

Bronchial Asthma in Pregnancy

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Asthma is the most common potentially serious medical problem to complicate pregnancy. Studies have shown that pregnant asthmatic women have an increased risk of adverse perinatal outcomes¹, whereas controlled asthma is associated with reduced risks².

Asthma is a complex syndrome with many clinical phenotypes in both adults and children. Its major characteristics include a variable degree of airflow obstruction, bronchial hyper-responsiveness, and airway inflammation³ (Figure1). For many patients, the disease has its roots in infancy, and both genetic factors (atopy) and environmental factors (viruses, allergens, and occupational exposures) contribute to its inception and evolution⁴.

This chronic inflammatory disorder of the airways exhibit many cells and cellular elements, in particular, mast cells, eosinophils, T-lymphocytes, macrophages, neutrophils, and epithelial cells².

In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning that are usually reversible, but that can be severe and sometimes fatal. Other disorders with similar clinical presentations may need to be excluded when the diagnosis is in question. Diagnosis of asthma focuses on establishing episodic airway obstruction and the reversibility of the obstruction⁵.

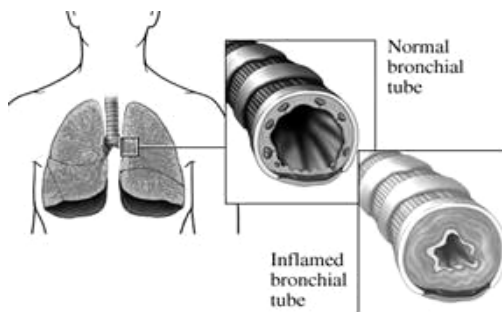


Figure 1. Bronchial inflammation in asthma

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It was observed that asthma affected between 3.7 and 8.4% of pregnant women in the United States between 1997 and 2001, the observation that this is a disease affecting more pregnant women each year. Why Is the Incidence of Asthma Increasing? Air pollution, nutrition, exposure to allergens, hygiene, and infection suggest that atopy and allergy are the costs of industrialization⁶.

Asthma and Pregnancy

Asthma course may worsen, improve, or remain unchanged during pregnancy, and the overall data suggest that these various courses occur with approximately equal frequency⁵.

The mechanisms responsible for the altered asthma course during pregnancy are unclear. There are multiple biochemical and physiologic changes during pregnancy that could potentially ameliorate or exacerbate gestational asthma^{5,7}. It might be the increased progesterone level leading to increase PG-f2⁸, suppressing β 2-adrenergic receptors and increasing sensitivity of adenosine receptors⁹ which may exacerbate asthma. Other immune functions might be also responsible due to hormonal effects as decreased NK cells phagocytic activity and cytotoxicity¹⁰ together with suppression of cellular immune functions, decreased release of interferon and shift towards Th2 immune response (IL-4,5) over Th1 (IL-2,10 and INF- γ) thus favoring exacerbation¹¹. Others had proposed that hormone fluctuations rather than the hormone level (especially estrogen) that produces this altered cytokine shift (Th-2 over Th-1), which may explain exacerbations at time of labor^{12,13}.

Two observations may be mechanistically and clinically important regarding the course of asthma during pregnancy. First, more severe asthma tends to worsen during pregnancy, whereas less severe asthma tends to remain unchanged or tends to improve². Secondly, there is a significant concordance between rhinitis course and asthma course during pregnancy. It was found that those women who experienced improvement in asthma symptoms during pregnancy also had improvement in rhinitis symptoms. This suggests that the same mechanisms may influence both levels of the airway during pregnancy; that gestational rhinitis course may predict asthma course during pregnancy; and, possibly, that rhinitis management during pregnancy may improve asthma⁷.

Controlled studies that have evaluated outcomes of pregnancy in asthmatic compared with nonasthmatic women have suggested that maternal asthma may increase the risk of hyperemesis gravidarum, pre-eclampsia, low birth weight infants, preterm births and perinatal mortality compared with nonasthmatic women^{14, 15}. These data suggest that poor asthma control, by causing acute and/or chronic maternal hypoxia, may be the most remedial responsible factor, and support the important generalization that aggressive asthma control during pregnancy is important in improving maternal-fetal outcome. Underestimation of asthma severity and undertreatment of exacerbations are two common errors that may lead to adverse maternal and fetal outcomes. Another possible explanation for increased perinatal complications in the infants of asthmatic mothers is maternal medication¹⁶.

