

Asthma in Pregnancy. Review of Current Literature and Recommendations

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ABSTRACT

Background: Asthma is the most common respiratory disorder affecting women during pregnancy. Although it is a reversible disease, it may adversely affect maternal quality of life and perinatal outcomes, especially in severe and inappropriately managed cases. Conversely, pregnancy influences the course of asthma through the physiological respiratory, hormonal, and immune system changes. Exacerbations are a key feature of asthma, representing a significant problem if severe, requiring aggressive medical intervention, hospital and even ICU admission.

Purpose: The purpose of this article is to summarize the current knowledge and to provide a comprehensive overview of asthma in pregnancy. We also want rising awareness among patients and clinicians on the importance of proper asthma management during pregnancy.

Data sources: A comprehensive literature search in PubMed, Medline, and Taylor & Francis was performed. We have searched for review articles as well as prospective and retrospective studies published in English, investigating the bilateral relationship between asthma and pregnancy, using the key words mentioned below. Manual search through both national and international guidelines as well as relevant journals and publications on the topic has been also conducted.

Conclusions: Optimal asthma control, preventing, detecting, and treating the exacerbations are of the utmost importance to minimize the adverse effects for both the mother and fetus/neonate. Guidelines recommend active asthma management during pregnancy. Strong support prior and throughout the pregnancy and individualized treatment, guided by a multidisciplinary team, is suggested. Education on the importance of anti-asthmatic therapy, avoiding triggers, frequent and accurate monitoring are essential for good asthma management. Considering the pandemic, we are facing and the potential impact of COVID-19 on asthma, Global Initiative for Asthma (GINA) guideline recommendations for physicians are mentioned in the present article.

Keywords: asthma, pregnancy, treatment, adverse effects, exacerbations, management.

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INTRODUCTION

Asthma is a chronic inflammatory disease of the airways (1). The course of bronchial asthma is one of exacerbation and remission caused by a cascade of events (2): smooth muscle spasms, persistent inflammation (with infiltration of eosinophils, mast cells and lymphocytes), excessive production of mucus, leading to increased airway responsiveness, obstruction and reduction of airflow (2-4).

Respiratory symptoms and signs characterizing asthma vary over time in intensity and are often getting worse at night. This variation could be triggered by certain factors, most often upper respiratory tract infections and smoking (4, 5).

The majority of women with asthma have normal pregnancies and the risk of complications is small in those with well-controlled asthma (4). According to Schatz *et al.* (6), approximately 1/3 of asthmatic pregnant women experience an improvement of asthma during pregnancy, 1/3 remain stable and 1/3 of women experience a deterioration of asthma (6).

The goals of effective asthma management in pregnancy are to maintain the best possible asthma control and prevent deteriorations/exacerbations (7). Exacerbations of asthma represent a major clinical problem during pregnancy (7). They are more common between 17 and 24 weeks of gestation (8). Unfortunately, evidence shows that a significant proportion of pregnant women with asthma stop or decrease asthma medications in early pregnancy (9). Only half of women continue their bronchodilator therapy in pregnancy, while the other half discontinue pharmacological treatment, diminishing the control of asthma (3, 10). It is believed that this is the consequence of inadequate education and fear that medical treatment could affect the health of the fetus (3).

Many studies and guidelines support the fact that suboptimal treatment of maternal asthma increases the risk for adverse complications in fetuses and mothers, especially for those with severe or uncontrolled asthma during pregnancy (11-16). Clinical strategies on the management of women with asthma – monitoring and treatment – aiming to improve outcomes have been well-described (17, 18).

Physiological changes during pregnancy

In order to meet the metabolic requirements of the developing fetus and placenta, and to prepare the mother for labor and delivery, there are several physiological changes that take place during pregnancy (14, 19). When asthma is involved, some of the changes have beneficial effects, but others may be deleterious (20).

Pregnancy physiological respiratory, hormonal, immune system changes have the potential to interfere with the course of asthma.

