

# **Asthma Management during Pregnancy: Case Report & Literature Review**

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A 27 year old pregnant female; gravida 2, para 1+0, known asthmatic on salbutamol tablets presented to chest specialist with cough productive of sputum for last 2 months. She is seven and a half months pregnant and was paying regular visits to her OB/GYN doctor who prescribed multiple antibiotics and salbutamol inhaler which were unable to relieve her condition. Cough was more during the morning and night. Sputum was white in color. She gave no history of any known allergies and was having sleepless nights due to her recurrent symptoms. Her last pregnancy was uneventful. On examination she was tachycardiac, afebrile with diffuse wheeze bilaterally.

Keeping in view her pregnancy how should this patient be treated\*?

- a) salbutamol nebulization
- b) salbutamol nebulization and systemic steroids
- c) add antibiotics to b
- d) systemic steroids, long acting beta agonists, inhaled steroids and leukotriene inhibitors
- e) admit to hospital

\*see below for answer

Asthma is one of the most common conditions that complicates pregnancy and may have its onset for the first time during pregnancy or may be worsened by pregnancy. Usually it is considered that about 1/3<sup>rd</sup> of the patient will have stable disease, 1/3<sup>rd</sup> will have exacerbation of the disease and 1/3<sup>rd</sup> will have improved control. Either way, under treated or uncontrolled asthma during pregnancy can have serious effects on both the mother and the fetus. Consequently every pregnant patient with asthma should be considered as potentially high risk.

Many asthmatic patients experience deterioration of their symptoms during the course of pregnancy because they discontinue or reduce medication due to concerns (either their own or those of their medical adviser) regarding its safety<sup>1</sup>.

Pregnancy is a period of profound physiologic modification in a women's body. These inimitable reforms affecting nearly every organ system challenge clinicians handling disease states during pregnancy and affect the choice of medications highly suited to manage their patients. Keeping in view the teratogenic effects of different medications and the unique pharmacokinetics of pregnancy, the drug therapy may need to be adjusted. Throughout pregnancy drug effects may influence fetal growth and functional maturity. Teratogenic hazard to the fetus is highest during first trimester, which is the period of organogenesis. Major congenital malformations can occur in a developing fetus exposed to teratogens. It should be noted that no pharmacologic agent can be guaranteed absolutely safe in pregnancy and judgments on safety are determined by what experience is reported in the medical literature. All orally given medications enter fetal circulation and no medication should be considered entirely safe. Table 1 outlines the categories of medications used in pregnancy. The biggest danger to the mother and fetus comes from under controlled or poorly controlled disease. Unchecked asthma in a pregnant patient has been associated with emergency department visits, hospitalizations, respiratory failure, preeclampsia, and death. It can also adversely affect fetal outcome, and has been associated with increased incidence of low birth weight, premature delivery, and fetal demise. Although all this fear of teratogenic effects of medications and the fact that previous experience like thalidomide-induced malformations in thousands of new born are real, does not mean that we should avoid use of necessary medications during pregnancy. Since the thalidomide era we have learned a lot about the use of medicines during pregnancy. The number of medicines that are coming with their safety records during pregnancy is increasing as we get more information with animal and human studies. Medications used during pregnancy are classified according to the safety data either in humans and/or animals. Most of the information that has been gathered about the effects of medications on a fetus has been collected retrospectively and observationally, as prospective placebo-controlled, double-blinded studies are impossible on ethical grounds<sup>2</sup>.

