

Review Article

Treating Asthma in Pregnancy - An Update

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Abstract :

Asthma is one of the most common chronic medical conditions affecting the lungs during pregnancy. At any given time, up to 8% pregnant women have asthma. During pregnancy, asthma not only affects the woman, but it can also cut back on the oxygen to fetus. But this does not mean that having asthma will make pregnancy more difficult or dangerous to fetus. Pregnant women who have asthma that is properly controlled generally have normal pregnancies with little or no increased risk to pregnant women or their developing babies. Currently available national guidelines for the treatment of asthma during pregnancy emphasize the objective measurement of control, patient education, motivation, caution and medication adherence. The article reviews the available literature highlighting the appropriate selection of medications in the treatment of asthma during pregnancy, and to identify those factors which may influence the asthma care provider's ability to successfully manage this condition, and also illustrate that maintaining asthma control with long term medications in pregnancy is safer than the risk of uncontrolled asthma or untreated exacerbations for both the mother and the fetus. Women's drug treatment during pregnancy should be regularly assessed in the light of asthma control criteria.

Key words : Asthma in pregnancy.

Introduction :

Asthma is an important chronic disorder of the airways with significant morbidity and mortality. Around 300 million people currently have asthma worldwide. It is estimated that there may be additional 100 million people with asthma by 2025. According to First National Asthma Prevalence Study (NAPS) 1999, in Bangladesh about 7 million people (5.2% of the population) are suffering from current asthma¹. Asthma accounts for about 1 in every 250 deaths worldwide, although modern management, which obviously includes patient education, can prevent 80% of deaths. Asthma is the most common pre-existing medical

condition encountered in pregnancy². It affects between 3% and 12% of pregnant women worldwide. The prevalence of asthma among pregnant females is increasing. In an estimates in the USA suggests that 3.7-8.4% of pregnant females had asthma in 1997-2001, an increase from 3.2% from 1988-1994. In Australia the prevalence is 12.4% among the pregnant women³. Maternal asthma increases the risk of perinatal death, toxemias of pregnancy, premature birth, and infants of low birth weight, while better controlled asthma is associated with decreased risks.

Diagnosis :

The diagnosis of asthma during pregnancy relies on the same principles as in the non-pregnant patient without pregnancy. In the appropriate clinical setting of intermittent pulmonary symptoms such as wheezing, cough, shortness of breath, and chest tightness, the history should focus on potential asthma triggers, as well as the existence of possible co morbid conditions such as gastro esophageal reflux disease, vocal cord dysfunction, chronic sinus disease or rhinitis which could either simulate the symptoms of asthma or potentially contribute to poor control⁴. Spirometry with bronchodilator reversibility should be obtained to evaluate for reversible airflow obstruction, with a $\geq 12\%$ and 200 ml increase in forced expiratory volume in one second (FEV₁) after administration of a short-

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However, the presence of normal spirometry does not exclude the diagnosis of asthma, and it may give a useful baseline for follow up during the whole period of pregnancy, where the normal physiologic changes of pregnancy can be expected to have minimal effects on this parameter⁶. Methacholine challenge test should be deferred until after pregnancy due to the potential risk of bronchospasm⁷.

Effects of pregnancy on asthma

Asthma is the most potentially serious illness to complicate pregnancy. Asthma may begin or be diagnosed during pregnancy, or the severity of asthma may change in association with pregnancy. The natural

Table - I : Classification of Asthma Severity or Control in Pregnant Patients & Stepwise Approach to initiating or Adjusting Treatment