Respiratory physiological changes in pregnancy are of the utmost importance when dealing with pregnant women affected by a pulmonary disease (21).

The progressive uterus distension causes diaphragmatic elevation up to 4 cm, increase of sub-costal angle up to 50% (68 ° -> 104 °) and chest diameter by up to 2 cm (22, 23). The upper respiratory tract undergoes mucosal edema, hyperemia, capillary congestion, altogether causing rhinitis of pregnancy, beginning in the first trimester, with a peak in the third trimester (22). All above-mentioned changes lead to alterations of lung volumes.

Diaphragmatic elevation causes a decrease in functional residual capacity (FRC) by up to 20%, but diaphragmatic excursion remains unchanged and therefore, the vital capacity (VC) is maintained. Expiratory reserve volume (ERV) decreases along with the FRC (22). Inspiratory reserve volume (IRV) is reduced early in pregnancy, but it increases in the third trimester (19). Forced expiratory volume in one second (FEV1) as well as peak expiratory flow rate (PEFR), diffusion capacity (DLCO), total lung capacity (TLC), and lung compliance are all essentially unaffected by normal pregnancy (19, 22, 23).

Respiratory rate has no significant variations during healthy pregnancy. We must remember that a healthy respiratory rate is 12–20 breaths/minute at rest. A persistent respiratory rate at rest >24 breaths/minute is abnormal (1) and should be further investigated.

There is an important increase in metabolic rate during pregnancy (~15%) that causes a high consumption of oxygen (increases ~20%) (24). Pregnant women may experience varying degrees of dyspnea and a subjective sensation of “air hunger” (25). However, it should not interfere with normal daily activities. Dyspnea of pregnancy is

characterized by a gradual onset. When it is accompanied by wheezing or coughing, it is likely to be caused by asthma. A diagnosis of asthma should be based on patient's history, physical examination, and pulmonary function tests (24). We should be aware that, in pregnant asthmatics, the sensation of dyspnea could cause apprehension and subsequent exacerbations (14).

Maternal hyperventilation leads to a mild respiratory alkalosis that is compensated by metabolic acidosis (24) – the partial arterial pressure of oxygen (PaO₂) rises and compensatory, the partial arterial pressure of carbon dioxide (PaCO₂) falls (19, 22).

During pregnancy, it is extremely important to maintain fetal oxygenation preventing maternal hypoxia (26).

It is believed that *hormonal changes* represent the main cause of ventilatory changes (27).

Progesterone increases gradually from 25 ng/mL, at six weeks, up to 150 ng/mL by 37 weeks (27). It is one of the most influential hormones in pregnancy, being responsible for stimulating the respiratory center of the medulla and increasing the respiratory frequency; hyperemia and mucosal edema, causing nasal congestion; reducing the muscle tone produce bronchodilation acting synergistically with free cortisol (19). Free cortisol has the potential to protect against inflammatory triggers (3). Prostaglandin E2 has a potential protective effect against asthma, being partially responsible for bronchial relaxation (26). Also, the levels of some bronchoconstrictors, such as Prostaglandin F_{2α}, increase in pregnancy (3).

Immune system changes during pregnancy are mostly caused by the hormonal storm. Estradiol increases maternal innate immunity and cell- or humoral-mediated adaptive immunity. Progesterone inhibits the maternal immune response and changes the balance between Th1 and Th2 responses (26). Cortisol has been proven to decrease circulating monocytes and T-cells (3).

Modification of cell-mediated immunity may influence maternal response to infection and inflammation (1), hypothesis that is also supported by a meta-analysis by Murphy et al (28).

Impact of asthma on pregnancy

Several studies investigating the impact of asthma on pregnancy, with worrying results, have been

published so far. The majority of them have reported that maternal asthma had serious implications not only on the mother and her pregnancy, but also on the fetus/neonate's poor outcomes.

