
Variables affecting asthma course during pregnancy

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Background: The course of asthma is frequently altered by pregnancy, but the mechanisms remain undefined.

Objective: The purpose of this study was to identify specific maternal or pregnancy characteristics that are related to the course of asthma during pregnancy.

Methods: A secondary analysis of a previous prospective study identified 568 pregnant women whose patient-reported asthma course during pregnancy was compared with the women's usual disease course. Potential explanatory variables were compared between groups defined by their pregnancy versus usual course (better, worse, same).

Results: Improvement of asthma during pregnancy was noted in 33.6%, worsening was reported in 36.3%, no change was reported in 26.4%, and the course was uncertain in 3.7%. There was a significant concordance between asthma course and course of rhinitis during pregnancy. Rhinitis improved in 51.1% of patients whose asthma improved during pregnancy and worsened in 19.8% of these women. Rhinitis worsened in 55.9% of patients whose asthma worsened during pregnancy and improved in 2.1% of these women. No significant relationships were found between gestational asthma course and maternal demographic factors, panic-fear score, smoking, maternal weight, infant birth weight, or infant sex.

Conclusions: The relationship of gestational asthma course to rhinitis symptoms may have clinical and mechanistic significance. Further studies will be necessary to test this hypothesis.

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INTRODUCTION

The course of asthma seems to be altered by pregnancy. Retrospective studies have shown that on average, asthma worsens in approximately one-third of women, it remains the same in one-third of women, and it improves during pregnancy in one-third of women.¹ A recent meta-analysis by Juniper and Newhouse² of the available studies concurred with these results. The mechanisms by which these changes take place are not known. Some studies have shown that severe asthmatic patients are more likely to experience worse symptoms during pregnancy compared with milder asthmatic patients.³ Gluck and Gluck⁴ found that 16% of mild asthmatic patients were worse during pregnancy, 12% improved, and 72% were unchanged. In contrast, these investigators found that 83% of severe asthmatic patients worsened during pregnancy, 17% remained unchanged, and no patients improved.¹ Other studies have shown that patients with mild or moderate asthma before pregnancy are less likely to have exacerbations during pregnancy than patients with severe asthma.^{4,5} Additionally, it has been shown that approximately 73% of women return to their prepregnancy asthma state within 3 months after giving birth, suggesting that something intrinsic to the pregnancy state is related to the change in gestational asthma course.^{3,5–7}

Other variables related to pregnancy and asthma course have been studied, but their causal relationship to changes in

gestational asthma course have not been proven. In one prospective study, it was found that women with female fetuses experienced more asthma symptoms during pregnancy than women carrying male offspring.⁸ One possible explanation for this phenomenon is that male fetuses produce a surge in androgens during weeks 12 to 16 that could account for the difference in symptom severity.⁸ Other studies demonstrated that an increased level of total serum immunoglobulin E (IgE)¹ or cockroach-specific IgE⁹ are associated with worsening of asthma symptoms during pregnancy. Viral infections also seem to play a role in the course of asthma during pregnancy. Viral infections have been reported to be the most common cause of severe asthma exacerbation during pregnancy.¹⁰ Finally, a number of characteristics may increase symptoms in nonpregnant asthmatic patients, such as cigarette smoking,¹¹ increased body weight,¹² and high panic-fear status,¹³ but the relationship of these variables to gestational asthma course has never been evaluated.

The present study was undertaken to identify specific maternal and pregnancy characteristics that are related to the course of asthma during pregnancy. Such relationships may generate or support mechanistic hypotheses.

METHODS

Data from the first phase of the Kaiser-Permanente Prospective Study of Asthma During Pregnancy described the frequency and direction of changes in asthma course during pregnancy, the time course of such changes, and the relationships of these gestational changes to postpartum asthma course and the asthma course in previous pregnancies.⁶ Subsequently, data from the entire study were used to describe

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perinatal outcome of the pregnancies of 671 women with documented asthma and 556 nonasthmatic controls.¹⁴ The current study is a secondary analysis of data from the 671 women with documented asthma. The Kaiser-Permanente Prospective Study of Asthma During Pregnancy was approved by the Kaiser Foundation Institutional Review Board.

Charts of asthmatic subjects enrolled in this study were reviewed to determine information regarding the asthma course during pregnancy and to determine prespecified variables that may have contributed to changes in asthma course.

Patients were asked at the end of pregnancy to classify their asthma severity during pregnancy compared with their usual severity. The classifications were as follows: 1) better, 2) worse, 3) same, or 4) uncertain. This information was recorded on patient charts in 652 of 671 study pregnancies. Of these pregnancies, 84 were repeat pregnancies. To avoid confounding by multiple pregnancies, only the first (or only) pregnancy was included in the analysis ($n = 568$).

