

Asthma and pregnancy

Key words: Asthma, asthma morbidity, pregnancy

Asthma, probably the most common medical condition occurring during pregnancy, can increase maternal and fetal mortality and morbidity. Conversely, the mechanical, hormonal, and metabolic stresses imposed by pregnancy might exacerbate asthma in the expectant mother. Accordingly, a knowledge of the complex interaction between these 2 conditions is essential if the health of the mother and fetus is to be maintained.

Pregnancy affects thoracic configuration, lung volumes, metabolic rate, and ventilatory drive in the expectant mother.¹ Specifically, the diaphragm moves in a rostral direction and becomes more curved, probably increasing its ability to generate pressure. The thoracic anterior-posterior diameter increases, leading to a more barrel-chested appearance. The functional residual capacity, residual lung volume, and total lung capacity decrease, but the vital capacity is unchanged. Of interest, the FEV₁ and peak expiratory flow rate are unchanged, and airway resistance is decreased despite the reduction in end-expiratory lung volume, suggesting that lower airway caliber is increased, at least in the large airways.² Data in a very small number of subjects suggest that non-specific airway reactivity assessed by means of methacholine challenge might decrease during pregnancy.³

During pregnancy, oxygen consumption, carbon dioxide production, and alveolar ventilation increase. However, increases in alveolar ventilation are disproportionate to increases in carbon dioxide production (an effect of increased progesterone), such that arterial PCO₂ decreases and arterial PO₂ increases to greater than nonpregnant values. These changes in ventilation increase the work of breathing and likely explain the physiologic dyspnea that occurs in many women during pregnancy.

Of importance, asthma severity changes during pregnancy are not unimodal. Rather, asthma symptomatology appears to worsen, improve, or remain unchanged in roughly equal proportions.⁴ Approximately 10% of pregnant asthmatic patients seek urgent care at some time during their pregnancy, especially those not taking inhaled corticosteroids.^{4,5} Although exacerbations of

asthma can occur any time during pregnancy, the period of greatest incidence appears to be in the third trimester, from weeks 24 to 36.⁴ Thereafter, in the last month of pregnancy, asthma exacerbations are infrequent and usually mild. The reasons for this time course are unknown.

In this issue of the Journal, Schatz et al⁶ report the effects of pregnancy on asthma and relate asthma morbidity to asthma severity in the largest prospective study performed to date. Investigators from the 16-center Maternal Fetal Medicine Units Consortium studied 1739 pregnant asthmatic patients. As might be expected from the location of the centers, the study population was primarily urban and was comprised largely of single African American women receiving subsistence income. Asthma severity was classified as mild, moderate, or severe on the basis of the schema described by the 1993 National Asthma Education Program Working Group on Asthma and Pregnancy modified to incorporate medication use.⁷ The vast majority of participants were classified at study entry as having mild (50.2%) or moderate (46.8%) disease. Very few (3%) were classified as having severe disease. Unfortunately, the medications used to control asthma in this population are not described in this report.

Schatz et al⁶ report that asthma morbidity, as reflected in hospitalizations, urgent care visits, oral corticosteroid use, and asthma symptoms during labor and delivery, correlated closely with the asthma classification applied at entry into the study; that is, all the above parameters of asthma morbidity increased in prevalence as the classification increased from mild to severe. These data are not surprising and are in accordance with our expectations in nonpregnant patients.

Of considerable interest, however, a high percentage of subjects switched categories during pregnancy. For example, 30% of subjects who initially were in the mild category converted into the moderate-to-severe category, and 23% of subjects in the moderate-to-severe classification converted into the mild classification. The fact that approximately 30% of the subjects in the mild category (or almost one sixth of all subjects) converted to the moderate to severe category is cause for concern. This is especially true because this study was performed by a group of academic medical centers in an era (1994-1999) when the National Asthma Education Guidelines and the importance of inhaled corticosteroids were emphasized. Unfortunately, the factors leading to this category change were not explored in this article but need to be because of their obvious clinical importance.

Beyond its effects on the mother, the importance of maternal asthma lies in its effects on fetal health. Abnormalities in lung gas exchange produced by worsening asthma can cause fetal hypoxia. Previous large and retrospective studies on the basis of a review of health records have suggested that the incidence of preterm labor, low-birth-weight pregnancies, preeclampsia, and congenital

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anomaly are increased in asthmatic women.^{8,9} In contrast, smaller prospective studies involving close observation of subjects and participation of physicians with expertise in asthma suggest that pregnancy outcome is similar in asthmatic and nonasthmatic women.⁴ In all likelihood, however, the well-being of the fetus depends on the severity of asthma. In fact, fetal birth weight, a global index of fetal growth and development, correlates with the mother's FEV₁.¹⁰ Babies of women with the lowest percent predicted FEV₁ tend to have the lowest birth weights.