In 2011, Murphy *et al.* published a meta-analysis (13) which summarised the literature between 1975 and 2009 concerning the risks of adverse perinatal outcomes in women with asthma. The authors found that maternal asthma was associated with an increased risk of low birth weight (relative risk-RR 1.46, <2500 g, mean birth weight was 93 g lower), small for gestational age (RR 1.22, <10th percentile for gestational age), preterm delivery (RR 1.41, birth prior to 37 completed weeks of gestation) and preeclampsia (RR 1.54, elevated blood pressure of either >140 mm Hg systolic or >90 mm Hg diastolic, accompanied by proteinuria). In the same study, they showed that the RR of preterm delivery and preterm labor was reduced to non-significant levels by active asthma management (13). A more recent meta-analysis conducted by the same study group indicated that maternal asthma was also associated with a significantly increased risk of congenital malformations [(RR :1.11) 11% more susceptible compared with infants of non-asthmatic women; cleft lip with or without cleft palate (RR: 1.30)], neonatal death [(RR:1.49), death up to one month of age], neonatal hospitalization [(RR: 1.50), treatment in, or admission to, a neonatal intensive care unit or neonatal medical/surgical unit] (29). Concerning the infant respiratory distress syndrome, the meta-analysis did not identify an increased risk among infants of asthmatic mothers (29).

Baghlaf *et al.* (30) have also studied the influence of maternal asthma on pregnancy, delivery and neonate on a large population-based database in the USA. Their results are similar to Murphy *et al.*'s analysis (13, 29). They linked maternal asthma to several pregnancy complications, such as gestational diabetes, preeclampsia, placenta previa, placental abruption, preterm premature rupture of membranes, chorioamnionitis, and preterm delivery. It is thought that asthma could also have an impact on labor by causing postpartum hemorrhage and even maternal mortality. Cesarean sections were more common on asthmatic persons (30). Kim *et al.* (31) also support this finding; furthermore, they emphasize that it is the acute asthma exacerbation that causes a greater incidence of cesarean section in asthmatic

women. One study (32) found that asthma variations during pregnancy could even influence the fetal presentation. Breech presentation was found to be more common in pregnant women with asthma compared to non-asthmatic women (32).

Not surprisingly, Baghlaf *et al.* have noticed that pregnant asthmatics had a greater risk of deep vein thromboembolism (DVT) and pulmonary embolism (PE) than non-asthmatics (30). This finding is also supported by Mendola *et al.* (32). It is well-known that pregnancy is characterized by a high-risk of hypercoagulability and venous stasis, features that predispose to developing thromboembolism. Besides, asthma itself has also proven to be a prothrombotic state (33).

Asthma impacts the neonates by increasing the risk of congenital anomalies and small for gestational age state (30). According to a study on a cohort of 4,344 pregnancies from 3,477 asthmatic women, published by Blais *et al.* in 2008 (34), women who experience an asthma exacerbation during the first trimester of pregnancy have a 50% increased risk of congenital malformations (34). It is generally agreed that the first trimester of pregnancy is the critical period for the development of the fetus, because it is the time when the organogenesis occurs. The decrease in fetal blood oxygen caused by maternal hypoxia and respiratory alkalosis has dramatic consequences on the fetus, resulting in congenital malformations. However, in 2015, the same group (35), who analysed a cohort of 36,587 pregnant asthmatics, observed that only severe exacerbations during the first trimester of pregnancy were significantly associated with an increased prevalence of congenital malformations, while moderate asthma exacerbations were not (35).

Impact of pregnancy on asthma

In a study performed by Schatz *et al.* on 330 pregnant women, asthma deterioration was observed in 35% of them, while in 33% the course of the disease remained stable, and 28% women declared an improvement (4%- uncertain) (6).

Stenius-Aarniala *et al.* (8) prospectively followed a cohort of 504 pregnant women with asthma and observed that 47 of them experienced acute attacks (8). Moreover, they found that the majority of acute attacks occurred between the 17th and 24th week of pregnancy, which was explained based on the hypothesis that the majority

of patients with asthma reduced and even stopped their medication in the first part of pregnancy, with symptom worsening occurring a few weeks later (8).

