
Pregnancy and Asthma*

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Asthma has been reported to occur in 0.4 to 1.3 percent of pregnant women. Unfortunately, the literature offers few data on prognostic information regarding potential changes in asthma during pregnancy. While it is generally impossible to predict the effect of pregnancy on asthma for an individual patient, it is established that uncontrolled asthma during pregnancy has been associated with maternal and fetal mortality. However, when women with severe asthma have their disease stabilized with oral and/or inhaled corticosteroids, maternal and fetal mortality can be avoided. This article will highlight some of the following: (1) physiologic alterations associated with pregnancy and consider their effects on asthma; (2) effects of pregnancy on the course of asthma; (3) management of acute and chronic asthma; and (4) labor and delivery.

Physiologic Alterations Associated With Pregnancy

Cardiovascular Changes

Total body water increases 6 to 8 L, of which approximately 67 percent is extracellular. Plasma volume increases in the first and second trimesters, and red cell mass increases 20 to 40 percent. The increase in plasma volume results in hemo-dilution so that hemoglobin falls to the range of 11 to 12 g/dl. Cardiac output rises 20 to 50 percent, highest levels noted at 20 to 24 weeks' gestation. In late pregnancy, the arteriovenous oxygen difference is greater than in the non-pregnant state, caused by increased oxygen consumption and peripheral extraction by mother (and fetus). Uterine blood flow, approximately 100 ml/min in the first trimester and 200 ml/min by the 28th week, may rise to 500 ml/min at term.

Fetal Oxygenation

In 1971 Wulf et al10 published data on the influence of differing concentrations of inspired oxygen (7 to 100 percent) on placental gas exchange. Women were at term and not described as having asthma or underlying pulmonary disease. Maternal arterial blood was compared with fetal blood from umbilical vessels immediately after delivery. Figure 1 illustrates results of 64 mothers breathing room air. They were not hyperventilating. When the mothers inspired 100 percent oxygen, fetal umbilical vein oxygen tension rose to a mean of 40 mm Hg when maternal oxygen tension was 583 mm Hg, emphasizing the large shunt effect. Oxygen saturation increased about 15 percent associated with this 8-mm Hg increase. When inspired oxygen was lowered to 15 percent, maternal arterial blood contained a Po2 of 65 mm Hg and PO2 of 39 mm Hg. Fetal umbilical vein revealed a Po2 of 26 mm Hg and PCO2 of 47 mm Hg. The maternal values might simulate measurements during an acute attack of asthma. Maternal alkalosis from hyperventilation may result in decreased fetal oxygen tension by: (1) relative decrease in uterine blood flow (vasoconstriction); (2) decreased maternal venous return; (3) decrease in umbilical blood flow; or (4) shift in maternal and fetal oxyhemoglobin dissociation curves to the left. Oxygen administration is considered beneficial even if hypocapnia and respiratory alkalosis result. In the studies of Wulf et al10 fetal oxygen delivery was thought to be compromised when pH exceeded 7.60 and PCO2 was 15 mm Hg, values unlikely to be reached in acute asthma. Clinically, maternal hypoxemia coupled with respiratory failure is a threat to the mother's health and survival of the fetus.

To describe quantitatively the process of oxygen transfer from mothers to fetus (Fig 1), one would need to know rates of blood flow in each system, oxyhemoglobin dissociation curves for fetus and mother, hemoglobin concentrations, whether active transport occurs, whether CO2 is transferred, and the permeability of oxygen.11 Such data are not fully available; however, because the system has characteristics of a nonideal concurrent exchange system, umbilical venous oxygen tension must be less than maternal placenta levels. Fortunately, compensatory mechanisms exist to achieve satisfactory oxygen delivery to fetal tissues. Because of the shape of the fetal oxyhemoglobin dissociation curve, small changes in oxygen tension can produce significant falls in oxygen saturation.

