

Asthma and pregnancy

Abstract

Asthma is the most common chronic medical illness that affects pregnant women; uncontrolled forms and its exacerbation may adversely affect both mother and baby. With a careful monitoring by a multidisciplinary team and timely implementation of therapy, these complications can be significantly prevented. This article reviews the aspects related to asthma diagnosis and treatment during pregnancy, focusing on the recently published studies about asthma control, asthma medications or common pathogenesis factors as contributors to adverse perinatal outcomes.

Keywords: asthma, medical illness, pregnancy, medications

Introduction

Asthma is the most common chronic medical illness that affects pregnant women. Uncontrolled forms and its exacerbation may adversely affect both mother and baby. The prevalence of asthma among pregnant females has been reported in up to 8.4% of women annually in the USA⁽¹⁾, and it is currently increasing. Approximately 10% of patients have an asthma crisis during labor, and status asthmaticus has occurred in 0.2% of pregnancies^(1,2). However, despite these possible complications, the evolution of asthma in pregnancy is not always so dramatic. It is thought that one-third of pregnant women with asthma remains stable, one-third has an improved disease outcome, and for one-third, the condition worsens during pregnancy^(3,4). The asthma monitoring in pregnancy should start even in the pre-pregnancy period, given the fact that a worse outcome may be related to baseline severity, patients with moderate to severe asthma demonstrating more exacerbations⁽⁵⁾. Many studies showed that asthma symptoms are usually worsening in the late second or early third trimester, but severe exacerbations are quite rare during labor and peripartum^(3,4,6,7). Any asthmatic woman requires a close monitoring during the entire course of pregnancy, performed by a multidisciplinary team, including intensivists, pulmonologists, neonatologists, allergologists, and obstetricians experienced in high-risk pregnancies, to reduce complications during the peripartum period, morbidity and mortality of the mother and fetus⁽⁸⁾. This approach is particularly important if mechanical or non-invasive ventilation becomes necessary due to respiratory failure. With carefully monitoring and timely implementation of therapy, these complications can be significantly prevented.

This review will discuss aspects related to asthma diagnosis and treatment during pregnancy, focusing on the recent published studies on asthma control, asthma medications or common pathogenesis factors as contributors to adverse perinatal outcomes.

Normal Physiologic Changes of Pregnancy

During pregnancy, both the hormonal changes and the enlarging uterus can interact with the pathophysio-

logic activities of asthma. High estrogen levels increase the mucosal edema and hypervascularity in the upper airways⁽⁹⁾. The elevation of the diaphragm by 4-5 cm due to enlarging uterine cavity leads to a near 20% loss in the functional residual capacity, which represents the volume of air that remains after normal exhalation^(2,9).

Pregnancy is associated with a 15% increase in metabolic rate, followed by a 20% increase in oxygen consumption, a 30% increase of tidal volume (i.e. the volume of air that is exchanged with normal respiration), and a 40-50% increase of minute ventilation⁽⁹⁾. These changes are the consequence of the progesterone-mediated effect on the respiratory center either by direct stimulation or by increasing its sensitivity to carbon dioxide^(9,10). The increasing of minute ventilation results in a subsequent respiratory alkalosis with renal bicarbonate wasting as compensation.

During pregnancy breathing and cardiac output activity increases. Oxygen consumption increases and a mild respiratory alkalosis appear due to secondary increased minute ventilation. The typical arterial blood gas (ABG) analysis will show a PaCO₂ of 28 - 32 mmHg, but with a near normal pH of 7.40 - 7.45, due to concomitant metabolic acidosis^(2,9). When evaluating the ABG of a pregnant woman, a "normal" value of PaCO₂ may actually represent a degree of CO₂ retention and possible impending respiratory failure. Alternatively, chronically elevated values of PaCO₂ may constitute a state of uncontrolled asthma. The increased level of maternal PCO₂ will affect the fetus's ability to excrete acid and will ultimately lead to fetal acidosis^(9,11). The value of PaO₂ during pregnancy is normally mildly elevated, between 106-110 mmHg; the maternal hypoxemia will be rapidly followed by a decreased oxygen content supplied to the fetus, and chronic hypoxemia could result in an intrauterine growth restriction and low birth weight⁽⁹⁾.