Table 1: Categories of medications used during pregnancy

A	<i>Controlled studies show no risk</i> – Adequate, well controlled studies in pregnant women have failed to demonstrate risk to the fetus
B	<i>No evidence of risk in humans</i> - Either animal finding show risk but human findings do not, or if no adequate human studies have been done animal findings are negative
C	<i>Risk cannot be ruled out</i> - Human studies are lacking and animal studies are either positive for fetal risk or lacking as well. However, potential benefits may justify the potential risk
D	<i>Positive evidence of risk</i> - Investigational or post marketing data show risk to the fetus. Nevertheless, potential benefit may outweigh the risk
X	<i>Contraindicated in pregnancy</i> - Studies in animal or humans, or investigational or post marketing reports have shown fetal risk which clearly outweighs any possible benefit to the patient

Table 2: Common medications for treating asthma

MEDICATIONS	FDA CATEGORY
Salbutamol (Ventolin)	B
Salmeterol (Serevent)	C
Cromolyn (Intal)	B
Beclomethasone (Becotide, Becloforte)	C
Triamcinolone (Azmacort, Nasacort)	C
Budesonide (Pulmicort)	B
Budesonide (Rhinocort aqua)	C
Flunisolide (Aerobid)	C
Fluticasone (Flixotide)	C
Montelukast (Singulair)	B
Zafirlukast (Accolate)	B
Methyl xanthenes	C

Although some medications used to treat adult asthma patients are not always appropriate for the developing fetus, they are often prescribed in the pregnant woman to prevent possible direct or indirect consequences of unmanaged asthma. Concerns include, for example, the potential of certain agents to induce congenital malformations; medications are a possible but uncommon cause of congenital malformations in gravida with asthma. A prospectively monitored cohort study to assess the safety of asthma medications including 824 pregnant with and 678 pregnant women without asthma was unable to find any significant association between use of most common asthma medications during pregnancy and adverse perinatal outcomes<sup>3</sup>.

A clinical meeting of a pregnant patient with asthma should comprise an intensive evaluation, an attempt to categorize asthma according to type and severity (table 3) and commencement of pertinent treatment (table 4).

The assessment of a pregnant lady with asthma should encompass history, physical examination, spirometry measurement, and laboratory testing as indicated. Laboratory testing might contain pulse oximetry, arterial blood gases, chest roentgenogram, allergen skin testing, or other tests for the identification of any complicating factor as suggested.

The pregnant patient with asthma should be classified on the basis of type or severity of disease (table 3). "Type of asthma" is generally applied to the primary etiologic mechanism<sup>4</sup> including:

1. Allergic
2. Non-allergic
3. Mixed (allergic and non-allergic)
4. Occupational
5. Exercise induced
6. Aspirin sensitive asthma

Asthma severity helps in the assessment of the progression of patient's asthma and determines if that patient is likely to suffer the poor consequences.

Treatment of the pregnant asthma patient should include a discussion of preventive measures and avoidance of known asthma triggers. Asthma management should also include medications appropriate in pregnancy (as reviewed in Table I).

Medications are mandatory for acute and chronic treatment, or treatment at the time of labor and delivery.

Concerning emergency dealing of a pregnant patient with asthma, they should receive oxygen and beta-agonist treatment as indicated. If experiencing severe dyspnea from asthma, she may benefit from epinephrine subcutaneously or successive treatments with a beta-agonist, such as Salbutamol. In this setting, the patient should be started on systemic corticosteroids immediately because they may take hours to become effective. The use of theophylline in acute treatment remains controversial. It should be noted that patients may present in acute respiratory failure and require intubation and mechanical ventilation. Termination of pregnancy in rare cases has been used as a last refuge in an attempt to reverse seemingly intractable status asthmaticus.

TABLE 4 lists the recommended medications by level of severity in adults, while brief description of some of the drug groups will be reviewed here:

### **CONTROLLER MEDICATIONS:**

It covers medications consumed daily on a long term basis in order to maintain control of persistent asthma:

#### a) Inhaled glucocorticosteroid (IG):

At all levels of severity inhaled glucocorticosteroids are the preferred treatment for patients with persistent asthma. Glucocorticosteroids contradict in potency and bioavailability after inhalation and are currently the most effective anti-inflammatory medications. Their efficacy has been demonstrated by several studies regarding improving lung function, abating airway hyperresponsiveness, lessening symptoms, curtailing frequency and severity of exacerbation and improving quality of life <sup>7-9</sup>. Add-on therapy with another class of controller is preferred over increasing the dose of inhaled glucocorticosteroids as it provides little further benefit in terms of asthma control while increasing the risk of side effects. There is however, a positive relationship between the dose of IG and deterrence of acute exacerbation of asthma <sup>10</sup>. The safety profile of higher doses of IG is clearly better than that of oral glucocorticosteroids <sup>11</sup>. The systemic effects of different IG stand apart, with budesonide and fluticasone propionate (FP) having less systemic effects than beclomethasone dipropionate (BDP) and triamcinolone <sup>12</sup>.