Pulmonary Function

The increases of progesterone during pregnancy have been associated with increased tidal volume (450 to 600 ml) resulting in minute ventilation rises of 40 to 50 percent.13 Vital capacity and frequency of respiration are usually unchanged. Functional residual capacity (FRC) is reduced in the last half of pregnancy, resulting from decreases in expiratory reserve volume and residual volume.14 Total lung capacity is reduced but probably has no clinical importance. These changes were recorded in normal pregnant women. Generally, there are no significant changes in flow rates of large and small airways in the nonasthmatic pregnant

![Figure 1. A simplified drawing of oxygen transport from mother to fetus. Oxygen tension in mm Hg.](http://journal.publications.chestnet.org/pdaccess.ashx?url=/data/journals/chest/21451/ on 06/27/2017)
Hormonal Changes

Many hormonal changes are documented in the literature. Progesterone's effect on respiration is accepted, although the clinical relevance remains unclear. Estrogen secretion increases but may have no clinical ramification. Plasma cortisol rises (both free and bound), but it does not appear that increases in endogenous cortisol concentrations prevent episodes of asthma. Minute quantities of prostaglandins (PGF₂α, PGE₁, PGE₂) have been detected in amniotic fluid, but studies in asthmatic patients have not been reported. Measurement of urinary metabolites of PGF₂α, a bronchoconstrictor, revealed a threefold elevation during pregnancy with a 10- to 30-fold rise during labor. Perhaps data on levels of leukotrienes may provide insight into episodes of wheezing during pregnancy. On the other hand, because of their de novo synthesis on mast cell degranulation, increases of leukotrienes only may reflect ongoing bronchospasm. It is unclear what effect fetal production of histamine has on asthma or its interaction with histaminase, which is produced by the mother.

Effects of Asthma During Pregnancy on the Mother and Fetus

The literature reports increases in prematurity (7.4 percent vs 5.0 percent in controls), defined as gestations of less than 37 weeks, and in low birth weight infants, defined as weighing less than 2,500 g (7.1 percent vs 3.7 percent in controls). Gordon et al. described devastating outcomes for 18 women with uncontrolled wheezing during pregnancy. Four patients died, and five of their pregnancies were associated with perinatal deaths. These data are not accompanied by treatment regimens, and the pregnancies occurred during 1959 to 1965. Asthma pharmacotherapy has improved substantially since then. When "uncontrolled asthma" or recurrent episodes of asthma are brought under control with available pharmacotherapy and appropriate environmental control, for example, more favorable pregnancy outcomes can result, even in women who require systemic corticosteroids. When confronted with an asthmatic patient who desires to become pregnant, the physician should attempt to prevent disabling wheezing, nocturnal asthma, emergency room visits, and status asthmaticus. With current therapy, these goals can be achieved without increased risk to the mother or fetus. Although several studies note exacerbations or lack of amelioration of severe asthma during pregnancy, an occasional patient may require all available anti-asthma therapy, including prednisone, during her first and third pregnancies with only intermittent theophylline required during her second pregnancy.

Management of Asthma During Pregnancy

The risks of inadequately controlled asthma are associated with hypoxemia and either respiratory alkalosis (which may decrease uterine blood flow) or acidosis (which may result in a fatality or need for mechanical ventilation). Available pharmacotherapy can assist physicians in providing improved care during pregnancy without increasing the risk to the mother or fetus. Figure 2 illustrates some of the factors that could contribute to a physician making a choice among therapeutic regimens. The deficiencies with utilizing the Physicians' Desk Reference are well known. Although the Food and Drug Administration does not disallow a drug being prescribed for unlabeled indications, the physician may be vulnerable from a medical-legal standpoint should a coincidental malformation occur. For the investigator, the evaluation of drug safety in pregnancy is not usually possible. Confirmation of safety of a drug in pregnancy may be impossible to achieve if the sample population is small. Table 1 lists recommended pharmacotherapy for the pregnant asthmatic patient. These modalities have been shown to be safe by published data or by long-term use. For acute wheezing dyspnea, epinephrine may be administered and does not appear to cause long-term sequelae in the fetus. Its rapid metabolism likely explains its safety. Given subcutaneously, its effects are primarily as a β-adrenergic agonist. It cannot be used successfully for tocolysis during premature labor because of its rapid inactivation. Some physicians prefer to administer terbutaline subcutaneously for acute asthma during pregnancy. Presumably this results from the desire to avoid potential α-adrenergic stimulation with epinephrine of uterine vessels that would reduce blood flow. To date, literature documenting its safe use in early pregnancy cannot be found. Terbutaline has been used widely by obstetricians for