Kim *et al.* (31) evaluated the impact of pregnancy on asthma by comparing 3,357 pregnant asthmatic patients with 50,355 non-pregnant asthmatic patients. They found that pregnant asthmatic patients have a tendency to undergo more asthma-related hospitalizations than non-pregnant asthmatic patients and the proportion of hospitalized patients increased throughout the pregnancy (first trimester: 0.2%; second trimester: 0.5%; and third trimester: 0.7%). In their group, the prevalence of asthma exacerbations during pregnancy was 5.3%. The authors have noticed that patients with acute exacerbations during pregnancy needed more intensive asthma-related healthcare (emergency department admission, intensive care unit admission and outpatient visits). It was concluded that pregnancy affected the use of asthma-related healthcare (31).

A prospective cohort study of 146 asthmatic pregnant women (28) noticed that severe exacerbations happened in 36% of cases (53 women) and found that 34% of them were caused by viral respiratory infections and 29% were due to discontinuation of inhaled corticosteroid medication (28).

According to the available literature, psychological changes that generally occur during pregnancy, have also a potential effect on asthma of (7, 36). It is well-known that women become emotionally vulnerable during pregnancy; besides, pregnancy itself can get to be very stressful, especially for women who live this experience for the first time. Intense emotions action like triggers for asthma exacerbations.

Management of asthma during pregnancy

Recently updated National and International Guidelines provide information and recommendations for optimal asthma care in pregnancy. They strongly recommend an active asthma management during pregnancy using pharmacological and non-pharmacological strategies. Individualized treatment guided by a multidisciplinary team is suggested (12, 37, 38).

The main goals of optimal asthma treatment should be to improve the quality of life of pregnant asthmatics and to minimize the risk of con-

genital anomalies. The goals could be accomplished by developing a written asthma control plan, regular follow-up and adjusting the treatment according to patient's control level (26) in order to prevent asthma exacerbations and pregnancy complications.

As mentioned before, asthma, and especially asthma exacerbations, could cause poor outcomes for both the mother and fetus, but it has been demonstrated that these could be prevented if appropriately managed.

Proper diagnosis and assessment of asthma control is extremely important (39) during pregnancy, especially because the well-being of the fetus must be taken into consideration (40). Pharmacological and non-pharmacological strategies should be used in parallel (3).

Non-pharmacological strategies

If we take into consideration that a significant proportion of pregnant women stop or decrease asthma medications in early pregnancy (9), we tend to believe that education is one of the most important non-pharmacological strategies.

Education of both patients and physicians regarding the safety of asthma medication plays an essential role in the improvement of asthma control during pregnancy (39). Both physician's reluctance to treat and patient's fear of using medications that may affect the fetus result in non-adherence to therapy (41). Unfortunately, there are cases when physicians can provide wrong information concerning the safety of treatment. Studies have found that almost 25% of family doctors would recommend their patients to decrease or even stop asthma medication during pregnancy (42).

The best time to begin patient's education is preconceptionally. Patients should also be given the opportunity to express their concerns and ask questions (23), and preconception counseling might be the best opportunity to clarify concerns about any possible adverse effects of prescribed drugs on the fetus and to ensure asthma control, especially in the first trimester. Pregnant women should be informed about the nature of the disease, therapy used during pregnancy, complications, avoidance of triggers, adequate use of devices, and the importance of adherence to therapy (3). It is believed that self-management education is an important asthma tool that can be delivered antenatally (43). It has been proven to reduce

hospital admissions, unscheduled visits, days off work and nocturnal asthma symptoms in both non-pregnant and pregnant women (5).

Guidelines (17, 37, 38) agree that avoiding triggers is an important component of asthma management. Stimuli such as pollen, animal dander, dust, exercise, changes in weather, emotions, upper respiratory tract infections, medication, cigarette smoking should be avoided, or at least reduced, as much as possible.