Whether the relationship between maternal asthma severity and infant outcome is exclusively an effect of asthma per se or depends also on the confounding effects of asthma medication is unclear. (Women with more severe asthma are more likely to require a more intense medical regimen, including high-dose inhaled or oral corticosteroids for control.) In fact, corticosteroids in a dose equivalent to 10 mg of oral prednisone daily decrease fetal birth weight and are associated with an increased risk of preeclampsia.^{11,12} In this regard it will be interesting to see the data in the 1739 asthmatic women in the Maternal Fetal Medicine Units Consortium relating asthma severity to pregnancy outcome. These data will be reported in a separate publication, hopefully describing the medications used.

What can we conclude from the article by Schatz et al⁶ and other studies?^{4-7,12} First, because the best fetal and maternal outcomes have been reported by centers using a multidisciplinary approach to the assessment and care of the pregnant asthmatic patient, pregnant asthmatic patients should be cared for jointly by physicians with expertise in asthma, as well as obstetrics. Second, because a significant percentage of pregnant asthmatic patients with mild or well-controlled disease might convert to a severe or uncontrolled category, pregnant asthmatic patients should be monitored closely with pulmonary function testing (ie, peak flow, FEV₁, or both). Third, because the adverse effects of uncontrolled asthma on the health of the fetus and the mother are generally believed to outweigh the risks of drugs on the health of the fetus,^{7,12} a risk-benefit analysis suggests that asthma should be treated as aggressively during pregnancy as in its absence.

What do we still need to learn? First, the mechanism or mechanisms underlying the variable effects of pregnancy on the control of asthma are poorly understood. Several possibilities come to mind. Changes in the severity of asthma might be a result of changes in medications prescribed, specifically the use (or lack thereof) of corticosteroids. Worsening asthma might also be related to environmental factors or infection. Finally, changes in asthma symptomatology might be the result of highly individual variables, such as changes in hormonal levels or gastroesophageal reflux disease, a common occurrence during pregnancy. Of interest, the effects of pregnancy on asthma tend to be reproducible from pregnancy to pregnancy, suggesting that physiologic or environmental factors rather than differences in medication use or infection might be most important.⁴

Second, a risk analysis for fetal outcome needs to be performed for the newer drugs now available to treat asthma (ie, leukotriene receptor antagonists; fluticasone and budesonide, alone and in combination with long-acting β -agonists). The classic National Collaborative Perinatal Project performed in the 1960s and 1970s examined the teratogenic effects of commonly used drugs then in use in approximately 50,000 subjects.¹³ This study suggested that epinephrine and α -adrenergic compounds other than pseudoephedrine increase the risk of congenital anomalies and should be avoided during pregnancy. Smaller studies performed since have not demonstrated an increased risk of major congenital anomalies with first-trimester use of inhaled beclomethasone and oral corticosteroids, inhaled and oral β -agonists, theophylline, and cromoglycate.⁷ However, theophylline and oral corticosteroids appear to increase the risk of preeclampsia, and corticosteroids decrease fetal birth weight.¹²

Third, the effects of pregnancy-related changes in female sex hormones (progesterone and estrogen) on airway function and nonspecific airway reactivity need to be assessed at each stage of pregnancy. Although the data obtained to date suggest that progesterone decreases airway reactivity and improves airway function in female asthmatic patients,³ the numbers of subjects studied are small. In fact, progesterone in particular exerts complex effects. For example, progesterone induces mucosa hyperemia in the upper and possibly lower airway but relaxes airway smooth muscle directly and potentiates β -adrenergic agonist-induced relaxation.¹⁴ On the other hand, progesterone competes with glucocorticoids for occupancy of the glucocorticoid receptor and prevents its nuclear translocation, raising the possibility that the physiologic effects of endogenous and exogenous corticosteroids might be antagonized.^{15,16}

In the past several years, much has been learned that is relevant to the management of asthma in pregnancy. The important study by Schatz et al⁶ in this issue of the *Journal* provides more useful information but also raises new questions. New knowledge relevant to the several issues raised above will likely further advance our management of the pregnant asthmatic patient. As such, they are a fertile area for investigation.

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