Efficacy studies have established a significant decrease in the rate of asthma exacerbation during pregnancy in those treated with steroids and also

demonstrate a 25% lower birth weight of infants in asthmatic women who were not treated with inhaled steroids in pregnancy set against those who did acquire the therapy. Consensus statements from the American College of Obstetricians and Gynecologists and the American College of Allergy, Asthma, and Immunology recommend inhaled steroids to augment outcome in all pregnant women who have at least mild persistent asthma.

b) Systemic glucocorticosteroids (SG):

For long term therapy oral glucocorticosteroid are superior to parenteral steroids. Long term oral glucocorticosteroids therapy (daily or alternate day) may be required to control severe persistent asthma. Oral glucocorticosteroids such as prednisone, prednisolone, or methyl prednisolone are preferred because of their nominal mineralocorticoid effect, their respective shorter half life, and their minimal effects on striated muscles.

c) Cromones (sodium cromoglycate and nedocromil sodium)

They may be used as controller therapy in mild persistent asthma. Administered prophylactically these medications constrain early and late phase allergen-induced airflow limitation and acute airflow limitation after exposure to exercise, cold dry air, and sulfur dioxide. There is little to suggest that it's preferable to inhaled steroid in a woman with mild persistent asthma, since no outcome data are applicable during pregnancy comparable to what we have for inhaled steroids. Consider using these however, in a woman whose asthma was well controlled with it before pregnancy.

d) Methyl xanthines:

Many studies have shown the effectiveness of sustained release theophylline, used for long term, in improving lung function and control of symptoms. It may be used in patients with milder disease and as an add-on therapy to low or high doses of inhaled glucocorticosteroids when further asthma control is needed<sup>13</sup>. As an add-on therapy it's less effective than long acting beta 2 agonists; however it's a less expensive option. Although theophylline has been used extensively in pregnancy without causing teratogenic effects, still it is not a straightforward medication to use in this setting as it has a significant capacity for toxicity with a low

therapeutic index. Its volume of distribution is increased in 3<sup>rd</sup> trimester of pregnancy due to reduced protein-plasma binding. It may worsen or lead to GERD which may further deteriorate asthma control especially in later pregnancy.

e) Long acting inhaled beta 2 agonists:

These include salmeterol and formoterol. Their duration of action lasts more than 12 hours. Formoterol is a full agonist at beta 2 receptors while salmeterol is a partial agonist. They should be considered when standard introductory doses of inhaled glucocorticosteroids fail to achieve control of asthma before raising the dose of IG. Salmeterol should be considered in women with moderate to severe asthma who have responded well to therapy before pregnancy.

f) Long acting oral beta 2 agonists:

These include gradual release formulations of salbutamol or terbutaline and bambuterol, a prodrug that is converted to terbutaline in the body. They may be helpful in controlling nocturnal symptoms of asthma.

g) Leukotriene modifiers:

These include cystienyl leukotriene 1 (cysLT1) receptor antagonists (montelukast, pranlukast, zafirlukast) and a 5-lipoxygenase inhibitor (zileuton). They are less effective than long acting inhaled beta 2 agonists as add-on therapy. Their advantage is that they are available in oral form. Some patients with aspirin sensitive asthma may respond well to leukotriene modifiers. Both montelukast and zafirlukast are generally considered to be safe and may be use in pregnancy if clearly indicated. In the pregnant patient who was not previously on these agents, consider using them to cut down the dosage of chronic systemic steroid therapy. Zileutin should be used in pregnancy only in women with severe refractory asthma with good feedback prior to pregnancy.

