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Effect of pregnancy and stage of pregnancy on asthma severity: A systematic review

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KEY WORDS

Asthma

Pregnancy

Although pregnancy is purported to affect maternal asthma, the literature has not been reviewed systematically. The purpose of this systematic review was to determine, among pregnant women with asthma, whether pregnancy and stage of pregnancy influence maternal asthma severity. Six electronic databases were searched in January 2003 for prospective studies of currently asthmatic, pregnant women who were enrolled before the third trimester and assessed with objective measures of asthma severity or validated severity scales. Three studies reported 54 pregnant women with asthma who met the inclusion criteria. The most valid study indicated that bronchial hyper-responsiveness to methacholine improved between preconception and pregnancy in 69% of the women, although it deteriorated in 31% of the women. Further, this improvement peaked in the second trimester, reverted after delivery, and was greatest among those women who were most hyperresponsive initially. Lung function also showed a trend towards improvement during pregnancy that was not significant. Large, well-conducted population-based studies that explore different aspects of asthma severity are needed to substantiate these preliminary results.

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Case reports that date from >70 years ago¹ have described an effect of pregnancy on the severity of a woman's asthma, but the literature has been inconsistent, and the nature of the effect, if any, remains uncertain. An earlier review that supports the generalization that the condition of one third of women with asthma improves during pregnancy, that the condition of one third

of women with asthma gets worse, and that the condition of one third of women with asthma remains the same failed to set forth explicitly the selection criteria for study inclusion and produced, perhaps inappropriately, a pooled estimate of the effect of pregnancy on maternal asthma from highly clinically and statistically heterogeneous studies.²⁻⁵

Asthma is an increasingly common chronic illness⁶ and a substantial potential source of morbidity among pregnant women.⁷ Recent data from national health surveys estimate the prevalence of asthma among pregnant women in the United States to be between 3.7% (95% CI, 2.7%, 4.7%) and 8.4% (95% CI, 7.1%, 9.8%).⁸ According to these estimates, approximately 88,573 to 190,650 pregnant women who are 18 to 44 years of

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age in the United States are affected by asthma currently. Higher rates of asthma among younger women of childbearing age foretell a continuing increase in the prevalence of asthma during pregnancy.

There is currently no agreed on standard for the assessment of asthma severity in epidemiologic studies.⁹ Different asthma severity classification schemes have included symptom measures, functional limitations, pulmonary function, bronchial hyperresponsiveness (BHR), hospitalizations and emergency room visits, and medication use. In the absence of properly validated measurement schemes,^{10,11} biologic assessments may provide the most objective and reliable measurements of asthma severity. Standard clinical factors that include measures of lung function, symptoms, and rescue β -agonist use appear to contribute independently to asthma severity, although BHR and markers of airway inflammation may provide additional information about disease activity.¹² Heterogeneity in the underlying pathophysiologic process and difficulty in distinguishing the effects of asthma control from the effects of asthma severity may help to explain the complex relationships between the different aspects of asthma severity.¹³ Most recently, guidelines of the Global Initiative for Asthma¹⁴ that categorize asthma severity according to the cross-classification of current therapy with symptoms and lung function have been promulgated.

Material and methods

Objective

The objective of this review was to determine whether, among pregnant women with asthma, pregnancy and stage of pregnancy influence the severity of maternal asthma. Subgroup analyses were contemplated by different methods of assessment of asthma severity (eg, lung function measures, measures of BHR, markers of airway inflammation, or a validated severity scale).

Search and study selection

Several electronic databases were searched: CINAHL on Ovid (1982 to December 2002), Current Contents on Ovid (1993 to January 2003), EMBASE on Ovid (1980 to January 2003), MEDLINE/PUBMED (1966 to January 2003), OLDMEDLINE on NLM Gateway (1957 to 1965), and Science Citation Index Expanded on Web of Science (1945 to January 2003). The following search strategy was used: (asthma or asthmatic) and (pregnancy, pregnancies, or pregnant). Studies were not excluded on the basis of language. However, most papers that were published in non-English languages appeared to be either reviews or case series and were

excluded on that basis. Reference lists of all available primary studies and previous reviews were hand-searched to identify potentially relevant citations.

