

Asthma in Pregnancy: A Concise Review

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ABSTRACT

Respiratory disorders affect pregnancy; asthma is the common cause of respiratory disorders. It affects maternal and fetal outcomes when not managed properly. Pregnancy also influences the course of asthma through physiological respiratory, immune, and hormonal changes. Asthmatic exacerbations are an important feature of asthma; some may need intensive care admission. Managing critical asthma syndrome (CAS) and near-fatal asthma (NFA) remains challenging. Immediate and prompt intervention with medications and supportive care will reduce exacerbations and symptoms of asthma. The purpose of this article is to provide an overview of asthma in pregnancy and summarize the current knowledge. This review aims to create awareness among patients and physicians on the importance of managing asthma during pregnancy. To conclude, early and prompt detection of asthma and its exacerbations, optimal control of asthma, and prevention of its adverse effects will help both mother and fetus. Educating mothers on the importance of antiasthmatic therapy, avoiding triggers, and frequently monitoring symptoms are *sine qua non* for good asthma management.

Keywords: Asthma, Critical asthma syndrome, Near fatal asthma, Pregnancy.

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INTRODUCTION

Asthma is an obstructive airway disease, with the course being frequented by exacerbations and remissions influenced by several factors. Infiltrating eosinophils, mast cells, lymphocytes, and other inflammatory cells lead to spasms of bronchial smooth muscles, thereby obstructing airways, hyperresponsiveness, and reduction in airflow resulting in air trapping.^{1,2} Clinical features vary in intensity over time, often getting worse at night. It is triggered by several factors, including infections, smoking, climate changes producing diverse allergens like pollens, molds, and spores, and air pollution including ozone, particle pollution, etc. Most often inciting factors are respiratory tract infections and smoking.^{3,4}

Most pregnant women with asthma have normal pregnancies, and those with well-controlled asthma have minimal complications. Schatz et al, in their study, have mentioned that about one-third of asthmatic pregnant women experience an improvement of asthma during pregnancy, while one-third remains stable, and the remaining one-third worsens.⁵ The major concern remains the exacerbation of asthma, more commonly seen between 17 and 24 weeks of gestation. Therefore, prevention of these exacerbations remains the primary goal of Asthma management in pregnancy.³

Evidence shows that about half of pregnant women discontinue bronchodilators during pregnancy due to the fear of potentially harming the fetus, thereby resulting in suboptimal treatment of asthma, resulting in increased asthmatic exacerbations. Educating women and allaying their fears remains a key step in the proper management of asthma in pregnant women.⁶⁻⁹ Strategies in the management of pregnant women with asthma and chronic obstructive pulmonary disease (COPD) are monitoring and treatment to improve outcomes.

MATERIALS AND METHODS

The peer review literature was searched using PubMed, Embase, and Google Scholar. The time period ranged from 1988 to 2022.

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The following keywords are "asthma," "asthma and pregnancy," and "asthmatic drugs and pregnancy." Furthermore, the references of the above-identified papers were manually searched for additional useful articles.

Physiological Changes during Pregnancy

During pregnancy, the metabolic needs of the developing fetus and placenta are to be met. Therefore, many physiological changes take place during pregnancy. In asthmatic pregnant women, some of the changes may be beneficial, but others are detrimental.¹⁰ One should have an insight into respiratory physiological changes when dealing with pregnant women with asthma/COPD.

Progressive uterine distension will result in diaphragmatic splinting (elevation of the diaphragm) and increased chest diameter and subcostal angle. There are also physiological changes seen in the upper respiratory tract, such as mucosal edema, hyperemia, and capillary congestion which might result in rhinitis in pregnant women. The above changes alter lung volumes in pregnancy. Diaphragmatic elevation results in a reduction in functional residual capacity by 20%. Inspiratory reserve volume is reduced in the early trimester but increased in the third trimester. Expiratory reserve volume is reduced throughout pregnancy. Forced expiratory volume 1, peak

expiratory flow rates, total lung capacity, vital capacity, and lung compliance remain unchanged. No significant variations in respiratory rate are noted in a normal and healthy pregnancy, but a respiratory rate above 24/minute warrants clinical attention.^{11,12} Pregnant women will have decreased systemic vascular resistance and pulmonary vascular resistance, increased heart rate, and cardiac output. Pulmonary wedge pressure remains unchanged during the pregnancy.

