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Asthma and Pregnancy

by Harold S. Nelson, M.D.

Asthma is one of the most common medical problems that can seriously complicate pregnancy.^{1,2} Approximately three to five percent of all pregnant women have asthma and approximately 20 percent have some type of allergic disorder.

Uncontrolled asthma can have an adverse effect on pregnancy or the fetus. Uncontrolled pregnant asthmatics have an increase in preterm births and infants with low birth weights, decreased mean birth weight, increased neonatal mortality, increased neonatal hypoxia, hyperemesis gravidarum, vaginal hemorrhage, toxemia, and induced and complicated labors.³ These problems are most often associated with maternal hypoxemia, hypocapnia, alkalosis or combinations of these abnormalities.^{1,2}

Severe asthma during pregnancy also may cause maternal mortality.⁴ Deaths are usually from mucus impaction causing asphyxiation or from tension pneumothorax.⁵

However, pregnant asthmatic women do not have increased spontaneous abortions nor increased fetal congenital malformations,⁴ and, with good management during the pregnancy, even women with the most severe types of asthma can have



a normal pregnancy with minimal effects on themselves and their children.^{6,7,8}

Effect of pregnancy on asthma

The reported effect of pregnancy on asthma is variable. One recent study reported a significant improvement in asthma severity during pregnancy as demonstrated by a reduction in medication requirements.⁹ Overall the results vary significantly from study to study because of differences in the groups studied (see chart on next page). Generally, it appears that asthma improves, worsens or stays the same with equal frequency during pregnancy.¹⁰ However, the course of the asthma is often consistent in an individual woman's successive pregnancies.¹¹

Women with more severe asthma prior to pregnancy are more likely to experience severe asthma during pregnancy.¹ Patients with mild or moderate asthma are likely to improve throughout the pregnancy, particularly during the last trimester, but, in more than one-third, that improvement may be followed by post-partum deterioration.¹⁰

The peak incidence of flares during pregnancy appears to be between the 24th and 36th weeks of gestation, particularly in women whose asthma worsens with pregnancy.¹⁴ Fewer symptoms are

experienced by all pregnant asthmatic women during weeks 37 to 40.^{14,11}

The changes are attributable to the effects of pregnancy rather than the natural course of the asthma because most women revert to their pre-pregnancy

well as associated atopic and medical conditions and a physical examination.

It should be noted that in the first two trimesters of pregnancy, the majority of pregnant women experience dyspnea.²

Authors	Year	Numbers	Better	Worse	No Change
Schaefer and Silverman	1961	293	3%	4%	93%
Hiddlesone	1964	83	39%	26%	35%
Gluck and Gluck	1976	47	14%	43%	43%
Gibbs et al.	1984	67	49%	21%	20%
Stenius-Aarniala	1988	198	18%	42%	40%
Schatz et al. ¹¹	1988	330	28%	35%	33%
White et al.	1989	31	69%	6%	22%

asthma levels within one to three months post-partum.^{9,11}

Evaluation of pregnant asthmatics

An initial evaluation of a pregnant asthmatic should include an assessment of respiratory status, a careful history to ascertain relevant immunologic or irritant triggers of asthma symptoms, as

“Uncontrolled asthma can have an adverse effect on pregnancy or the fetus ... However, with good management, even women with the most severe asthma can have a normal pregnancy with minimal effects on themselves and their children.”

The earliest change in respiratory function is hyperventilation, due primarily to an increase in tidal volume. Other pregnancy-induced changes in respiratory physiology may include a 20 percent decrease in the functional residual volume and a decrease in the arterial pCO₂ resulting from increased alveolar ventilation.⁵

In order to distinguish this typical dyspnea of pregnancy and to assess the severity of asthma in individual patients, several other parameters need to be considered, including exercise tolerance, presence of nocturnal respiratory symptoms, coughing following inhaled medications, current medications, excessive use of bronchodilators, and recent hospitalizations or emergency therapy for asthma.

Management of chronic asthma during pregnancy is a team effort among the patient, the obstetrician and the physician managing the asthma. A combination of drug therapy, education and support is essential for optimal results.

For all women, pregnancy can be a time of stress. In pregnant asthmatic women, these stresses are especially important because for some, stress may lead to an exacerbation of symptoms. These women also have the additional worry about how the disease and its medications are affecting their babies. Support for these very real concerns is warranted, along with education on the

management and effects of asthma in pregnancy.

It is important for the patient to be aware of any asthma triggers and for those triggers to be eliminated (as much as possible) from the environment. In women with mild asthma, removal of these triggers may eliminate or reduce the amount of medication required.

The goals of outpatient asthma therapy for pregnant women are identical to the treatment goals for all asthmatics, with the single exception of protection of the fetus:

- Prevention of severe asthma episodes,
- Prevention of asthma that interferes with sleep or normal activity,
- Maintenance of optimal pulmonary function,
- Use of minimal medication and
- Avoidance of medication with uncertain or deleterious effects on the fetus.