It has been demonstrated that pregnant women were more susceptible to viral upper respiratory tract infections due to immune system changes during pregnancy. As mentioned before, viral infections are frequent triggers of asthma exacerbation. Physicians are advised to educate asthmatic women of childbearing age on the importance of annual influenza vaccination (24). As far as medication is concerned, beta-blockers, aspirin and non-steroidal anti-inflammatory drugs should be avoided (24).

The National Asthma Council (NAC) (38) recommends an appropriate control of comorbidities such as allergic rhinitis and gastro-esophageal reflux, which may mimic or worsen asthma symptoms. Also, stress and mental illnesses should be well-controlled in order to prevent asthma exacerbations.

Active and passive smoking is recognized as critical factor influencing the course of asthma (39); moreover, even in non-asthmatic pregnant women, it is known to have adverse effects on the fetus such as low birth weight, premature birth, and infant mortality, so it should be totally avoided.

Pharmacological strategies

Most of the times, the main question is "Asthma treatment – is it safe for the fetus"? Murphy *et al.* (13) answered the question by publishing the results of a meta-analysis that found that the relative risk of preterm delivery and preterm labor were reduced to non-significant levels by an active asthma management. They concluded that asthma management had the potential to reduce the number and severity of exacerbations in pregnancy, and consequently, their impact on both the mother and neonate (13).

According to Global Strategy for Asthma (GINA) (12), pregnant patients with asthma should be advised that poorly controlled asthma and exacerbations expose their baby to a much greater

risk than that posed by current asthma treatments. It is worth mentioning that most of the medication used before pregnancy can be safely continued during pregnancy (3). Despite clear guidelines for the management of asthma during pregnancy, there is evidence of suboptimal management in primary care (7).

Many authors and guidelines argue that the treatment for pregnant asthmatics follows the same broad principles as for non-pregnant patients (3, 5). There are different opinions on the implementation of the stepwise approach. While in non-pregnant patients the control level of asthma is assessed at three months after use of controller medication (patients with good asthma control are treated with *step-down treatment*, while those with persistent asthma symptoms or acute exacerbation receive a *step-up treatment*) (26), in pregnant asthmatics guidelines recommend that asthma control and lung function should be monitored and assessed monthly (12, 38). GINA emphasizes the *step-down treatment* is not a priority during pregnancy (12).

Asthma medications are divided into long-term controller medications and rescue therapy (41). Here is a summary of the most commonly used drugs, which are also considered to be safe during pregnancy.

Long-term controller medications used for maintenance therapy to prevent asthma symptoms worsening (41) are represented by inhaled corticosteroids (ICSs) (guidelines highlight the importance of maintaining their use during pregnancy or in preparations for pregnancy) (12, 37); long-acting β -agonists (LABA); leukotriene receptor antagonists (LTRAs) (with limited data concerning the safety of LTRAs in pregnancy, although SIGN (37) suggests that LTRAs should not be withheld during pregnancy); sodium cromoglicate and Nedocromil sodium (with no major risk during pregnancy) (37); and theophylline (SIGN (37) recommends the use of oral and intravenous theophyllines as normal during pregnancy).

Rescue therapy provides immediate symptom relief (41) and is represented by inhaled short-acting β -agonists (SABA) (37).

Oral corticosteroids (OCS) can either be used as a rescue therapy or chronic therapy for severe persistent asthma (41). SIGN (37) recommends OCS use as normal when indicated during pregnancy for women with severe asthma and they emphasize that oral OCS should never be with-

held because of pregnancy. All women should be advised that the benefits of treatment with OCS outweigh the risks (37).

There is controversy concerning the use of Omalizumab and Allergen immunotherapy (AIT) in pregnancy. A few studies do support their safety, but guidelines suggest there is still insufficient data (12, 13). For AIT, considered to be the only treatment for the etiology of asthma, authors support the fact that sublingual and subcutaneous administration is safe during pregnancy (26). Even though GINA (12) accepts the option, SIGN (37) totally disagrees with the administration of AIT.