Asthma Severity	Asthma Control	Symptom Frequency/Salbutamol Use	Nocturnal Awakenings	Interference with Normal Activities	FEV ₁ or PEFR (% predicted)	Daily Medications
Step 1 Mild intermittent	Well controlled	≥ 2 days/week	No more than twice monthly	None	>80 %	1. Preferred controller-None required: as needed short acting B ₂ agonist only 2. Alternative controller-None required
Step 2 Mild persistent	Not well controlled	2 days/week but not daily	Three or four times a month	Minor limitation	≥ 80 %	1. Preferred controller-Low dose ICS 2. Alternative controller-LTRA, cromolyn, theophylline
Step 3 Moderate persistent	Not well controlled	Daily	At least once a week but not nightly	Some limitation	>60 but < 80 %	1. Preferred controller-Moderate dose ICS or low dose ICS plus LABA 2. Alternative controller- Low dose ICS plus either LTRA or theophylline
Step 4 Severe persistent	Very poorly controlled	Throughout day	Often seven times a week	Extremely limited	<60 %	1. Preferred controller-Medium dose ICS plus LABA 2. Alternative controller- Medium dose ICS plus either LTRA or theophylline
Step 5 Severe persistent						Preferred controller- High dose ICS plus LABA
Step 6 Severe persistent						Preferred controller- ICS High dose plus LABA plus prednisolone orally

NAEPP (National Asthma Education & Prevention Program) ^{4,12}.

FEV₁ (forced expiratory volume in one second), ICS(inhaled corticosteroid), LABA(long acting B agonist), LTRA(leucotrine receptor antagonist), PEFR(peak expiratory flow rate)

history of asthma during pregnancy is extremely variable. The factors that increase or decrease the risk of asthma attacks during pregnancy are not entirely clear. The conclusions of a meta-analysis of 14 studies is in agreement with commonly quoted generalization that during the period of pregnancy about one third of asthmatic patients have an improvement in their asthma, one third have a worsening of symptoms and one third remain the same⁸. There is also evidence that the course of asthma is similar in successive pregnancies⁹. In general most women experience an increase of asthma symptoms, with a peak in the late second or third trimester, with the majority of women returning to their pre-pregnancy state within three months of delivery¹⁰.

Effects of asthma on pregnancy

A systemic review has shown that asthma severity does determine what happens to the course of asthma in pregnancy and asthma may affect the risk of adverse outcomes. Studies of women with asthma have shown that uncontrolled asthma is associated with many maternal and fetal complications, including hypertension, hyperemesis, toxemias' of pregnancy, vaginal hemorrhage, complicated labor, fetal growth retardation, premature birth, increased perinatal death, and neonatal hypoxia¹¹. In contrast, if asthma is well controlled throughout pregnancy there is little or no increased risk of adverse maternal or fetal complications⁹. Pregnancy should therefore be an indication to optimize therapy and maximize lung function in order to reduce the risk of acute exacerbation.

Main differential diagnosis in pregnant women with dyspnoea

- * Asthma
- * Physiological dyspnoea of pregnancy
- * Pulmonary embolism
- * Pulmonary oedema
- * Peripartum cardiomyopathy
- * Amniotic fluid embolism

Asthma Management during Pregnancy

After the diagnosis of asthma has been confirmed guidelines published by the National Asthma Education & Prevention Program (NAEPP)^{4,12} recommend initiating therapy based on the level of severity for those patients not currently on controller therapy, or adjusting medication on the basis of the assessed level of control in those on maintenance therapy just as one would in the patient without pregnancy, with particular attention given to the potential risk-benefit for each medication. If the diagnosis is suspected but cannot be confirmed, it is reasonable to initiate therapy & reassessed for continued need in the post-partum period⁷. A stepwise approach to therapy is

recommended which equates asthma symptoms with increasing medications & dosages until control is achieved. Once control has been achieved for several months, a step-down therapy may be considered, but should be approached with caution during pregnancy to prevent loss of asthma control or an exacerbation^{5,12}. In fact, many will advocate that step-downs in therapy should be deferred until after delivery (see Table 1).

Assessment of asthma control

Asthma control assessment should be performed at each visit using validated screening tools such as the Asthma Therapy Assessment Questionnaire (ATAQ) & Juniper Asthma Control Questionnaire (ACQ)^{4,5,12}. These tools provide consistent data collection for comparison & trending over time & serve to initiate discussions with patients who may not subjectively perceive the same degree of impairment. Asthma symptom diaries are also valid instruments but less discriminatory, comparatively¹³. Spirometry, PEF, & exhaled nitric oxide (eNO) measurements are generally unaffected by pregnancy & provide objective markers of airflow obstruction & airway inflammation, which can be useful in determining severity of disease or risk of exacerbations⁴. The use of an eNO -targeted treatment protocol has recently been shown to reduce exacerbations during pregnancy & to facilitate patient-specific titration of therapy.