Prospective studies that investigated the course of maternal asthma during pregnancy were eligible for inclusion. Retrospective studies, case-control studies, case series, and case reports were excluded because of concern about their validity. To be considered, studies had to include women with diagnosed asthma and evidence of current disease who were enrolled before their third trimester and followed through pregnancy. Women were assessed for the effect of pregnancy on asthma severity and the effect of stage of pregnancy on asthma severity. That is, asthma severity was analyzed in the pregnant versus the nonpregnant state (within-person comparisons were included and a separate comparison group was not required) and by stage of pregnancy (ie, months, weeks, trimester). Studies that examined either or both of these lines of analysis were considered for inclusion. To be considered, studies had to include 1 of their primary reported outcome measures, a biologic measure of asthma severity (eg, lung function measures, measures of BHR, markers of airway inflammation) or an asthma severity scale that had been tested for standard clinimetric properties, which included validity and reliability.¹⁵⁻¹⁷ Studies that were concerned primarily with the effect of maternal asthma on pregnancy outcomes rather than with the effect of pregnancy on maternal asthma were not included.

Quality assessment

The Methods Work Group for the US Preventive Services Task Force (USPSTF) has provided criteria for the assessment of the internal validity of individual studies by study design, which includes observational studies.¹⁸ USPSTF quality ratings of good, fair, and poor were used on the basis of these criteria. A *good* study was defined as meeting all criteria; a *fair* study was defined as failing to meet ≥ 1 criteria, but not including an important limitation that could invalidate its results; and a *poor* study was defined as possessing an important limitation. The USPSTF quality criteria, which were modified to apply specifically to observational studies, included the following items:

Initial assembly of comparable groups: Consideration of potential confounders with either restriction or measurement for adjustment in the analysis

Important differential loss to follow-up or overall high loss to follow-up

Measurements (of outcome): Reliable and valid (includes masking of outcome assessment)

Analysis: Adjustment for potential confounders

Data analysis

One of the original goals of this review was to combine the data quantitatively. However, because heterogeneity of outcome measurement and asthma treatment precluded this, emphasis instead was placed on consideration of the possible sources of clinical heterogeneity between study results, which included methods issues and possible effect modification by baseline severity.^{4,5,19,20}

Results

Seven prospective studies were identified from the literature search.²¹⁻²⁸ Among these, 3 studies met the inclusion criteria (Table I).^{23,25,28} Clarification of details of these 3 studies was obtained successfully by contact with the authors. Excluded studies are described in Table II.

Description of included studies

Sims et al²³ studied changes in lung function over time among 27 pregnant women with a history of asthma attacks in the previous 3 years and 12 pregnant women without a history of respiratory disease who were selected randomly from the same medical and obstetrics clinic before 20 weeks of gestation. However, only 11 of the 27 women were considered to have active asthma, which are the women who were considered for this review. The women were assessed with spirometry every 4 weeks until 28 weeks of gestation, twice weekly until 36 weeks of gestation, weekly through the end of pregnancy, 48 hours after delivery, and 6 weeks after delivery.

Juniper et al²⁵ recruited 26 women with asthma of childbearing capacity before conception of whom 6 women withdrew from the study, 16 women subsequently conceived, 3 women failed to conceive, and 1 woman had a miscarriage. They reported the change in BHR to methacholine challenge in the 16 pregnant women and 3 nonpregnant control subjects and change in asthma medication use compared to preconception among the 11 pregnant women with asthma who required medications. BHR was defined as the concentration of methacholine that was needed to provoke a fall in forced expiratory volume in 1 second (FEV₁) of 20% (PC₂₀). In addition, the results of measures of lung function, FEV₁ and forced vital capacity, were reported figuratively. Although change in medication requirement was the main outcome used to determine asthma severity in their study, the scale that they used was not validated (personal communication, E. Juniper, January 2, 2003). Therefore, we chose to focus on their objective measurements of BHR and lung function. Data for the women were analyzed with mean preconception measures, once

each during the second and third trimesters and 1 month after delivery.

Nittner-Marszalska et al²⁸ prospectively studied 27 pregnant women with a history of asthma >12 months who were recruited during their first trimester (personal communication, M. Nittner-Marszalska, May 15, 2003). At the initial assessment, subjects were classified according to the guidelines from the Global Initiative for Asthma for asthma severity.¹⁴ Follow-up examinations that were performed at the end of each of the 3 trimesters included physical examinations, lung function tests, peak expiratory flow values, and arterial blood gas measurements. The results of lung function tests were reported figuratively. The overall change in asthma severity during pregnancy compared with the year before pregnancy was reported on the basis of the presence of exacerbations and responsiveness to treatment, but no evidence was given that this scheme had been validated for research. Thus, we focused on their report of objective measures of lung function during pregnancy, specifically FEV₁ and forced vital capacity.