An increase in metabolic rate in pregnancy causes high oxygen consumption by approximately 20%. Pregnant women experience dyspnea and air hunger.¹³ These changes will not alter day-to-day activities. Dyspnea, when associated with wheezing or cough then it, is likely to be an obstructive airway disease.¹⁴ History and careful physical examination, and pulmonary function test (PFT) will help in the diagnosis of asthma/COPD.

Hormonal changes in pregnancy will often cause hyperventilation, thereby causing mild respiratory alkalosis and compensatory metabolic acidosis. Progesterone levels gradually increase from 25 ng/mL (6th week) up to 150 ng/mL (37 weeks of gestation).¹⁵ Progesterone is the most influential hormone, which is responsible for stimulating the respiratory center and increasing respiratory rate, hyperemia, and mucosal edema, resulting in nasal congestion and bronchodilation. Progesterone, along with cortisol, causes bronchodilation. Cortisol (prostaglandin E₂) protects against inflammatory substances and is protective against asthma by virtue of its bronchodilator effect.¹⁶ Bronchoconstrictors like PGF₂ also increase in pregnancy.¹⁷

The hormonal storm will alter immune system functions; Murphy et al.¹⁸ have hypothesized that cell-mediated immunity modification influences response to inflammation and infection.

Effect of Asthma on Pregnancy

Several kinds of literature have confirmed that asthma has ill effects on both mother and fetus.

A meta-analysis done by Murphy et al.,⁸ which studied various kinds of literature published between 1975 and 2009, concluded that asthma resulted in low birth weight (LBW) (mean birth weight was 93 gm lower), small for gestational age, and preeclampsia. The same group did one more meta-analysis recently, and the authors showed that asthma in pregnancy resulted in congenital fetal malformations. This was 11% higher than those with nonasthmatic individuals; cleft lip with or without cleft palate [Relative risk (RR)—1.30], neonatal death (RR—1.49), and neonatal hospitalization (RR—1.50).⁸ Baghlaf et al.,¹⁹ who studied on effects of asthma in pregnancy, their conclusion was in concurrence with the results of Murphy et al. They related maternal asthma to several complications like preeclampsia, placental complications (like previa, accreta, and abruption), premature rupture of membranes, chorioamnionitis, preterm labor, and increased incidence of cesarean deliveries. It is well-known that pregnant women are more predisposed to a prothrombotic state; asthma itself has been proven to increase the risk of embolism. Mendola et al. showed that the occurrence of deep vein thrombosis and pulmonary embolism is more common in asthmatic pregnant women than in nonasthmatic pregnant women.²⁰

Effect of Pregnancy on Asthma

In a study conducted on 504 pregnant women with asthma, Stenius-Aarniala et al.²¹ observed that 47 of them experienced acute attacks. In one prospective trial, which followed 336 pregnant women, authors found that asthma worsened in 35%, improvement was seen

in 28%, whereas the remaining 4% showed no change. Another study which included 308 pregnant women, observed that asthma control remained the same at 60% and worsened at 40%. This study used unsupervised machine learning.²² One of the limitations of this study was the failure to identify a group of women whose asthma improved during pregnancy. Many studies suggest that the baseline severity of asthma before pregnancy is an important predictor of asthma severity during pregnancy. In 330 asthmatic pregnant women, the following trends were noted.^{5,10}

In women who improved, the improvement was gradual with the progression of pregnancy.

Asthmatic exacerbations were more common between 29 and 36 weeks of gestation in women whose asthma worsened during pregnancy.^{5,10}

The severity of asthma was generally less in the last 4 weeks of pregnancy. The databases show variable usage of inhaled glucocorticoids during pregnancy. It shows that inhaled glucocorticoid use was decreased during the first trimester, compared with prepregnancy, increased during the second trimester, and decreased again in the third trimester.²³ It has been demonstrated that many pregnant women either decrease or stop their asthma medications shortly after conceiving, which can lead to deterioration in controlling asthma. Particularly, inadequate use of inhaled glucocorticoids may increase the risk of exacerbation. One study shows women who took inhaled glucocorticoids continuously after conceiving; only 4% of them had exacerbation of asthma when compared with 17% who were not taking glucocorticoids.²¹

Management of Asthma during Pregnancy

Optimal asthma care during pregnancy is provided by guidelines; they recommend using both pharmacological and nonpharmacological approaches for the management of asthma in pregnancy.^{24,25} International and National guidelines suggest individualized treatment guided by a multidisciplinary team. Improving the quality of life and minimizing congenital malformations are goals of the management of asthmatic pregnant women.^{24,25} Regular follow-up, adjusting treatment as per the patient's control level to prevent asthmatic exacerbations, and a written treatment plan are to be inculcated to accomplish the above-mentioned goals.¹⁶