Patient Education

Learning more about asthma may help pregnant women to manage symptoms better, prevent attacks & react quickly when attacks do occur. The education can be particularly reassuring & useful during the period of pregnancy. Asthma education helps to recognize the signs & symptoms of asthma, avoiding attacks of triggers, and using asthma controlling medications correctly. Avoiding triggers, several simple steps can help to control environmental factors that worsen asthma & attacks of triggers. The steps include:

- * Avoid exposure to specific allergens that are known to cause asthma symptoms, especially pet dander (such as fur or feathers), house dust, & nonspecific irritants, such as tobacco smoke, strong perfume, & pollutants
- * Cover mattresses & pillows with special casings to reduce exposure to dust mites.

- * Avoid sleeping on upholstered furniture (e.g., couches, recliners)

- * Pregnant women should not smoke or permit smoking in their home. Active smoking is associated with more frequent & more severe maternal asthma exacerbations, low birth weight, IUGR, premature delivery, & sudden infant death syndrome¹⁴. Regular smoking cessation counseling & appropriate referrals are needed to improve success of cessation efforts during pregnancy. Women, who will be pregnant during flu season, should get a flu shot; there is no known risk of the flu shot for the fetus that is developing. Flu shots are generally given once in each year.

In addition, patient education at each provider visit, accompanied with reinforcement of an asthma action plan for individualized self-management of asthma symptoms, has been shown to improve medication adherence, asthma control, & quality of life in non-pregnant patients, & appears to have similar effectiveness in the pregnant population. Asthma education also improve adherence to ICS use, improve inhaler technique, & increase knowledge about asthma medications¹⁵ & thereby increase the effectiveness of medication.

Selection of Medication for Use in Pregnancy

Though no medication has been proven entirely safe for use during pregnancy, the physician will carefully balance medication use and symptom control. The treatment plan will be individualized so that the potential benefits of medications outweigh the potential risks of these medications or of uncontrolled asthma.

Asthma is a disease in which intensity of symptoms can vary from time to time, or season to season irrespective of pregnancy. This is why a treatment plan should be taken based both on asthma severity and experience during pregnancy with those medications. It should be remembered that the use of medications should not replace avoidance of allergens or irritants, because avoidance will ultimately reduce medication needs.

In general, asthma medications used in pregnancy are chosen based on the following criteria:

- * Medications in the form of inhalation are generally chosen because they have a more localized effect with only small amounts entering the bloodstream.

- * When possible, time-tested medications which are older are preferred since there is more experience with their use during pregnancy.

- * Medication use is limited in the first trimester of pregnancy as much as possible when the fetus is growing. Birth defects from therapy are rare (no more than 1 % of all birth defects are attributable to all medications).

- * Usually, the same medications when used during pregnancy are also appropriate during labor and delivery and when nursing.

Short-acting bronchodilators (SABAs) are recommended as rescue therapy for all asthmatics, with salbutamol considered the preferred agent in pregnancy^{5,12}. SABAs are Food and Drug Administration (FDA) pregnancy category C and in three large cohorts have not been associated with impaired fetal growth or congenital anomalies¹⁶. Prospective, observational, and case-control studies have also shown that short acting bronchial dilators are safe during pregnancy.

Inhaled corticosteroids remain the cornerstone of treatment for persistent asthma, regardless of its severity. For women with persistent asthma, a daily controller medication is indicated. ICS is preferred over leucotriene receptor antagonists (LTRAs) or theophylline^{5,12}. Of the currently available ICSs, budesonide has been most extensively studied in pregnancy and is the only ICS classified as FDA category B. For those patients not currently taking an ICS, budesonide is considered the agent of choice in pregnancy¹⁷. However, there are no data to suggest that the other ICSs (Pregnancy Category C) are unsafe, and it is acceptable to continue any ICS already controlling asthma symptoms during pregnancy.