Explanatory variables were compared among three groups defined by their pregnancy versus usual course: 1) better, 2) worse, or 3) same. Patients who described the change in severity as "uncertain" were excluded from these analyses. The explanatory variables compared were as follows: 1) Panic-fear scale score, derived from a Minnesota Multiphasic Personality Inventory administered during pregnancy¹³; 2) gravidity (mean); 3) parity (primipara vs multipara); 4) mean maternal age; 5) maternal age >35 years; 6) race; 7) season of delivery (seasons were defined as winter, December through February; spring, March through May; summer, June through August; fall, September through November); 8) preeclampsia; 9) preterm labor (<37 weeks); 10) mean length of gestation (weeks); 11) preterm delivery (<37 weeks); 12) smoking history (smoking was defined as >10 cigarettes per day for >1 month of the pregnancy); 13) mean birth weight; 14) low birth weight (<5.5 pounds); 15) high birth weight (>8.0 pounds); 16) sex of offspring; 17) change in nasal symptoms during pregnancy; 18) mean maternal weight at the time of the last menstrual period; and 19) mean maternal weight gain during pregnancy.

Hypothesis testing for comparisons of dichotomous variables between groups was conducted by means of Pearson χ^2 analysis. Continuous variables were compared between groups by means of one-way analysis of variance. A two-sided P value <0.0025 (0.05 divided by 19) was considered significant, using the Bonferroni correction to adjust for the 19 separate comparisons evaluated in this study.¹⁵

RESULTS

Of the 568 asthmatic subjects studied, 191 (33.6%) reported that their asthma improved, 206 (36.3%) reported worsened asthma, and 150 (26.4%) reported that their asthma remained unchanged during pregnancy. An additional 21 (3.7%) of the subjects were uncertain about changes in their asthma course during pregnancy.

Comparisons of the potential explanatory variables between groups are shown in Table 1 for patient characteristics

Table 1. The Relationship of Potential Patient Explanatory Variables to Asthma Course during Pregnancy

Explanatory Variable	Better	Same	Worse
Age			
Mean (SE)	27.8 (0.4)	28.1 (0.4)	28.2 (0.4)
> 35	6.8%	4.6%	7.8%
Race			
Asian American	1.6%	2.0%	1.0%
Hispanic	12.0%	6.0%	8.7%
African American	3.7%	4.6%	5.8%
White	81.2%	86.1%	81.1%
Panic-fear score (SE)	5.20 (0.21)	5.13 (0.24)	4.67 (0.21)
Smoking	8.9%	9.3%	14.1%
Rhinitis improved*	51.1%	7.0%	2.1%
Rhinitis worsened*	19.8%	27.5%	55.9%
Weight (pounds) at LMP (SE)	139.7 (2.4)	138.7 (2.9)	141.6 (2.1)

* $P < 0.0025$.

SE, Standard error; LMP, last menstrual period.

and Table 2 for pregnancy characteristics. The only significant relationship was between gestational asthma course and course of rhinitis during pregnancy. Patients whose asthma improved during pregnancy were much more likely to have improvement in rhinitis than women whose asthma worsened during pregnancy, and the converse was true regarding worsening of rhinitis during pregnancy (Table 1).

Trends were seen regarding certain pregnancy characteristics, including parity, season of delivery, and preterm labor. Women whose asthma improved were more likely to be primiparous, whereas women whose asthma worsened were more likely to be multiparous. Women whose asthma course did not change during pregnancy were also somewhat more likely to be multiparous. Women whose asthma did not change or whose asthma worsened were more likely to deliver in the winter compared with women whose asthma

Table 2. The Relationship of Potential Pregnancy Explanatory Variables to Asthma Course during Pregnancy

Explanatory Variable	Better	Same	Worse
Gravidity (SE)	2.4 (0.1)	2.5 (0.1)	2.6 (0.1)
Primipara	54.5%	44.4%	44.2%
Multipara	45.6%	55.6%	55.8%
Weight gain (pounds) (SE)	33.5 (1.0)	31.0 (1.0)	32.5 (1.0)
Season of delivery winter	17.3%	23.2%	23.3%
Season of delivery other	83.1%	76.8%	76.7%
Preeclampsia	11.0%	9.3%	8.3%
Mean gestation (weeks) (SE)	39.7 (0.2)	39.5 (0.2)	39.2 (0.1)
Preterm labor	7.9%	3.3%	3.4%
Preterm birth	4.2%	4.7%	5.9%
Mean birth weight (grams) (SE)	3489 (45)	3397 (50)	3398 (39)
Low birth weight	4.2%	2.7%	4.4%
High birth weight	43.5%	36.4%	34.6%
Offspring gender			
Male	52.4%	53.0%	54.4%
Female	52.4%	47.0%	45.6%

SE, Standard error.

improved. Of those women whose asthma improved during pregnancy, 7.9% reported preterm labor, whereas only 3.3 to 3.4% of those women whose asthma remained unchanged or whose asthma worsened experienced preterm labor. These relationships did not achieve statistical significance. In addition, no significant relationships were found between gestational asthma course and 1) maternal age, gravidity, race, panic-fear scale, or smoking; 2) maternal weight or weight gain during pregnancy; 3) occurrence of preeclampsia or preterm birth; 4) mean, low, or high birth weight; or 5) sex of the offspring.