Method quality of included studies

With the USPSTF criteria, the study by Juniper et al²⁵ was judged to be “fair,” although the studies by Sims et al²³ and Nittner-Marszalska et al²⁸ were judged to be “poor.”

With regards to the comparability of the groups, Juniper et al²⁵ scheduled clinic visits at least 4 weeks after any known exposure to potential confounders. Potential confounders, which included heartburn and flatulence (proxies for gastroesophageal reflux), allergen exposure, and upper respiratory tract infections, were measured, but only if the clinic visit had not been scheduled in this manner. This is the only study that assessed the effect of pregnancy on asthma that assembled women with asthma preconception, which provided nonpregnant control data on women with asthma that was gathered prospectively during both the preconception and postpartum periods. They also used a nonpregnant asthmatic comparison group, although it is uncertain whether this group of women who did not conceive after 1 year of attempting to do so was systematically different from the group of women who were able to conceive. For instance, the nonpregnant women appeared to be slightly older than those who conceived (Table I). Sims et al²³ used a nonasthmatic pregnant comparison group and intrasubject postpartum measurements as nonpregnant control data. They did not report measuring any potential confounders. Although Nittner-Marszalska et al²⁸ systematically investigated possible factors that were responsible for exacerbations of asthma that occurred during pregnancy (Table I), they were not able to present statistically valid results on potential confounders

Table I Characteristics of studies

Study	Methods	Participants	Comparisons	Outcomes
Sims et al ²³	Study design: Prospective cohort study	Subjects included (analyzed): 27 pregnant women with asthma (including 11 women with active asthma) and 12 pregnant women without a history of respiratory disease	Pregnancy vs postpartum period	Method for outcome measurement: Change in FEV ₁ /FVC% ^{†*} and FVC (% predicted) using spirometry
	Blinding: No	Baseline condition: History of asthma attacks in previous 3 years	Pregnant women with asthma vs pregnant women with no asthma	Frequency: Every 4 weeks until 28 weeks of gestation, twice weekly until 36 weeks of gestation, weekly through the end of pregnancy, 48 hours and 6 weeks after delivery
	Potential confounders measured: None reported	Demographics: Mean age, 28 y (active asthma) and 29 y (no asthma)	Stage of pregnancy, by week	No significant change in lung function observed between pregnancy and postpartum period nor by stage of pregnancy
	Withdrawals: Unknown	Setting: Combined medical and obstetrics clinic in the United Kingdom		
	Analysis: No longitudinal analysis, no control of confounders Quality rating: Poor			
Juniper et al ²⁵	Study design: Prospective cohort study	Subjects included: 16 Asthmatic women and 3 nonpregnant asthmatic women	Pregnancy vs preconception	Method for outcome measurement: Change in BHR; change in FEV ₁ , FVC, FEV ₁ /FVC% using spirometry; change in asthma medication use (not considered)
	Blinding: Yes (subjects and technicians)	Baseline condition: Current asthma symptoms and BHR*	Pregnant asthmatic women vs nonpregnant asthmatic women	Frequency: Preconception, once each during the second and third trimesters, 1 mo after delivery; every 3 months for up to 12 months (non pregnant asthmatic women)
	Potential confounders measured: Heartburn and flatulence (proxies for gastroesophageal reflux), allergen exposure, upper respiratory tract infections	Demographics: Mean age, 27 y (pregnant) and 32 y (nonpregnant)	Stage of pregnancy, by trimester	BHR improved preconception to pregnancy in 11/16 (69%), worsened in 5/16 (31%)

