taper, and inhaled beclomethasone (34 patients). Of the patients who received beclomethasone, 12% were readmitted compared with 33% of those who did not receive beclomethasone ($P < .05$).

Data regarding beclomethasone and congenital malformations have been reassuring.^{28,29,33} In regard to other potential adverse effects, the first study of beclomethasone³³ was not totally reassuring in the sense that there was a 14% incidence of low-birth-weight infants. However, this study examined patients with severe asthma: most had required oral corticosteroids,

and a number had required hospitalization. Thus the possible increased incidence of low-birth-weight infants could not be attributed to the inhaled steroids alone. Dombrowski et al³⁴ have recently evaluated birth weight in 14 infants of women treated with inhaled beclomethasone and 15 women treated with inhaled triamcinolone compared with 25 women treated with theophylline. No significant differences were found. Additionally, Schatz et al²⁸ evaluated 149 patients treated with inhaled steroids during pregnancy, 137 of whom had received beclomethasone.²⁸ They did not find any independent associations between inhaled corticosteroid use during pregnancy and adverse pregnancy outcomes.

Finally, we come to oral corticosteroids. Perlow et al¹³ reported that the incidence of low-birth-weight infants and preterm births was significantly higher in the pregnancies of 50 women with steroid-dependent asthma compared with 31 women with non-steroid-dependent asthma and that preeclampsia was many times higher but did not reach statistical significance. However, Stenius-Aarniala et al¹⁰ reported a statistically significant increase in preeclampsia in asthmatic women requiring corticosteroids compared with asthmatic women not treated with steroids. These data suggest that patients treated with steroids are at increased risk of perinatal complications, but they did not differentiate asthma severity from poor control or from a medication effect. The confounding aspects of severe asthma are not a problem in one study published in *Science* a number of years ago.³⁵ These were not asthmatic patients, but they were patients who were having trouble staying pregnant. Patients were treated with prednisone, 10 mg daily, throughout pregnancy. Birth weights for 119 infants born to these patients were compared with birth weights of 67 similar patients from that clinic who were not treated with steroids. A significant ($P < .0001$) lowering of birth weight was found for the infants of patients treated with prednisone, paralleling changes noted in concurrent animal experiments. Subsequent information has suggested that using prednisone in the first trimester and/or in lower doses does not decrease birth weight,^{36,37} indicating that

this may be a dose-dependent and/or duration-dependent effect.

In an attempt to sort out the effect of medications from other factors, a multivariate analysis was conducted in a population of 824 pregnant women with asthma.²⁸ The authors examined asthma medications, as well as older age, parity, smoking, African-American race, weight gain during pregnancy, incidence of acute asthmatic episodes, and mean gestational FEV₁. Schatz et al²⁸ then evaluated the 3 outcomes most commonly reported to be increased in pregnancies of asthmatic women: preeclampsia, preterm births, and low-birth-weight infants. Oral corticosteroids were independently associated with an approximate doubling of the incidence of preeclampsia. On the other hand, no medications but only African-American race and lower weight gain were significantly associated with preterm births and low-birth-weight infants ($P < .01$). We can conclude from this study that oral corticosteroids may be associated with preeclampsia, but, at least from our data, no other adverse medication effect was documented. Although this oral corticosteroid effect could have been a direct medicine effect, there is another potential mechanism.

In addition to poor asthma control and medications, a third mechanistic possibility regarding the association between maternal asthma and increased adverse perinatal outcomes is that patients with asthma may have pathogenetic factors that may not only cause their asthma but also may cause pregnancy complications (eg, preeclampsia). One such pathogenetic factor might be autonomic nervous system abnormalities that could affect bronchial, vascular, and uterine smooth muscle. In fact, some data suggest that patients with asthma manifest vascular α -adrenergic hyperreactivity³⁸ and β -adrenergic hyporeactivity,³⁹ which could lead to peripheral hypertension and decreased uteroplacental blood flow. A relationship between bronchial hyperreactivity and uterine muscle hyperreactivity is suggested by data showing that patients with idiopathic preterm labor had an increased likelihood of bronchial hyperreactivity compared with patients who did not experience preterm labor.⁴⁰ In addition, mediators, such as angiotensin and endothelin, may be involved in preeclampsia⁴¹ and may also cause bronchoconstriction.^{42,43} It is very difficult to sort out the effects of such common pathogenetic factors from the effects of other factors, particularly if the common pathogenetic factors are more prevalent in patients with more severe asthma.

In summary, we can make several conclusions. First, asthma can change course during pregnancy. These changes are variable, and we do not yet understand the mechanisms involved. About one third of patients with asthma experience improvement, one third experience worsening of symptoms, and one third remain the same. The important point is that all pregnant patients with asthma need to be followed up particularly closely. The data are certainly not totally consistent regarding the effect of asthma on pregnancy, but enough studies have shown increased adverse outcomes to cause us to believe

that there is an effect. Here again, the mechanism is not clear. Some data support the hypothesis that the better controlled the asthma, the more favorable the outcome; but other factors, such as medications or common pathogenetic factors, may be involved. For example, oral corticosteroids may contribute to increased preeclampsia as a drug effect. However, even so, that risk is probably much less than the risk of severe uncontrolled asthma to both the mother and the baby.

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