DISCUSSION

This study represents the largest single cohort evaluated for change in asthma course during pregnancy. The overall results regarding gestational asthma course (33.6% improved, 36.3% worsened, and 26.4% unchanged) are consistent with previous reports.^{2,6} This study demonstrated a significant relationship between asthma course during pregnancy and rhinitis course. It did not confirm the previously reported relationship with sex of the infant. Further, this study did not support an association between asthma course during pregnancy and other potentially relevant patient-specific or pregnancy-specific parameters.

It is not surprising that worsening rhinitis was associated with worsening asthma, as much evidence has been published confirming that rhinitis and asthma are the same disease process in contiguous areas of the same airway.^{16,17} It is well known that uncontrolled rhinosinusitis may exacerbate asthma. Conversely, treatment and control of rhinitis symptoms are associated with reduced asthma symptoms.^{17,18} These results support the aggressive treatment of worsening rhinitis in pregnant women as a means of improving asthma control during pregnancy. These findings also suggest that worsening gestational nasal symptoms may be a useful clinical marker for women whose asthma may worsen during pregnancy.

The observed relationship between gestational asthma course and gestational rhinitis course also has mechanistic implications. It suggests that factors affecting both the upper and lower airways may be important determinants of asthma course during pregnancy. One such factor could be IgE-mediated reactivity involving both the nose and the lungs. In this regard, our findings would be consistent with previous studies showing that increased levels of total IgE¹ or increased levels of cockroach-specific IgE⁹ are associated with worsening asthma symptoms during pregnancy. Another pathogenic mechanism involved in both the upper and lower airways is eosinophilic inflammation. Hamano et al¹⁹ studied the effect of sex hormones on eosinophilic inflammation in the nasal mucosa. These authors treated peripheral eosinophils from allergic rhinitis patients with sex hormones and found that β -estradiol enhanced eosinophil adhesion to human endothelial cells. They also found that eosinophils stimulated with a combination of β -estradiol and progesterone displayed significantly enhanced degranulation, whereas testosterone decreased eosinophil adhesion and viability. Be-

cause both of these hormones increase by 100-fold to 1,000-fold during pregnancy, their effects on eosinophils could explain worsening of both rhinitis and asthma during pregnancy. In contrast, increased serum-free cortisol has been suggested as a mechanism of improved gestational asthma.³ This change would also be expected to improve eosinophilic rhinitis during pregnancy; thus, the concordance observed in this study between asthma and rhinitis course would be consistent with this mechanistic hypothesis. That rhinitis and asthma improve in some women during pregnancy but worsen in others suggests that either of the above conflicting effects of gestational hormones on respiratory disease may predominate in individual pregnant women.

In the current study, several expected findings did not appear, and in one instance, our findings conflicted with previous data. We did not find that women who smoked were more likely to have worsened asthma during pregnancy, even though smoking is a risk factor for the fetus during pregnancy,¹¹ and smoking is also known to exacerbate asthma. Similarly, we did not find an association between worsening gestational asthma and increased weight or panic-fear status, both of which have been associated with increased asthma symptoms in nonpregnant patients.^{12,13} There may be something intrinsic to pregnancy, such as the biochemical changes described above, that mitigates the effects of factors known to exacerbate asthma in the nonpregnant state.

Beecroft et al⁸ reported that women with female fetuses had more asthmatic symptoms during pregnancy than women with male fetuses. A possible explanation is that male fetuses produce a potentially protective surge of androgens at 12 to 16 weeks of gestation. In our study, it was found that the sex of the fetus did not affect asthma course. The number of participants in the study by Beecroft et al⁸ was much smaller than the number of participants in our study, and their results may have represented a type I error.

There are two main limitations to the present study. First, the method of evaluating asthma course during pregnancy was based on subjective symptom evaluation as discerned by the women themselves. It was not possible to confirm objectively the patients' assessments of their asthma severity during pregnancy compared with their usual course because most patients were not followed before pregnancy. Second, a number of patient characteristics that would have been useful to know were not available in the data set. These include atopic status of the patient, changes in environmental factors during pregnancy, and actual infections experienced during pregnancy. In addition, it would have been very interesting to evaluate differences between groups in hormonal or other physiologic changes, but this was beyond the scope of the current study.

CONCLUSION

Asthma course during pregnancy appears to be directly related to rhinitis course. The course of rhinitis during pregnancy may help to predict the asthma course. Further studies are required to determine whether treating worsening rhinitis

during pregnancy would improve gestational asthma and to delineate the exact mechanisms underlying the association between asthma and rhinitis course during pregnancy.

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