Table I Continued

Study	Methods	Participants	Comparisons	Outcomes
Nittner-Marszalska et al ²⁸	Withdrawals: 6 Subjects (23%) Analysis: Longitudinal analysis; controlled for confounders Quality rating: Fair	Setting: Allergy clinic in Ontario, Canada, with additional recruitment from general practitioners and the news media		Greatest improvement in BHR between preconception and the second trimester Reversion to preconception BHR 1 month after delivery Those most hyperresponsive initially showed the greatest improvement No significant change in lung function by stage of pregnancy (trend towards improvement in second trimester)
	Study design: Prospective cohort study	Subjects included: 27 Pregnant asthmatic women	Pregnancy vs year before pregnancy (not considered)	Method for outcome measurement: Change in FEV ₁ and FVC (% predicted) with spirometry, change in asthma severity by exacerbations and medication requirements (not considered)
	Blinding: No Potential confounders measured: Smoking, atopy, aspirin Withdrawals: 2 Subjects (7%) Analysis: No longitudinal analysis, no control of confounders Quality rating: poor	Baseline condition: History of asthma >12 months Demographics: Mean age, 27 y Setting: Allergy clinic in Poland	Stage of pregnancy, by trimester	Frequency: Initial examination, once at the end of each trimester No significant change in lung function by stage of pregnancy (trend towards improvement in second trimester)

FEV₁, Forced expiratory volume in 1 second; FVC, forced vital capacity, BHR, bronchial hyperresponsiveness (PC₂₀ methacholine < 16mg/mL).

because of sample size limitations (personal communication, M. Nittner-Marszalska, May 15, 2003).

Regarding loss to follow-up, Juniper et al²⁵ initially enrolled 26 women who met the study criteria. Six women withdrew (23%) after the first clinic visit (3 women stopped attempting to conceive; 2 women did not like spirometry; 1 woman was withdrawn because of noncompliance); of the remaining women, 16 women carried their pregnancy to the third trimester. Follow-up

of <80% of subjects, as experienced by this study, may sometimes be viewed with scepticism.^{29,30} Nittner-Marszalska et al²⁸ lost 2 women because of miscarriage (personal communication, M. Nittner-Marszalska, May 15, 2003). Sims et al²³ did not report data on withdrawals or losses to follow-up.

With regards to measurements, Juniper et al²⁵ described in detail the procedures for determining BHR to methacholine and clinical asthma severity. Although

Table II Characteristics of excluded studies

Study	Study characteristics	Reasons for exclusion
Gluck and Gluck ²²	47 Pregnant women with a history of ≥ 1 asthma attack in the past 5 y who were recruited from the prenatal clinic or gynecology emergency room of a Florida hospital were studied prospectively Within-subject comparison with prepregnancy state	Lack of objective measure of change in asthma severity as a primary outcome measure with results reported (Clinicians' subjective assessment of wheeze and amount of medication use)
Stenius-Aarniala et al ²⁴	181 Pregnant women with 198 pregnancies who satisfied the 1975 criteria for asthma by the American Thoracic Society and the American College of Chest Physicians who had been referred to a hospital in Finland were studied prospectively 198 Nonasthmatic women were assembled retrospectively from labor records and matched for age, parity, and time of delivery; within-subject comparison with prepregnancy state	26% of women enrolled in third trimester Lack of objective measure of change in asthma severity as a primary outcome measure with results reported (Objective criteria used, but unvalidated)
Schatz et al ²¹ and Kircher et al ²⁷	330 Pregnant women with 366 pregnancies with a documented reversible obstructive airway disease were recruited while registering for prenatal care at a California health pregnancies maintenance organization were studied prospectively Secondary analysis of completed sample with 568 pregnant women ²⁷ Within-subject comparison with prepregnancy state	Lack of objective measure of change in asthma severity as a primary outcome measure with results reported (Women's subjective measure of overall severity during pregnancy compared to before pregnancy)
White et al ²⁶	31 Pregnant women who answered "yes" to the question, "Do you have asthma?" and who were recruited from a prenatal clinic in a Bristol hospital were studied prospectively Within-subject comparison with prepregnancy and postpartum states	Lack of clear evidence of asthma diagnosis Lack of objective measure of change in asthma severity as a primary outcome measure with results reported (Women's self-perception of symptom score)

it was not possible for Juniper et al to blind the research assistant who performed the methacholine challenge tests and spirometry to the pregnancy status of the subjects, both the research assistant and the subjects themselves (who were recording symptoms and medication scores) were blinded to the study hypothesis. Blinding did not occur in either the study by Sims et al²³ (personal communication, M. de Swiet, February 4, 2003) or in the study by Nittner-Marszalska et al²⁸ (personal communication, M. Nittner-Marszalska, May 15, 2003).