In those patients in whom symptoms cannot be controlled on a low dose ICS alone, the therapy should be increased a stepwise fashion according to published guidelines^{4,12} until control is achieved. Options include increasing doses of ICS alone or in combination with long-acting B agonists (LABAs), adding theophylline or LTRAs, or progressing to oral corticosteroids if indicated.

While data are lacking regarding the safety of LABAs during pregnancy, the toxicological profile of LABAs is considered to be similar to that of SABAs and they are generally considered safe for use. Notably, a possible association between the use of LABAs and asthma-related deaths has been observed in non-pregnant patients¹⁸. Despite the safety concerns associated with LABAs, when prescribed appropriately the improved asthma control, improved PEFr, and reduced rescue inhaler use associated with LABA plus ICS therapy is superior to ICSs alone. Currently, it is recommended that these agents only be used in

combination with ICSs and only for the duration needed until further information becomes available. Due to the limited safety data regarding LABAs in pregnant women and the other potential concerns noted, it may be preferable to step up therapy to medium doses of inhaled corticosteroids prior to adding LABAs in women with pregnancy.

Theophylline (Pregnancy Category C) combine of with ICS is an alternative to the addition of LABAs in moderate to severe asthma but it has been associated with more maternal side effects and greater discontinuation rates⁴. In addition, the use of theophylline has been associated with pre-eclampsia, preterm delivery, and increased fetal breathing movements in late pregnancy, but no significant congenital malformations¹⁹ or stillbirths.

The LTRAs montelukast and zafirlucast (Pregnancy Category B) can be used as alternative therapy to ICS in mild persistent asthma or in combination with ICS in moderate asthma⁴. Prospective post-marketing surveillance of 250 infants exposed to montelukast at any time during pregnancy from a voluntary registry has also been reassuring, with no increased incidence of major fetal malformations, low birth weight, or preterm delivery²⁰ noted. At present, 5-lipoxygenase inhibitor zileutin is not recommended for use in pregnancy due to limited study data in humans and association of fetotoxicity in animal studies⁴.

Patients with severe asthma who are managed on omalizumab (Pregnancy Category B), a humanized monoclonal antibody to immunoglobulin E, may continue the medication during pregnancy if indicated. Due to the potential risk of anaphylaxis following the administration of omalizumab, this medication should not be initiated during pregnancy¹².

The use of oral corticosteroids in pregnant women with asthma has been associated with an increased risk of pre-eclampsia²¹ preterm labor, and low birth weights in the offspring of asthmatic women, even after adjusting for possible confounding variables. However, it remains quite difficult to separate any potential effects of poorly controlled maternal asthma from possible medication effects in these studies. In a meta-analysis of case-control studies evaluating first-trimester use of systemic corticosteroids for any reason Park-Wyllie et al estimated that there is a 3.4 fold increased risk of oral clefts in infants exposed to these agents, but suggested that this represents actual attributable risk of use in

pregnancy of 0.2-0.3% compared with a normal background incidence of 0.1%²². However the corticosteroids are the most effective for the treatment of patients with more severe asthma and their significant benefit usually far exceeds their minimal risk.