Pharmacological therapy should be complemented with regular assessments and above-mentioned non-pharmacological therapeutic options (3).

Monitoring of asthma and assessment of lung function is recommended to be offered regularly [National Asthma Education and Prevention Program (NAEPP) (17) recommends spirometry assessment, followed by monthly evaluation of asthma symptoms and measurement of pulmonary function; National Asthma Council Australia (NAC) (38) suggests that evaluation should be done every four weeks, assessing asthma control by using validated questionnaires: Asthma Control Test, Asthma Control Questionnaire; GINA (12) suggests monthly monitoring of asthma and supports the Fractional Exhaled Nitric Oxide (FENO) technique (inflammation-based) of asthma assessment; Hyaluronic acid is another marker of systemic inflammation, and its benefits as screening tool for asthma control during pregnancy are still evaluated (41)].

Management

Intrapartum management

Evidence shows that only approximately 10% of asthmatic patients experience acute exacerbations during labor and delivery (5, 20, 26). However, hyperventilation during labor may cause bronchoconstriction. GINA (12) recommends they should be managed with SABA.

Pain is recognized as a trigger for exacerbations of asthma; consequently, analgesia should be maintained during labor and delivery, lumbar epidural being the preferred option (24). It is known to reduce minute volume and oxygen consumption and may help prevent hyperinflation in patients with active symptoms (26). Oxytocin is al-

lowed for the induction of labor and control of an eventual postpartum hemorrhage. Prostaglandins E1 and E2 are also accepted in labor (24). Ergotamine and ergot derivatives, prostaglandin F2, morphine, and meperidine should be avoided as they may be associated with an increased risk of bronchospasm (26).

Women receiving OCS at a dose exceeding Prednisolone 7.5 mg per day for more than two weeks prior to delivery should receive parenteral Hydrocortisone 100 mg at every 6–8 hours during labor (37).

Management of exacerbations during pregnancy

Intense fetal and maternal monitoring are of the utmost importance when exacerbations occur. Maternal oxygen saturation should be maintained 94-98% to prevent fetal hypoxia (24, 37). GINA (12) recommends an aggressive treatment with SABA, oxygen inhalation and early administration of systemic corticosteroids. Blood glucose should be monitored closely in because of the significant effects of hyperglycemia on the fetus (24). Neonatal hypoglycemia may be seen, especially in pre-term babies, when high doses of beta-agonists have been given within the last 48 hours prior to delivery. If high doses of SABA have been given during labor and delivery, blood glucose levels should be monitored also in the baby for the first 24 hours (12).

Asthma during COVID-19 pandemic

Given the current COVID-19 pandemic, in April 2020 GINA (12) published special recommendations for physicians dealing with general asthmatics, which we consider worth mentioning:

1. Advise patients with asthma to continue taking their prescribed asthma medications, particularly ICS and OCS if prescribed.

2. Make sure that all patients have a written asthma action plan.
3. Where possible, avoid use of nebulizers due to the risk of transmitting infection to both other patients and healthcare workers.
4. Avoid spirometry in patients with confirmed/suspected COVID-19.
5. Follow infection control recommendations if other aerosol-generating procedures are needed.
6. Follow local health advice about hygiene strategies and use of personal protective equipment, as new information becomes available in your country or region. □

CONCLUSIONS

Optimal asthma control, preventing, detecting and treating the exacerbations are of the utmost importance in order to minimize the adverse effects for both the mother and fetus. Guidelines recommend an active asthma management during pregnancy. Preconception counseling and during pregnancy and individualized treatment guided by a multidisciplinary team is suggested. Education on the importance of anti-asthmatic therapy, avoiding triggers, frequent and accurate monitoring are essential for good asthma management. Physicians who treat asthmatic patients during the pandemic of COVID-19 should increase vigilance and take supplementary measures for the safety of both themselves and patients. □

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