With regards to their analysis, Juniper et al²⁵ used a method for the analysis of data longitudinally, repeated measures analysis of variance, and attempted to control for the potential confounders in their analysis. Sims et al²³ did not adjust for potential confounders (personal communication, M. de Swiet, February 4, 2003). Student paired and unpaired *t* tests were used, and multivariate analysis was not performed. In particular, failure to account for asthma

treatment in the study design or analysis was a critical omission, because medications were altered according to patient needs and the effects of asthma treatment may have confounded the study results completely. Nittner-Marszalska et al²⁸ used the Wilcoxon test and did not adjust for confounders in their analysis.

Effect of pregnancy on asthma severity

The heterogeneous methods of assessment of asthma severity and treatment of asthma in the 3 studies precluded any meta-analysis of the results. The discussion of results will focus on Juniper et al,²⁵ the most valid of the studies.

Juniper et al²⁵ failed to find a statistically significant change in lung function before, during, and after pregnancy. Likewise, Sims et al²³ did not observe any significant change in lung function between pregnancy and

the postpartum state in either the control or asthmatic group.

Juniper et al did report a statistically significant overall effect of pregnancy on BHR ($P = .033$). An improvement in BHR between preconception and both the second and third trimesters was noted in 11 of 16 subjects (69%); 5 of 16 subjects (31%) experienced deterioration of condition.

Effect of stage of pregnancy on asthma severity

The greatest improvement (an overall 2-fold improvement in BHR from a mean PC_{20} of 0.35mg/mL to 0.72 mg/mL) was observed by Juniper et al²⁵ from preconception to the second trimester. The difference between the second and third trimesters was not statistically significant. A reversion to preconception BHR occurred 1 month after delivery.

Lung function, as demonstrated figuratively by both Juniper et al²⁵ and Nittner-Marszalska et al,²⁸ appeared also to peak in the second trimester, although this effect did not reach statistical significance. Sims et al²³ did not demonstrate this trend towards improvement in lung function during pregnancy.

Analysis by baseline severity

The study by Juniper et al²⁵ was the only study to provide information on this relationship. They demonstrated a statistically significant inverse relationship between the initial level of BHR and a change in responsiveness between preconception and the second trimester: The greatest improvement was among those women who were most hyperresponsive initially.

Comment

Most reports in the literature on the effect of pregnancy and stage of pregnancy on maternal asthma have been uncontrolled case series and retrospective studies. The quality of studies thus far has been quite poor, even among those studies that were conducted prospectively. Most studies have relied on subjective assessments of change in asthma severity; even those studies that attempted to use more objective criteria did not validate their severity classification schemes (Table II). Although some of the excluded studies were larger than the studies that were included in our review, sample size is not a typical measure of study validity and was not used by us as such. A large study that subjectively excludes a substantial number of participants may be more biased than a smaller study that uses a more valid selection process. For example, in their analysis of wheezing among study

participants, Schatz et al²¹ included only 75 of 330 participants. This subset was selected arbitrarily, on the basis of participants' personal assessment of their asthma during pregnancy.

Of the 3 studies that did meet our selection criteria, the methods of 2 of the studies appeared to be too vulnerable to potential bias and confounding to be considered reliable. Preliminary conclusions that were based on the results of the third study indicate that pregnancy may affect the severity of a woman's asthma, as measured by BHR. Another measure of asthma severity, lung function, appeared to follow the same trend during pregnancy but was not statistically significant. The small number of subjects in each study raises the possibility of this being type II error (a false-negative result). If the change in lung function that occurs because of asthma during pregnancy is smaller than that of BHR, this also may have contributed to their null results. Alternatively, it may be that, when maternal asthma is well controlled, a statistically and clinically significant change in lung function does not occur during pregnancy. The extant research does not currently allow us to distinguish these possibilities.

Potential mechanisms for influence of pregnancy on asthma severity

A number of physiologic changes during pregnancy might affect the course of maternal asthma, including mechanically and hormonally mediated alterations in the respiratory system and immune functioning. Mechanical changes in the respiratory system include the expansion of the ribcage and pressure from the uterus on the diaphragm late in pregnancy that can result in dyspnea, which must be distinguished from shortness of breath that is related to asthma.³¹ In addition, airway closure that results from decreased functional residual capacity during tidal breathing might lead to exacerbation of maternal asthma.³