Timely diagnosis and assessing the severity of asthma remain important for the well-being of the fetus must be considered. Simultaneous pharmacological and nonpharmacological strategies should be implemented to prevent complications and management of asthmatic pregnant women.¹⁷

Pharmacological Management

Murphy et al.,⁸ in their meta-analysis, have concluded that the relative risk of preterm labor and preterm delivery were decreased to nonsignificant levels by active and timely management of asthma in pregnant women. Their results showed that active management of asthma had the potential to decrease the severity of exacerbations in pregnancy and thereby improve the outcome. Murphy et al.⁸ thus allayed the fear of pharmacological hazards to the fetus. Many guidelines have recommended continuing asthmatic medications during pregnancy. The Global Initiative for Asthma (GINA)⁷ has advised that pregnant asthmatic women should have adequate control of asthma, as exacerbations will pose a greater threat to their fetuses when compared to pharmacological medications used for asthma. Despite such clear recommendations,

there is evidence of inappropriate management of asthma in pregnancy.²⁶

Medications are classified into long-term controller medications and rescue therapy.

Long-term controller medications are used for maintenance therapy to prevent asthma²⁷ worsening; these include inhaled corticosteroids (ICS), long-acting β -agonists, leukotrienes antagonists, and theophylline (SIGN recommends the use of intravenous and oral theophylline as normal during pregnancy).²⁴ Many guidelines advocate the importance of inhaled steroids; leukotrienes antagonists should not be withheld during pregnancy (although data regarding the safety of LRTAs are limited). Montelukast did not increase the risk of congenital fetal anomalies in a multicentered prospective trial.²⁸ Rescue therapy gives immediate relief from symptoms which include short-acting β -agonists.²⁷ It is to be noted that oral steroids can be used as both rescue therapy and maintenance therapy for severe persistent asthma. Oral corticosteroids (OCS) can be used as normal during pregnancy for asthmatic pregnant women with severe symptoms.²⁴ SIGN²⁴ strongly recommends against the discontinuation of OCS during pregnancy in pregnant women with asthma. Since the benefits outweigh the harm, all pregnant asthmatic individuals should continue OCS. Lack of sufficient data regarding omalizumab and allergen immunotherapy use in pregnant women with asthmatic exacerbations, and there exists controversy in the usage of the above-mentioned agents in pregnant asthmatic women. SIGN recommends against their use, whereas GINA considers it as an option.^{24,7}

Bronchodilators play an important role in the management of asthma and COPD in pregnant women. Nebulization with β -agonists will benefit such patients. Practice research database shows that asthmatic drugs and bronchodilators did not increase the risk of congenital malformations when taken during the first trimester. Inhaled bronchodilators can be concomitantly administered with heliox (mixture of helium and oxygen), as helium provides more laminar flow by reducing the Reynolds number to <2000.^{14,29,28} George et al.³⁰ first described the successful use of heliox with inhaled bronchodilators in a case report. A combination of α and β -agonists is not recommended due to potential teratogenic effects and placental or uterine vasoconstriction.^{13,14}

National Asthma Education and Prevention Program (NAEPP)²⁹ recommends monitoring of asthma and assessment of lung function regularly by spirometry, followed by monthly measurement of PFT. National Asthma Council (NAC, Australia) suggests asthma evaluation should be done every 4 weeks, assessing asthma control by questionnaires such as Asthma control tests, asthma control questionnaires, etc.²⁵ GINA⁷ suggests monitoring asthma monthly and advocating the use of the fractional exhaled nitric oxide technique. Therefore, monitoring the severity should be an adjunct to pharmacological therapies in the management of asthma in pregnant individuals.²⁷

Methylxanthines (both aminophylline and theophylline) belong to category C drugs and, therefore, best avoided in asthmatic pregnant individuals. Methylxanthines are known to have a narrow therapeutic index and, therefore, are more prone to toxicity to both pregnant women and fetuses.