h) Antihistamines (H1-antagonists):

These include acrivastine, astemizole, azelastine, cetirizine, ebastine, fexofenadine, ketotifen, loratidine, mizolastine, and terfenadine. Their role in asthma has not been clearly established, but they are recognized to have

some inhibitory effects on the allergic response. Of them human safety data are available for chlorpheniramine, hydroxyzine, and cetirizine in pregnancy. Expectorant medications are not of particular value, since the foremost expectorant is adequate hydration.

## **RELIEVER MEDICATIONS:**

These medications act quickly to relieve bronchoconstriction and it's accompanying acute symptoms.

### a) Rapid acting inhaled beta 2 agonists:

These include salbutamol, terbutaline, fenoterol, reproterol and pirbuterol. Formoterol has both a rapid onset and long duration of action. They are medications of choice for the treatment of acute exacerbation. Regular treatment with rapid acting inhaled beta 2 agonists four times daily has largely been superseded by the use of long acting inhaled beta 2 agonists. Increased use or even daily use of rapid acting inhaled beta<sub>2</sub> agonists is an admonition of worsening of asthma and signify the need to institute or to intensify regular anti-inflammatory therapy.

Beta<sub>2</sub> agonists are not associated with an increased rate of fetal malformations and other adverse pregnancy outcomes.

### b) Systemic glucocorticosteroids:

Although their onset of action is 4-6 hours, they are important in the treatment of severe acute exacerbations because they prevent progression of asthma exacerbation, decrease the need for emergency department visits or hospitalizations, prevent early relapse after emergency treatment, and reduce the morbidity of illness. Oral therapy is preferred and is as effective as intravenous hydrocortisone<sup>14</sup>. Prednisone, prednisolone and methylprednisolone are conventionally continued for 3 to 10 days following initial treatment of exacerbation. The use of systemic steroids to treat severe asthma during pregnancy has been associated with good outcomes. Current treatment standards for asthma exacerbations include initiating systemic steroid therapy in all patients whose condition cannot be readily stabilized with repeated bronchodilator treatments. Before discontinuing the oral therapy, give inhaled steroids for a minimum of 5-7 days. Maintain steroid-dependent asthmatics on the lowest possible dose and consider a leukotriene receptor antagonist in patients who are not already on this medication.

### c) Anticholinergics:

These include inhaled ipratropium bromide and oxitropium bromide. In general they have a slower onset of action i.e. 30-60 minutes to maximum effect. It has an additive effect when nebulized together with a rapid acting beta<sub>2</sub> agonist for exacerbation of asthma.

### d) Methylxanthines:

Short acting theophylline may produce no additive bronchodilator outcome over adequate doses of rapid acting beta<sub>2</sub> agonists, but it may promote respiratory drive or respiratory muscle function and perpetuate or sustain the response to rapid acting beta<sub>2</sub> agonist between doses. Consider theophylline in severe asthmatics who have had a good therapeutic response to it before pregnancy. Monitor patient's blood levels at least every trimester and during acute exacerbations.

### **Management during labor and delivery:**

Finally, there are treatment considerations at the time of labor and delivery. Although labor involves uterine contraction, it has not been shown to induce bronchoconstriction. If the patient has required regular inhaled corticosteroids or oral or intravenous corticosteroids during pregnancy, it is advisable to administer "stress-dose" corticosteroids during labor and delivery period. A suggested regimen is hydrocortisone 100mg intravenously once upon presentation and then every 8 hours if needed. If an elective cesarean section is planned, prednisone can be given prior to the procedure to prevent an asthma exacerbation. A suggested regimen is prednisone 20mg to 40mg daily for the 4 to 5 days prior to the procedure. If the patient's asthma is active, higher doses of corticosteroids may be needed.