Therefore, the optimal management of asthma is of the greatest importance for both, pregnant woman and her fetus. Pregnancy does not affect the functional exhaled volume (FEV1) during the first second of a forced expiratory maneuver or the maximum flow during forced expiration. Pulmonary function test identifying

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the acute, reversible obstructive dysfunction remains the most valuable tool in diagnosing and monitoring asthma severity in pregnancy. Spirometry represents an easy, safe, accepted by women and accessible method indicated to monitor asthma during pregnancy.

Interactions of Pregnancy and Asthma

Asthma is an airways chronic inflammatory disease that leads to variable respiratory symptoms as wheeze, cough, chest tightness, and dyspnea. The interaction of the immunological changes associated with asthma and pregnancy remain unclear, this being the main reason of the unpredictable effect that pregnancy has on patient's asthma. The changes in maternal hormone status and/or impaired responsiveness of the beta-adrenergic receptor represent possible mechanisms of this interaction. Fetus gender might play a role, with several data showing that a female fetus can worsen the outcome of asthma^(12,13). In a very large prospective study, it was showed the correlation between the rates of severe asthma exacerbation and the degree of severity classification, patients with severe asthma reported an exacerbation rate of 51.9% and a hospitalization rate of 26.9%. The incidence of exacerbations and hospitalization rate in women with mild or moderate forms of asthma was 12.6%, and 2.3%, respectively 25.7% and 6.8%⁽¹⁴⁾. Knowledge of the asthma classification is very important in assessing the risk of exacerbation. In many cases gastro-esophageal reflux, sinusitis, and allergic rhinitis worsening during pregnancy could become risk factors for asthma exacerbation. Viral infections, smoke exposure and non-adherence (cessation or reduction) to inhale corticosteroid are major triggers for asthma exacerbations, which are more common in the second semester⁽¹⁵⁾.

Many retrospective studies associate maternal asthma with different complications, including preterm birth (RR = 1.41, 95% CI: 1.23-1.62), preeclampsia (RR = 1.54, 95% CI: 1.32-1.81), increase in spontaneous abortion (OR = 1.41, 95% CI: 1.33-1.49), low birth weight (RR = 1.46, 95% CI: 1.22-1.75), and small size for gestational age (RR = 1.21, 95% CI: 1.14-1.31)⁽¹⁶⁻¹⁸⁾. Different findings were revealed by other prospective studies, in which maternal asthma was not associated with many of these outcomes^(9,18). In a large controlled study, Murphy et al. revealed that pregnant women with severe asthma were at a significantly higher risk of gestational diabetes and preterm delivery⁽¹⁸⁾. Other two large studies found an increased risk of pregnancy to induced hypertension in patients presenting moderate to severe daily symptoms^(9,15). Pregnant women with severe asthma necessitating systemic corticosteroid treatment were found to be at risk of preeclampsia, decreased gestational age at birth and low gestational age and gestational diabetes^(9,18,19).

The influence of asthma on the developing fetus remains poorly understood. In a large study of 56.000 asthmatic pregnant women, no significant association with major malformation was found (RR = 1.31, 95%

CI: 0.57-3.02). The most frequent association were cleft lip with or without cleft palate infants (RR = 1.30, 95% CI: 1.01-1.68), secondary to first-trimester oral corticosteroid exposure⁽¹⁶⁾. Maternal hypoxemia, as a result of severe chronic asthma, repeated exacerbations, and status asthmaticus, along with smoking and altered placental function were thought to contribute to poor outcomes in patients with asthma⁽¹⁶⁾. Reviews suggest that patients with uncontrolled severe asthma are at risk of increasingly negative fetal and maternal outcomes, but an active disease management of their asthma has better outcomes^(2,9).

Asthma Management during Pregnancy

The recommended treatment for pregnant chronic asthmatics is a proper asthma control, including asthma education, tobacco cessation, compliance with asthma action plan, infection avoidance, and vaccination, and most important, preventing exacerbations⁽⁷⁾. In the case of expected pregnancy, women with asthma should be prepared by their physician about the evolution of their disease and the risks for the fetus, and those identified being at-risk patients should be closely followed-up. Maselli et al.⁽²⁰⁾ suggest that all asthmatic women who become pregnant should be considered as high-risk, and carefully managed. In fact, asthma management during pregnancy is not much different from non-pregnant patients, the long-term controller therapy being with inhaled corticosteroids.