“The vast majority of well-managed pregnant asthmatic women exhibit no symptoms of asthma during labor and delivery.”

Pharmacologic therapy

The ideal pharmacologic therapy during pregnancy is no pharmacologic therapy, especially during the first trimester when likelihood of fetal malformation is highest. No asthma medication licensed since 1980 meets the Food and Drug Administration's requirements for pregnancy category A. However, several asthma drugs do fall into categories B or C. The physician must weigh the benefits of the medication and avoidance of hypoxia against the potential teratogenic risks of the medication.

The effects of several medications have been studied in pregnant animals. Also the data from the Collaborative Perinatal Project (CPP) and several

individual studies have been used to investigate the possible teratogenic role of drugs used in pregnancy, particularly in the first four months.⁴

Use of specific medications in pregnancy⁴

Drug	FDA Category	Animal Teratogenicity	Human Teratogenicity
<i>Sympathomimetic bronchodilators</i>			
Albuterol (Proventil, Ventolin)	C	Yes (78 times)+	
Bitolterol	C	No (up to 557 times)+ Yes (23 times)+	
Epinephrine (Adrenalin)	*	Yes, No	Yes, No ²
Ephedrine	C ¹²		No
Isoetharine	*		
Isoproterenol (Isuprel)	*	Yes, No	No ⁸
Metaproterenol (Alupent, Metaprel)	C	No, Yes ¹²	No ¹³
Terbutaline (Brethine, Bricanyl)	B	No (1,042 times)+	
<i>Other asthma medications</i>			
Aminophylline	C ¹²		No
Cromolyn (Intal)	B ¹²	No	No
Theophylline	C	Yes, No	No
<i>Corticosteroids</i>			
Beclomethasone	*		No ^{2,13}
Prednisone	*	Yes	No ²

* FDA category not established
+ Normal human dose

Note:
In columns where both yes and no are listed, results from various studies were contradictory.

Drugs to avoid in pregnant asthmatic patients^{12,14}

- Aspirin
- Beta-adrenergic blocking agents
- Iodine-containing products
- Nonsteroidal, anti-inflammatory drugs
- Prostaglandins and ergonovine
- Streptomycin and kanamycin
- Sulfonamides
- Tetracycline

Because the hazards of uncontrolled asthma and development of acute respiratory failure are much more likely to endanger the life of both the mother and fetus, there should be no hesitation in the use of those drugs considered to be generally safe.

The sympathomimetics are considered generally safe for use in pregnancy. However, the CPP showed a significant increase in fetal congenital malformation with mothers who received epinephrine, and it is recommended that other, safer drugs such as terbutaline (Brethine) be used instead.¹⁵

Terbutaline and other beta-2 adrenergic agonists have an inhibitory effect on labor, and these drugs are used for the control of premature labor. For this use, doses frequently exceed those for asthma, and long-term follow-up has not revealed deleterious fetal effects.⁸

The inhaled form of the sympathomimetics is preferable because the amount absorbed is substantially less than in the oral or injectable forms, yet the inhaled form is immediately effective and is as long-acting as the oral form. Inhaled metaproterenol has been specifically studied in pregnancy and appears safe.¹³

Although manufacturers do not recommend the use of cromolyn sodium in pregnancy and lactation, there have been very few problems associated with it. There have been 296 reports of the use of cromolyn during all or part of pregnancy, with no evidence linking it with any abnormalities.¹⁶

Animal studies have suggested adverse effects of systemic corticosteroids on the developing fetus (see chart), but a large body of data in humans published in the past 25 years has not confirmed a substantial adverse effect.^{2,4,15} Inhaled steroid

medications such as beclomethasone have been shown to be safe and may allow a reduction in the oral steroid dose, reducing the frequency of side effects.^{2,13} The benefits of corticosteroids far outweigh the risks of potential fetal morbidity associated with status asthmaticus.

Management of chronic asthma in pregnancy

A working protocol for the management of chronic asthma in pregnancy has been developed from the current literature. It is as follows:⁴

Intermittent, mild symptoms (any or all of the following)

- No medication
- Inhaled terbutaline or metaproterenol, one to two puffs every 4 hours, as needed.

"No asthma medication licensed since 1980 meets the Food and Drug Administration's requirements for pregnancy category A. However, several asthma drugs do fall into categories B or C ... and ... there should be no hesitation in the use of those drugs considered to be generally safe."

- Theophylline tablets 200 mg every 6 to 8 hours, as needed.

More continuous, moderate symptoms (any or all of the following)

- Regular theophylline usually beginning with 200 mg (long-acting preparation), twice daily.
- Regular inhaled terbutaline or metaproterenol two puffs, four times daily.
- Cromolyn (following inhaled terbutaline or metaproterenol during initiation phase) two puffs, three or four times daily.

Symptoms not controlled with above

Mild to moderate

- Beclomethasone (following inhaled terbutaline or metaproterenol during initiation phase) two to three puffs, three or four times daily.

Moderate to severe continuous wheezing

- Clear with prednisone (generally beginning with 20 mg, two or three times daily) and consider (once clear) previous alternatives or, if necessary, chronic alternate day or daily prednisone.