Most of the research that is related to potential mechanisms for the effect of pregnancy on asthma has focused on the altered hormonal milieu of pregnancy and, in particular, the potential bronchodilating effects that are induced by steroids.³² In pig bronchus and guinea pig airway, smooth muscle, estradiol, progesterone, cortisol, and testosterone all potentiated the β -adrenergic-mediated relaxation of airway smooth muscle³³; progesterone directly inhibited airway smooth muscle contraction.³⁴ In mature rabbit lung tissue, β -adrenergic receptor activity was enhanced in the presence of estrogen, and the effect was reversed by progesterone.³⁵

Although further confirmation is needed, the results of animal studies appear to corroborate clinical observations of women who report exacerbations of asthma premenstrually or at menopause,³⁶ evidence of relief from severe premenstrual asthma exacerbations with

injections of progesterone,³⁷ and improvement in lung function with use of hormone replacement therapy.³⁸ In agreement with earlier clinical observations,³⁹ a recent prospective study in which subjects did not know the gender of their child before delivery demonstrated that women with asthma who were pregnant with girls were more likely than those women with asthma who were pregnant with boys to report increased symptoms of asthma during pregnancy.⁴⁰ Likewise, asthma medication use was noted to be greater among pregnant women with asthma who were pregnant with girls than those women who were pregnant with boys.⁴¹

However, studies thus far have failed to demonstrate a direct association between the reduction in BHR and progesterone and estradiol levels in pregnant women and in nonpregnant women whose cases were followed through their menstrual cycles.^{25,42,43} These negative results could be related to small sample sizes or competing bronchoconstrictive effects of other pregnancy-related factors (such as prostaglandin F₂, which may be enhanced by estradiol).³² Improvement in asthma during pregnancy might be explained additionally by other factors (such as free cortisol⁴⁴ and relaxin, a peptide hormone that reaches its highest concentrations during pregnancy and has exhibited antiasthmatic effects in guinea pigs).^{45,46} Ultimately, it may not be a single hormone that affects the course of asthma during pregnancy, but the overall effect of multiple, perhaps even competing, agents.⁴⁷

In addition to direct effects of hormones on the maternal respiratory system, pregnancy may affect asthma indirectly through increased comorbid conditions that exacerbate asthma or through behavioral or environmental changes. Maternal cell-mediated immunosuppression may increase maternal susceptibility to viral infections, which have been reported to be the most common precipitators of severe asthma during pregnancy.^{48,49} Increase in progesterone during pregnancy has been associated with relaxation of the smooth muscle of the lower esophageal sphincter, such that one third of pregnant women experience reflux, heartburn, and indigestion during pregnancy.² Bronchoconstriction is believed to occur when gastric acid is present in the esophagus, and gastroesophageal reflux has been reported to occur among 45% to 89% of patients with asthma.^{50,51}

The undermedication of pregnant women with asthma may contribute to worsening of asthma symptoms in some women during pregnancy.^{49,52} Concern over the potential effects of asthma medications on the fetus by physicians, or pregnant women with asthma themselves, may contribute to this problem. It is also possible that the frequent sense of well-being that is reported during pregnancy could mask symptoms and contribute to insufficient asthma control during pregnancy.⁵³

Implications for practice and research

Given the lack of current and valid data, no implications for practice could be drawn from this systematic review. It is noteworthy that clinical guidelines have been developed that had to rely on this very weak body of evidence.⁵⁴

Well-conducted studies of lung function and BHR in pregnant women with asthma that use more substantial sample sizes and control for important confounders are needed. The effect of pregnancy and stage of pregnancy on different aspects of clinical asthma severity, including symptoms and medication use, must be elucidated; validated severity scales, which are appropriate for pregnant women with asthma, must be developed. In addition, more direct assessments of airway inflammation are needed, perhaps with the use of sputum eosinophil count or exhaled concentration of nitric oxide,⁵⁵ although the feasibility of such techniques in pregnant women with asthma is uncertain and must be validated.

Because the study by Juniper et al²⁵ preceded the release of current guidelines for treating pregnant women with asthma⁵⁴ and would not reflect modern treatment of asthma, the study results may be limited in their generalizability. In addition, studies have shown that pregnant women with asthma who are in less controlled settings tend to be undermedicated and may experience worsening of asthma symptoms during pregnancy.⁵⁶ Further studies are needed to explore the effects of pregnancy on maternal asthma in population-based settings and to address possible effect modification by baseline asthma severity. Although studies on the course of asthma during pregnancy would elucidate possible mechanisms for the pathophysiologic condition of asthma, further research that directly investigates the mechanisms for pregnancy's putative effects on maternal asthma is also important.

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