Treatment in Critically Ill Asthmatic Patients

A total of one-third of pregnant women progress to CAS, which includes NFA and status asthmaticus.^{2,30} Early intervention and good asthmatic control (good compliance with asthmatic

medications) remain important strategies to prevent CAS.^{31–33} Admission to intensive care unit (ICU) for respiratory monitoring, aggressive bronchodilators, leukotriene receptor antagonists (montelukast), and inhaled/systemic steroids can be used in the management of CAS. In some cases, noninvasive ventilation is useful. An invasive endotracheal tube is done in most cases; an experienced person should perform rapid sequence intubation. Ventilator settings are to be adjusted based on physiological changes in pregnancy. The role of permissive hypercapnia remains controversial. Invasive hemodynamic monitoring is not routinely advocated, and one must be aware of complications associated with pulmonary artery catheters.^{34,35} Often asthmatic pregnant patients admitted to ICU, notwithstanding asthmatic medications, need sedatives, and paralytics. The safety of these drugs is not clearly understood.

Other medications used in critically ill asthmatic pregnant patients include magnesium sulfate (category A), which acts by bronchodilation and can be safely administered in pregnant women. In some cases, newborns may show magnesium toxicity in terms of respiratory and/or neurological depression.³⁶

Intubation in pregnant women with asthma may be more difficult (up to 8 times more difficult) when compared to normal pregnant women. A study done in the United Kingdom showed that failure incidence for tracheal intubation in pregnant women was one in 224. Laryngeal mask airway was most commonly used in 39 of 57 pregnant women.³⁷

When first-line pharmacological measures fail, isoflurane (category C) and Sevoflurane (category B) can provide further bronchodilation in pregnant patients with CAS. Therefore, these inhaled anesthetics should be used in severe cases only. In NFA pregnant patients, ketamine (category B) results in bronchodilation. It is associated with dissociative anesthesia, hallucinations, tachycardia, and hypertension.³⁸

Elsayegh et al., in their study, used propofol (category B) to intubate pregnant women with asthma. They noted that propofol would decrease uteroplacental blood flow, and higher doses might lead to reduced uterine muscle tone. No congenital anomalies were noted with propofol.³⁹

In ICU, analgesedation by opioids cannot be avoided even though they belong to category C/D classification.

Sedatives like benzodiazepines cross the placenta and are category D drugs. They are known to cause adverse effects on fetuses like preterm birth, LBW, pyloric stenosis, and atresia of the alimentary tract (Table 1), when benzodiazepines used in the late trimester are associated with floppy infant syndrome.³⁷

Other Treatments in the Critically Ill Pregnant Asthmatic

In asthmatic pregnant women with severe hypercapnia and metabolic acidosis, extracorporeal carbon dioxide removal (ECCO2R) may be useful as an adjunct in NFA where initial therapies fail. Elliot et al. showed the use of low resistance, pumpless, gas exchange membrane in two patients with life-threatening asthma. Both patients recovered fully and successfully weaned from mechanical ventilation. ECCO2R in pregnant asthmatic individuals needs further evidence.^{36,37}

Nonpharmacological Measures

Since many studies show that a significant number of asthmatic pregnant women discontinue therapies after conception and during pregnancy⁴¹, education remains the utmost nonpharmacological modality in the management of asthmatic pregnant women.⁴⁴

Table 1: Showing FDA classification of drugs in asthmatic pregnant women admitted to critical care unit

Drug	Food and drug administration category (FDA)	Remarks
Paracetamol	B	Must be used cautiously in hemolysis, elevated liver enzymes, low platelets and acute liver failure in pregnancy. Metabolized in liver.
B lactams—penicillin, ampicillin, and cephalosporins	B	There are no data suggestive of teratogenicity associated with these agents. Avoided in individuals with penicillin allergies.
Tetracyclines	D	May cause slowed bone growth and yellow teeth in fetus.
Methylxanthines (theophylline)	C	Have a narrow therapeutic index and are known to cause teratogenic effects in the fetus. Fatal arrhythmias in the mother.
Inhaled steroids (budesonide)	B	Possibility of cleft oral defect noted in 2014 pregnant females exposed to budesonide—Scandinavian registry.
Systemic corticosteroids	C	A small increase in the incidence of cleft lip with or without cleft palate. No sufficient evidence to show the occurrence of LBW, preeclampsia. ⁴²
Leukotriene receptor antagonist (montelukast)	B	Montelukast does not seem to have any teratogenic effect up to 400 mg/kg/day in animal studies.
Long-acting β -agonists (salmeterol)	C	A combination of α and β -agonists is to be avoided.
Short-acting β -agonists (salbutamol)	C	Inhaled β -agonists are not known to cause any teratogenicity.
Opioids (fentanyl and morphine)	C	Opioids can cause respiratory depression in neonates. When exposed in the first trimester may result in congenital heart defects and neural tube defects. [#]
Ketamine	C	Acts through N-methyl-D-aspartate receptors, it is a potent bronchodilator. Known to cause dissociative anesthesia. Can result in fetal neurotoxicity.
Benzodiazepines (lorazepam/midazolam)	D	Can cause respiratory depression in the fetus and floppy infant syndrome (hypotonia).
Succinylcholine	C	Pregnancy leads to reduced levels of plasma cholinesterase, which may cause skeletal weakness and paralysis in neonates.
Rocuronium	B	Some reports suggest paralysis in neonates. Generally, considered safe during pregnancy.
Volatile inhaled anesthetics (sevoflurane)	B	Used in refractory NFA/CAS. Sevoflurane is a bronchodilator, safe for pregnant women. Cause uterine muscle relaxation and hypotension.
Propofol	B	Hypotension—dose-dependent, causes uterine muscle relaxation.
Dexmedetomidine	C	High lipophilicity undergoes significant uteroplacental retention. ⁴³ May result in fetal and maternal bradyarrhythmias. Hemodynamic instability in the mother.
Omalizumab	B	It was assigned to category B by FDA based on study ^{##} . Its use in pregnancy is not approved.