The interesting hypothesis observed that the birth weight of female neonates of mothers not using inhaled corticosteroids was significantly reduced compared with females in the control and corticosteroid groups. There were no similar effects on growth observed in the male neonates¹⁷. It was hypothesized that the mechanisms behind these observations are related to placental 11 β -hydroxysteroid dehydrogenase type-2 activity. This enzyme prevents excess maternal cortisol from reaching the fetus by metabolizing cortisol to its inactive form, cortisone. Previous studies have demonstrated reduced enzyme activity in neonates with intrauterine growth retardation¹⁸. In support of this, the authors measured fetal cortisol concentrations in the umbilical vein at delivery and found higher levels in female fetuses from mothers not using inhaled corticosteroids. This implies that the female fetus may have an adverse effect on maternal asthma and, when not treated with inhaled corticosteroids, can lead to reduced fetal growth via reduced 11 β -hydroxysteroid dehydrogenase activity^{17, 18}.

Physiological changes in pregnancy

A relative hyperventilation during pregnancy is seen beginning in the first trimester, with minute ventilation increasing up to 48 percent by term. This change is due to an increase in tidal volume ("dyspnea of pregnancy"); respiratory rate is relatively unchanged. The hyperventilation of pregnancy is associated with significant changes in arterial blood gas with a resting arterial carbon dioxide tension (PCO₂) below 35 mmHg, partially compensated for by increased renal bicarbonate excretion¹⁹.

Total oxygen consumption and basal metabolic rate also increase by 20 % and 15%, accounting for increased maternal oxygen tension, ranging from 106 to 108 mmHg. In terms of pulmonary function, the following are seen by term: a decrease in residual volume, functional residual capacity, expiratory reserve volume, and total lung capacity; an increase in inspiratory capacity; and no change in vital capacity or forced expiratory volume in 1 second (FEV₁). In general, however, those measurements of pulmonary function in common clinical use (such as respiratory rate or FEV₁) do not change with pregnancy, so any changes in these measures should be considered abnormalities and treated as such²⁰.

Clinical Assessment

Objective measures of lung volumes or flow rates are essential for assessing and monitoring the severity of asthma. Using an office spirometer, the single best measure of pulmonary function for assessing severity is forced expiratory volume in 1

Table 1. Clinical Stages of Asthma²¹

<i>Classification</i>	<i>Days with Symptoms</i>	<i>Nights with Symptoms</i>	<i>FEV₁ (%of normal)</i>
<i>Mild Intermittent</i>	≤2/week	<2/month	≥80%
<i>Mild Persistent</i>	>2/week but <1/day	>2/month	≥80%
<i>Moderate Persistent</i>	daily	>1/week	>60- <80%
<i>Severe Persistent</i>	continual	frequent	≤60%

second (FEV₁) (used to classify asthmatics clinically, as shown in table 1)²¹.

Peak expiratory flow rate (PEFR), which can be measured reliably with inexpensive portable peak flow meters, correlates well with FEV₁. Home peak expiratory flow monitoring should be considered for patients who take medications daily. Peak flow measurement will also help differentiate asthma from other causes of dyspnea during pregnancy²².

In certain circumstances, selected skin (in vivo) or in vitro tests to determine specific IgE antibodies to common inhalant allergens can be done. (Useful for establishing the role of allergy in a pregnant patient's asthma and for guiding advice on specific environmental control measures)²¹.

Asthma Drugs

Anti-Inflammatory Agents

Corticosteroids

Among the most effective anti-inflammatory drugs for the treatment of asthma are corticosteroids. Corticosteroids can be administered parenterally, orally, or as aerosols²³. Although systemic absorption of inhaled corticosteroids can occur, the low plasma levels achieved by inhalation make it unlikely that fetal effects will be seen²⁴. Neither systemic nor inhaled corticosteroid use by the mother is a contraindication to breast feeding. **(all types are FDA category C, except budesonide is category B)**²⁵.

Cromones (Cromolyn sodium and Nedocromil)

These drugs are nonsteroidal anti-inflammatory agents for the chronic management of asthma. Their mechanism of action is stabilizing and preventing mediator release from mast cells. **(FDA category B)**^{26,27}.

Bronchodilators

Beta2-adrenergic agonists (beta2-agonists)

Beta2-agonists relax airway smooth muscle and may modulate mediator release from mast cells and basophils²⁸. Inhaled beta2-agonists are the medications of choice for initial treatment of acute exacerbations of asthma and for the prevention of exercise-induced asthma²⁹. Metaproterenol (orciprenaline), albuterol (salbutamol), pirbuterol, bitolterol, and terbutaline are commonly used selective beta2-agonists. Nonselective beta-agonists that activate both beta1 and beta2 receptors include epinephrine (adrenaline) and its isopropyl analog, isoproterenol. Epinephrine given subcutaneously in severe acute exacerbations may be considered, although other therapies are initiated first. **(All types are FDA category C, except terbutaline is category B)**³⁰.