The patient describe in the beginning of this discussion was classified as having severe persistent asthma and was offered an admission which was refused by the patient and the family. She was discharged from the clinic on step 4 therapy; including a short acting beta<sub>2</sub> agonist, a combination of long acting beta<sub>2</sub> agonist and potent inhaled steroid, oral steroids and H<sub>2</sub> blocker. Leukotriene inhibitors were not prescribed and were kept in reserve if patient does not respond in first 48 hrs. She was educated about the use of spacer and avoidance of triggers.

All fears regarding the use of drugs and their side effects including any risk to fetus was discussed. Patient was advised to contact the treating physician every day; and visit to the ER was recommended in case the contact could not be made or the late hours of the day. Fortunately this patient did well as an out patient and her symptoms rapidly improved and systemic steroids were rapidly discontinued. After three weeks of combination inhaler patient was switched to moderate doses of inhaled steroid and as needed short acting beta agonist; patient had uneventful pregnancy on these medications.

Table 3: classification of asthma severity

<p><b>MILD INTERMITTENT ASTHMA</b></p>	<p>Symptoms less than once a week Brief exacerbations Nocturnal symptoms not more than twice a month FEV1 or PEF <math>\geq 80\%</math> predicted PEF or FEV1 variability <math>&lt; 20\%</math></p>
<p><b>MILD PERSISTENT ASTHMA</b></p>	<p>Symptoms more than once a week but less than once a day Exacerbations affecting activity and sleep Nocturnal symptoms <math>&gt;</math> twice a month FEV1 or PEF <math>\geq 80\%</math> predicted PEF or FEV1 variability 20-30%</p>
<p><b>MODERATE PERSISTENT ASTHMA</b></p>	<p>Daily symptoms Exacerbations affecting activity and sleep Nocturnal symptoms <math>&gt;</math> once a week Daily use of inhaled short acting beta-2 agonist FEV1 or PEF 60-80% predicted PEF or FEV1 variability <math>&gt; 30\%</math></p>
<p><b>SEVERE PERSISTENT ASTHMA</b></p>	<p>Daily symptoms Frequent exacerbations Frequent nocturnal asthma symptoms Limitation of physical activity FEV1 or PEF <math>\leq 60\%</math> predicted PEF or FEV1 variability <math>&gt; 30\%</math></p>

Table 4: recommended medications by level of severity in adults <sup>15, 16</sup>

<b>Level of severity</b>	<b>Daily controller medications</b>	<b>Other treatment options</b>
STEP 1 Mild intermittent asthma	None necessary	None necessary
STEP 2 Mild persistent asthma	Inhaled glucocorticosteroid (</=500 mcg beclomethasone dipropionate or equivalent)	Sustained release theophylline, <i>or</i> Cromones, <i>or</i> Leukotriene modifier
STEP 3 Moderate persistent asthma	Inhaled glucocorticosteroid (200-1000 mcg BDP or equivalent) plus long acting inhaled beta-2 agonist	Inhaled glucocorticosteroid (500-1000 mcg BDP or equivalent) plus sustained release theophylline, <i>or</i> Inhaled glucocorticosteroid (500-1000 mcg BDP or equivalent) plus long acting oral beta 2 agonist, <i>or</i> Inhaled glucocorticosteroid at higher doses (>1000 mic.g BDP or equivalent), <i>or</i> Inhaled glucocorticosteroid (500-1000 mic.g BDP or equivalent) plus leukotriene modifier
STEP 4 Severe persistent asthma	Inhaled glucocorticosteroid (>1000mic.g BDP or equivalent) plus long acting inhaled beta 2 agonist, plus one or more of the following, if needed: Sustained release theophylline Leukotriene modifier Long acting beta 2 agonist Oral glucocorticosteroid	

All steps: in addition to regular daily controller therapy, rapid acting inhaled beta-2 agonists should be taken as needed to relieve symptoms, but should not be taken more than 3-4 times a day

All steps: once control of asthma is achieved and maintained for at least 3 months, a gradual reduction of the maintenance therapy should be tried in order to identify the minimum therapy required to maintain control

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