Patients taking medication before pregnancy

- Continue oral theophylline, inhaled metaproterenol, terbutaline, cromolyn or beclomethasone and oral prednisone at lowest effective dose.
- Try to substitute for or eliminate oral beta-2 adrenergic bronchodilators.

Annual influenza inoculation is recommended for women with chronic asthma, and for pregnant asthmatics, vaccination may be performed during the second or third trimester. Also allergen immunotherapy is considered safe and can be continued in women who are already receiving it. However, in most cases, it should not be initiated during pregnancy because of the risk of anaphylactic shock.²

Management of acute asthma during pregnancy

Approximately 10 to 15 percent of pregnant asthmatics may require hospitalization for treatment of status asthmaticus.¹⁷ The condition has been associated with maternal and fetal deaths as well as intrauterine growth retardation and the resulting infant morbidity.¹² In pregnancy, the arterial blood gas evaluations are heavily relied upon to determine the severity of an asthmatic attack. The worst combination is a low pO₂, low pH and a pCO₂ that is above normal for pregnancy. Fetal jeopardy exists when the maternal arterial pO₂ drops below 60mm Hg.⁵

The following steps are suggested for the treatment of acute asthma during pregnancy.⁴

1. Oxygen, glucose-containing fluids.
2. Inhaled terbutaline (2 mg) or metaproterenol (0.3 cc) by mechanical nebulizer (up to three doses, 20 to 30 minutes apart).
3. Subcutaneous terbutaline 0.25 mg (once or twice) should be considered for patients not tolerating inhaled bronchodilators or for patients in impending respiratory failure in spite of the above therapy.
4. Intravenous methylprednisolone should be given to steroid-dependent patients, to patients responding poorly to emergency treatment within the first hour and to patients presenting with particularly severe asthma. Doses of 1 mg/kg or 40 to 125 mg every 4 to 6 hours would appear to be appropriate.
5. Consider metered-dose ipratropium (Atrovent), four puffs with a spacer device, for patients refractory to the effects of inhaled terbutaline or metaproterenol. If effective, may repeat every 6 hours until it is no longer needed.
6. For patients not responding to the above or requiring hospitalization, intravenous aminophylline:
 - A. For patients not receiving oral theophylline, 5.6 mg/kg over 20 to 30 minutes.

B. For patients receiving oral theophylline, individual considerations (such as time and amount of the last oral theophylline dose, the duration and amount of the maintenance oral program and known theophylline levels) will determine whether a half-loading dose (2.8 mg/kg over 20 to 30 minutes) should precede continuous intravenous administration.

C. If continuous aminophylline is indicated, administration by IVAC infusion pump at a dose of 0.5 mg/kg/hr is recommended initially. Subsequent dose adjustments should be made on the basis of frequent theophylline level measurements. ✓

Labor and delivery

The vast majority of well-managed pregnant asthmatic women exhibit no symptoms of asthma during labor and delivery. Those who do exhibit symptoms usually only require the use of inhaled bronchodilators.¹¹ Steroid-dependent asthmatic patients may need supplemental steroids for the stress of labor and delivery. A current working protocol is as follows:⁴

1. Continue antepartum regimen of oral theophylline, inhaled cromolyn or inhaled beclomethasone during labor
2. For asthma symptoms during labor:
 - A. Inhaled terbutaline or metaproterenol, one to two puffs every hour, as needed.
 - B. If above not adequate, intravenous aminophylline (as described above).
 - C. If above not adequate, intravenous methylprednisolone (as described above).
3. For steroid-dependent patients: 100 mg hydrocortisone intravenously or intra-muscularly at admission to labor and delivery, followed by 100 mg intravenously or intra-muscularly every 8 hours for 24 hours or until the absence of complications is established.

“Breast-feeding need not be discouraged because of maternal ingestion of asthma drugs. Medications used in the treatment of asthma rarely are troublesome for the infant.”

If any anesthesia is required, local anesthesia is preferred with spinal anesthesia for Caesarean section. If general anesthesia is required, nitrous oxide and halothane are preferred. Cyclopropane should be avoided since it may cause bronchoconstriction.¹⁵

Breast-feeding

Breast-feeding need not be discouraged because of maternal ingestion of asthma drugs. Medications used in the treatment of asthma rarely are troublesome for the infant.

The appearance of theophylline in breast milk has been studied better than most other medications. The infant usually receives less than 1 percent of the mother's dose,⁸ but irritability and insomnia may appear in some infants.¹⁴

Inhaled beta adrenergic bronchodilators should appear in negligible amounts in breast milk compared with similar oral preparations.¹⁴

Very little prednisone is delivered to an infant via breast-feeding. It has been estimated that an infant would receive less than 20 percent of its daily physiologic corticosteroid requirement from a 50 mg oral dose of prednisone to the mother.¹⁸

To insure the lowest drug concentrations in the milk, nursing mothers can take any necessary medication 15 minutes after nursing. □

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