Theophylline

Theophylline is the principal methylxanthine used in asthma therapy. Although its precise mechanism is not known, theophylline serves as a mild-to-moderate bronchodilator, depending upon serum concentration. When given in a sustained-release preparation, it has long duration of action and is thus particularly useful in the control of nocturnal asthma. When used in combination with usual doses of inhaled beta2-agonists, theophylline may produce additional bronchodilation³¹. In addition, theophylline may also reduce respiratory

muscle fatigue and possess some degree of anti-inflammatory activity. Theophylline use during pregnancy has been extensive and without evidence of adverse effects to the neonate when doses are guided by appropriate serum levels (not exceeding 12 µg/mL). Approximately 1 percent or less of the maternal theophylline dose reaches the nursing infant; this is usually not clinically significant. **(FDA category C)**³².

Anticholinergics

Inhaled anticholinergic agents produce bronchodilation by reducing intrinsic vagal tone to the airways. Such agents also block reflex bronchoconstriction.

Caused by inhaled irritants. Ipratropium, a quaternary derivative of atropine given by inhalation, lacks atropine's adverse effects. It has been shown to be effective in treating acute exacerbations when used in nebulized form. Ipratropium is not contraindicated in pregnancy, although it is generally not used except for patients with severe asthma. **(FDA category B)**³³.

Leukotriene modifiers

The leukotriene receptor antagonists (LTRAs) montelukast and zafirlukast or 5-lipoxygenase inhibitor zileuton, are alternative, but not preferred, therapies for the treatment of mild persistent asthma. Leukotriene modifiers also may be used with inhaled corticosteroids as combination therapy in the treatment of moderate persistent asthma. **(FDA category B)**^{14,34}.

Immunotherapy

Immunotherapy may prevent allergic inflammation and has been shown to reduce asthma symptoms provoked by such allergens as house-dust mites, cat dander, grass pollen, and *Alternaria*. Immunotherapy may be considered for patients when avoiding allergens and irritants is not possible and when appropriate medication fails to control asthma symptoms. The principal concern with the use of immunotherapy during pregnancy has been the occurrence of systemic reactions (anaphylaxis). Accordingly, the general recommendation is that immunotherapy should not be started during pregnancy, but that ongoing immunotherapy may be continued at the current dose³⁵.

Management Plan

Asthma is a disease that varies among patients, and the degree of severity may change for individual patients from 1 month or season to the next or during pregnancy. Therefore, specific

therapeutic regimens must be tailored to individual needs and circumstances³⁶.

For mild intermittent asthma (step 1), short-acting bronchodilators, particularly short-acting inhaled β_2 -agonists, provide quick relief. For mild persistent asthma (step 2), daily, low-dose inhaled corticosteroid is the preferred treatment for long-term-control. Cromolyn, leukotriene-receptor antagonists, and theophylline are listed as alternative but not preferred treatments. There are two preferred treatment options for step 3, or moderate persistent asthma — either a low-dose inhaled corticosteroid plus a long-acting inhaled β_2 -agonist or increased dose of inhaled corticosteroid to the medium dose range. For step 4, or severe persistent asthma, the dose of inhaled corticosteroid (preferably budesonide) should be increased within the high-dose range. If asthma symptoms persist, systemic corticosteroid can be added³⁶.

Labor and Asthma

The patient's regularly scheduled asthma medications should be continued during labor and delivery. The patient's PEFr should be taken upon admission to labor and delivery and, subsequently, every 12 hours. Asthma is often quiescent during labor and delivery. However, if asthma symptoms develop, PEFr should be monitored after asthma treatments. The patients should be kept well hydrated and be provided adequate analgesia to limit the risk of bronchospasm. Patients who have required chronic systemic corticosteroids during pregnancy should be given hydrocortisone to treat for possible adrenal suppression³.

Narcotic analgesics that cause histamine release should be avoided; fentanyl is a preferred agent. Lumbar epidural analgesia reduces oxygen consumption and minute ventilation during first and second stages of labor, which offers patients with asthma considerable benefit. If a general anesthetic is necessary, preanesthetic use of atropine and glycopyrrolate may provide bronchodilatory effect. For induction of anesthesia, ketamine is the agent of choice. Low concentrations of halogenated anesthetics can provide bronchodilation to the patient with asthma³⁴.

For labor induction, oxytocin is the drug of choice. Prior to term, the use of prostaglandin F₂-alpha should be avoided because it may cause bronchospasm; use of prostaglandin E₂ suppositories or gel has not been reported to cause bronchospasm⁷. Misoprostol (Cytotec) a synthetic prostaglandin E₁ analog can be safely used in patients with asthma³⁷.

The treatment of preterm labor in a patient already receiving asthma medication creates the risk of dangerous drug interactions³⁴. During an asthma exacerbation, uterine contractions are common and usually do not progress to preterm labor.

Successful treatment of the exacerbation will usually abate the contractions. If tocolytic therapy is necessary, care should be taken to avoid the use of more than one type of beta₂-agonist. Magnesium sulfate or calcium channel blockers, such as nifedipine may be used to treat uterine contractions if the patient is already taking a systemic beta₂-agonist for her asthma. The use of indomethacin is relatively contraindicated in the patient with asthma³⁸.

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