[#]National Birth Defects Prevention Study (NBDPS) conducted one of the largest trials, concluding that when pregnant women are exposed to opioids in the early trimester, congenital anomalies are seen; ^{##}study conducted by Namazy et al. published in EXPECT (The Xolair pregnancy) registry; LBW, low birth weight

Educating both physicians and patients about the safety profile of asthmatic drugs remains a crucial step in the management and improving outcomes in asthmatic pregnant women.⁴⁴ Physicians provide inaccurate information concerning the safety of treatment; studies have shown that almost 25% of family physicians suggest either decreasing the dose or even stopping asthmatic drugs during pregnancy.⁴⁵ Educating patients should begin before conception through multiple counseling, allaying their fears, addressing their concerns, etc.¹² Pregnant women need to be briefed about the benefits of controlling asthma with medications, the nature of the disease, complications of asthma, avoiding triggers, proper use of asthmatic devices and the importance of adherence to the treatment. It has been shown that hospitalization, nocturnal exacerbations, and unscheduled visits to the hospital have

been reduced significantly by educating pregnant patients with asthma.⁴ Avoiding triggers (such as pollen, smoking, animal dander exposure, dust, exercise, sudden changes in weather, respiratory tract infections, etc.) remains a principal element in the management of asthma. Many guidelines^{24–26} have suggested avoiding triggers plays a vital role in preventing exacerbations of asthma. Pregnant women are more prone to viral respiratory infections due to changes in the immune system; therefore, yearly periodic influenza vaccination is recommended in asthmatic patients of childbearing age. Avoidance of certain medications which exacerbate asthmatic symptoms (like β -blockers, nonsteroidal anti-inflammatory drugs, and aspirin) is advised.¹⁴ Adequate control of comorbidities like allergic rhinitis and gastro esophageal reflux disease may worsen asthma. NAC²⁵ recommends good control of comorbidities, stress,

and mental health for the prevention of asthmatic symptoms. Smoking (both active and passive) has been shown to influence the course of asthma. It also has adverse effects on the fetus, such as LBW, premature labor, and infant mortality; therefore, it should be avoided.⁴⁴

Asthma during the COVID-19 Pandemic

The Global Initiative for Asthma (GINA) in April 2020 published certain recommendations for medical practitioners dealing with general asthmatics. The following are noteworthy recommendations⁷:

A written action plan for all patients.

- Continuation of asthmatic medications, especially ICS and OCS, if necessary.
- Avoiding spirometry in patients with confirmed/suspected individuals.
- If possible, avoidance of nebulizers in proven or suspected coronavirus disease 2019 asthmatic patients to prevent transmission of infection to other patients and health care professionals.

Strict infection control measures, particularly in aerosol-generating procedures. In one of the case reports,⁴² authors have successfully utilized the Venovenous extracorporeal membrane oxygenator in severe COVID-19 pneumonia with pregnancy. They concluded that the pregnancy should not be a contraindication for ECMO support if other measures fail.

CONCLUSION

Adequate and optimal control of asthma, prevention of exacerbations, and treatment complications are important to mitigate adverse effects for both pregnant mothers and fetuses. Education, counselling (ideally before conception), avoiding triggers along with pharmacological measures are essential in the management of asthmatic exacerbation in pregnant women.

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