Allergic Rhinitis in Pregnancy and its Management

Allergic rhinitis commonly occurs in women of child bearing age and often coexists with asthma, leading some to classify asthma and rhinitis as a physiologic extension of the same disease within the upper and lower airways. Kitcher et al. have shown a direct relationship between gestational rhinitis and asthma symptoms, and the treatment of allergic rhinitis has been shown to improve asthma control²³ in non-pregnant patients, supporting the need for aggressive treatment of allergic rhinitis during pregnancy. Control of allergic rhinitis should begin with allergen avoidance whenever possible but if symptoms persist, therapy with oral antihistamines may be considered. The first generation antihistamines chlorpheniramine and tripelemamine and the second-generation antihistamines loratidine and cetirizine have favorable safety profiles and may be used in pregnancy. Intranasal corticosteroids are the most effective treatment for allergic rhinitis and due to their minimal systemic absorption, are believed to have metabolic effects risk similar to those of inhaled corticosteroids. Beclomethasone and budesonide are classified as FDA Pregnancy Category B and are considered the nasal steroids of choice during pregnancy, however, it is not unreasonable to continue any nasal steroid already adequately controlling rhinitis symptoms during pregnancy²⁴. Cromolyn sodium nasal spray and ophthalmic drops are believed to have safety profiles and may be useful in treating those with allergic rhinoconjunctivitis. Oral decongestants have been associated with a small but increased risk of gastroschisis when used in early pregnancy and should be avoided during the first trimester whenever possible. Allergen immunotherapy can be safely continued in women who become pregnant, but dose advancement or initiation of therapy during pregnancy is not recommended due to potential risk of anaphylaxis. Non-pharmacologic treatments such as nasal lavage with hypertonic saline resulted in decreased symptoms and reduced oral antihistamine use in pregnant women.

Exacerbation of Asthma during Pregnancy and its Management

Acute severe attacks of asthma are dangerous and should be vigorously managed in hospital. Treatment is not different from the emergency management of acute severe asthma outside pregnancy. The goals of treating acute exacerbations during pregnancy mirror those in non-gravid patient and include rapid reversal of airflow obstruction with bronchodilators, reduction of the likelihood of recurrence with the use of systemic corticosteroids in most cases, and close monitoring of mother and fetus^{4,5,12}. Continuous fetal monitoring should be considered when appropriate and supplemental oxygen administered to maintain maternal oxygen saturations $\geq 95\%$, with the primary goal of preventing maternal and fetal hypoxemia. Salbutamol should be administered with ipratropium added in severe exacerbations. Currently available guidelines recommend the use of systemic corticosteroids in the treatment of acute exacerbations of asthma during pregnancy^{5,12} but disparities in the treatment of pregnant women presenting to emergency departments with asthma exacerbations have been demonstrated. Data indicate that emergency physician are much less likely to prescribe systemic corticosteroids to pregnant asthmatic women who experience exacerbations than to their non-pregnant counterparts, despite having exacerbations of similar severity²⁵ and that these differences in treatment may contribute to ongoing asthma symptoms and recurrent healthcare utilization²⁴. While the reasons for these differences in treatment have not been fully explained, patient preferences and physician concern about the safety of medications probably contribute.

Obstetrical Care

Coordination with patient's obstetrical care provider should be considered for determination of appropriate antenatal monitoring in pregnancies complicated by asthma. Serial ultrasound examination can be used to monitor fetal growth and patients should be instructed to changes in fetal activity⁵. Providers are advised to continue asthma medications throughout labor and delivery and to monitor adequate analgesia to ensure that the risk of bronchospasm is minimized⁵. The majority of women with asthma will not suffer any major symptoms with labor and delivery, the risk seems to correlate with asthma severity²⁶ and providers should be prepared to treat symptoms if necessary.

Safety of Asthma Medications and Breastfeeding

Women having asthma should be advised to breast feed. The risk of development of atopic disease in the child of an asthmatic mother is about one in 10, or one in three if

both father and mother are atopic. This risk may be reduced by breast feeding. All inhaled medications, oral corticosteroids and methylxanthines are safe when breast feeding²⁷. It should be remembered that short term use of prednesolone is considered safe, long term use should be minimized when possible. Zileutin should be used with caution due to possible teratogenicity noted in animal studies. To minimize infant exposure to medications, women should be advised to take medications immediately after breastfeeding whenever possible and to use the least effective dose²⁸.

Conclusions :

Asthma is one of the most common illnesses complicating pregnancy. The severity of asthma may change during pregnancy. Regardless of the severity, good asthma control appears critical to ensuring both maternal health and an appropriate environment for fetal growth and development. Long term management and monitoring is necessary to maintain maternal lung function and maternal-fetal oxygenation. Uncontrolled asthma during pregnancy may produce both maternal and fetal complications. When asthma is properly controlled, asthma in pregnancy does not significantly increase the risk to either the mother or the fetus, and a normal outcome of pregnancy is expected.

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