Patient Education

A partnership between pregnant women and health care providers is essential for a good management of asthma during pregnancy. Every patient needs to receive an individual asthma action plan consisting in recognition of symptoms in allergen avoidance and eviction of trigger factors, smoking cessation advice, information about the mechanism, secondary effects of medication and how to adjust asthma treatment (stepping-up and stepping down). Monthly pulmonary control is recommended during pregnancy.

Pharmacological Therapy

The principle governing the treatment of asthma in pregnant women is that a well-controlled disease decreases the risk of complications in mother and her fetus. The moderate and severe asthma are associated with poor control, especially when the medication is interrupted due to an idea that the medication could be harmful to the baby⁽²¹⁾. The high-blood pressure, pre-eclampsia, vaginal hemorrhage, premature delivery, low birth weight and increased perinatal mortality have been reported related to severe asthma, frequent exacerbations with hospitalization and emergency room visits⁽²²⁾. Specialists state that pregnant asthmatic women are better to be treated with asthma medication than being symptomatic. The main classes of treatment are the same like in non-pregnant women, and clinicians must choose the safest asthma medi-

Table 1

Pharmaceutical drugs classification after US Food and Drug Administration depending on the risk on the fetus when this are administered in pregnant women

Asthma medications	Category A The well-controlled drug studies in pregnant women have failed to demonstrate any risk to the fetus	Category B The animal drug studies have shown that there was no demonstrated fetal risk, but controlled drug studies have not been performed in pregnant women	Category C The studies in animals have revealed adverse effects on the fetus/ teratogenicity, and there are no controlled studies in women	Category D The studies have shown positive evidence of human fetal risks
Inhaled corticosteroids	Long-term control medication indicated in all persistent asthma cases Treatment for persistent asthma (partly controlled) - doses related with severity of asthma			
Budesonide		X is the preferred agent		
Beclometasone			X	
Fluticasone			X	
Other Inhaled Corticosteroids			X	
Anti-Leukotriene Montelukast		X few studies		
Long-Acting beta-2 agonist/ Salmeterol			X can be added if needed	
Theophyllines			X can be added in poorly controlled asthma	
Systemic corticosteroids (prednisone, methylprednisolone, hydrocortisone)			X can be used in severe forms and acute exacerbations of asthma	
IgE inhibitor Omalizumab		X Improve control in very severe asthma		
Short-acting selective beta-2 agonists and anticholinergic agents	Reliever medication Indicated like single medication only for intermittent and well- controlled asthma			
albuterol			X Is the most preferred agent	
anticholinergic agents		X		

cation in order to prevent hypoxic asthma attack in mother and insufficient oxygenation of the fetus⁽²³⁾. US Food and Drug Administration (FDA) classified the acceptable pharmaceutical drugs into four classes (A, B, C, and D) depending on the risk on the fetus when these are administered in pregnant women (Table 1)⁽²⁴⁾. The most advisable are drugs from A and B classes, but we can also use those from C classes when the positive effects exceed the risks. The advantages of using controller and reliever asthma medications to achieve good control of symptoms and prevent exacerbations outweigh any potential risk for fetus⁽²⁵⁾. The use of inhaled corticosteroids, montelukast, short and long β_2 -agonist and theophylline is not associated with increased major congenital malformations or adverse perinatal complications⁽²⁵⁾. Inhaled corticosteroids control the inflammation improving the FEV1 and reducing the risk of exacerbation. Budesonide is the preferable choice, belonging to category B of FDA classification. In the case of acute exacerbation aggressive treatment with oxygen and systemic corticosteroids should be

used. Influenza vaccine could be done in the second and third semester, and allergen immunotherapy could be continued⁽²⁶⁾. During labor and delivery, patients need to keep the usual controller medication. Some authors suggest administering “stressdose” corticosteroids during the labor and delivery period: hydrocortisone 100 mg intravenously once upon presentation and then every 8 hours if needed⁽²⁵⁾. In the case of increased doses of SABA having been administered prior delivery the neonatology should monitor the blood glucose level in the baby for the first 24 hours⁽²⁷⁾. Prostaglandin F2 α used by a gynecologist for uterine atony, should be contraindicated in asthmatics because it can cause airway bronchoconstriction⁽²⁴⁾.

In conclusion an appropriate management of asthma during pregnancy with control of symptoms to prevent the exacerbations could reduce the risk of fetal and maternal morbidity and mortality. With a careful monitoring by a multidisciplinary team and timely implementation of therapy, complications can be significantly prevented. ■

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