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<th>Drug</th>
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<td>Epinephrine</td>
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<td>Prednisone</td>
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<td>for status asthmaticus</td>
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<td>Cromolyn sodium</td>
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<td>Drugs that may be indicated for selected patients</td>
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<td>Penicillin derivatives</td>
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<td>Annual influenza vaccine</td>
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its tocoytic effects in the second and third trimesters. Higher doses of terbutaline are administered than in asthma and the expected effects of intravenous and high-dose oral \( \beta_2 \)-adrenergic stimulation occur (tremulousness, palpitations, and reflex tachycardia from fall in diastolic pressure). Some concern has been expressed regarding occurrence of pulmonary edema in patients receiving corticosteroids and \( \beta \)-adrenergic agents for premature labor. Precise fluid management may avoid this event. Albuterol similarly has not been demonstrated to be either safe or unsafe given during the first trimester of pregnancy. While inhaled \( \beta \)-agonists decrease drug delivery to the peripheral circulation (and to the placental vessels), a conservative approach is to avoid drugs that have not been studied in early pregnancy if alternatives exist.

Clearance of theophylline has not been studied prospectively in pregnancy. Preliminary data suggest no significant alterations in clearance. The principles for avoiding toxicity of theophylline in the nonpregnant state should be utilized. Cromolyn sodium is not recommended by the manufacturer for use during pregnancy, but a study of 296 women did not document increased risk of malformations.\(^7\) For status asthmaticus during pregnancy, the use of systemic corticosteroids seems to outweigh the unknown risks of giving high-dose corticosteroids. When managing severe or mild asthma with wheezing unresponsive to bronchodilators, prednisone is indicated to prevent status asthmaticus. It should be used in an effective dose initially (30 to 60 mg daily). Beclomethasone dipropionate has proved effective and safe when prolonged oral corticosteroids are required. There has been renewed interest in inhaled atropine for management of asthma. It is unknown whether atropine, which has been shown to be safe in early pregnancy, will be a valuable addition to current therapy. antibiotics should be administered for episodes of purulent bronchitis, but tetracycline and sulfonamides must be avoided. Ampicillin or erythromycin would be appropriate first-line agents. Allergen immunotherapy can be continued in a patient already receiving injections.\(^8\) In most circumstances, immunotherapy should not be initiated until the patient is post partum.

With the availability of new drugs for treatment of asthma that have been released without specific approval for or experience in pregnancy, the physician might decide to rely on established therapy until results of human studies become available. In any event, treatment of acute episodes of asthma and effective management of chronic asthma is without doubt in the best interest of the patient. Close interaction with the obstetrician is beneficial to deliver optimal care.

**Labor and Delivery**

During labor, minute ventilation can approach or exceed 20 L/min. Every effort should be made to prepare the asthmatic patient for labor and delivery by having her free of wheezing dyspnea, with stable pulmonary function. For women who have received systemic or inhaled corticosteroids during pregnancy, hydrocortisone 100 mg intramuscularly is given immediately and every eight hours until post partum.

**References**


**Status Asthmaticus**

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Status asthmaticus has not been well defined. It is generally considered as an acute exacerbation of bronchial asthma, characterized by severe obstruction and not relieved by usual treatment. However, how severe the obstruction, what modalities of therapy are included and over what time frame, are usually not specified. Acute asthmatic attacks account for nearly 1 million emergency room visits per year in the United States, with approximately 130,000 hospital admissions per year. From a practical point of view, a simple definition of status could include all patients requiring

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