

Maternal asthma during pregnancy and fetal outcomes: potential mechanisms and possible solutions

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Purpose of review

Asthma exacerbations during pregnancy can be a serious complication that have detrimental consequences for both mother and fetus. The pathophysiological mechanisms that cause worsening asthma during pregnancy are only just starting to be examined. This review will examine the recent literature on immune function in pregnant women, immune function in nonpregnant asthma patients and studies conducted on asthma during pregnancy.

Recent findings

Fifty-five percent of women with asthma will experience at least one exacerbation during pregnancy. This has significant effects on fetal growth and survival, especially if the fetus is male. A number of factors that may contribute to the development of worsening asthma during pregnancy include pregnancy-induced changes in maternal immune function, increased maternal susceptibility to infection, female fetal sex, noncompliance with medication and prepregnancy asthma severity. Interestingly, the immune changes in the maternal system in response to the presence of the fetus and placenta are very similar to the immune changes described in nonpregnant asthma patients with noneosinophilic asthma.

Summary

These studies highlight that worsening asthma during pregnancy cannot be attributed to pregnancy alone or asthma alone and may be a complex combination of factors and events.

Keywords

asthma, fetal growth, fetal sex, pregnancy, treatment

Introduction

There appears to be a circuitous relationship between a mother with asthma and the fetus during pregnancy. The presence of the fetus and placenta may alter maternal immune function and increase asthma severity. An increase in maternal asthma severity can result in a detrimental outcome for the fetus, which includes intrauterine growth restriction (IUGR), preterm delivery and still birth. IUGR has long-term implications relating to the development of diseases in adult life such as hypertension and diabetes [1,2]. Interestingly, these relationships between the mother with asthma and the fetus also appear to be influenced by the sex of the fetus. The interrelationship between mother and fetus raises questions of how pregnancy can alter asthma severity and what the mechanisms are that contribute to altered fetal growth and survival. The recent literature on immune function in pregnant women, immune function in nonpregnant women with asthma and studies conducted on asthma during pregnancy will be discussed.

Asthma exacerbations during pregnancy

The severity of asthma and the effect of asthma exacerbations during pregnancy on both mother and fetus have been underestimated due to the lack of longitudinal, prospective cohort studies conducted on pregnant women with asthma. A general dogma of 'one-third improve, one-third worsen and one third don't change in their asthma severity during pregnancy' is a miscalculation because it does not take into account the influence of prepregnancy asthma severity. In addition, there has been a misconception that inhaled glucocorticoid use is harmful to the fetus which results in a lack of compliance with medication use during pregnancy and results in an increased risk of acute exacerbations and poor fetal outcomes [3*,4*].

One of the most serious events in pregnancies complicated by asthma is acute exacerbation [5]. Recent studies indicate that mild or severe exacerbations can affect 55% of women with asthma during pregnancy, with the frequency of severe exacerbations being greater in women with severe asthma [6*]. Exacerbations were associated with self-reported noncompliance with inhaled glucocorticoid treatment, self-reported but unconfirmed presence of a viral infection, cigarette use and seasonal changes during pregnancy [6*]. A proportion of asthma exacerbations during pregnancy had an unknown cause [6*]. In

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Abbreviations

IUGR intrauterine growth restriction
Th T helper

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these cases it is possible that the cause may simply be the presence of the fetus and placenta and their effect on maternal immune function.

Effect of pregnancy on maternal immune function: possible mechanisms for worsening asthma during pregnancy

Pregnancy is an interesting immunological event in that the maternal immune system maintains immune tolerance to the presence of a genetically different fetus but at the same time continues to function actively against invading pathogens via the innate immune system [7,8]. The release of placentally derived factors into the maternal circulation has been proposed to redirect the maternal immune system away from cell-mediated immunity and T helper type 1 (Th1) cytokine production to humoral immunity and Th2 cytokine production [9,10^{••},11^{••}]. These maternal immune changes may upregulate asthma-related mechanisms.

Human pregnancy is associated with an increase in maternal blood concentrations of cells of the innate immune system, including monocytes and neutrophils [12]. Monocyte cytotoxic function appears to be down-regulated during pregnancy by placentally derived factors such as major histocompatibility (MHC) class I chain-related proteins A and B (MICs) [11^{••}] but these cells still mount an inflammatory response via interleukin (IL)-12 production [13]. Pregnancy-related neutrophil numbers are increased [14]. Both of these cell types are associated with the pathophysiology of asthma [15] and asthma exacerbations [16]. Asthma can be classified based on the presence and absence of sputum eosinophils and neutrophils, with some individuals having asthma symptoms associated with increased sputum neutrophils and no eosinophils [15]. This is presently known as non-eosinophilic asthma [15]. Viral-induced asthma exacerbations are associated with neutrophilic inflammation [16]. It is possible that changes in circulating immune cell profiles during pregnancy could exacerbate maternal asthma, especially in the presence of viral infection.

Another mechanism that may influence maternal asthma during pregnancy is placental exosomes. Exosomes are extracellular vesicles that allow membrane proteins to be secreted into the circulation and have been described to be central in dendritic cell modulation of inflammatory responses by inducing T-cell apoptosis [17]. Placental exosomes isolated from maternal sera of normal pregnancies express Fas ligand (FasL), a factor involved in apoptosis [10^{••}]. Taylor *et al.* [10^{••}] incubated isolated placental exosomes with a T-cell line (Jurkat cells) *in vitro*. The placental exosomes suppressed T-cell expression of IL-2, CD3- ζ and JAK-3 proteins. Suppression of these proteins was correlated with exosome FasL expression. This research suggests that placental exo-

somes mediate maternal immune tolerance during pregnancy via FasL-induced inhibition of Th1 cytokine signaling pathways of CD4⁺ T cells. This mechanism allows for Th2 predominance in circulating T cells during pregnancy. Interestingly, atopic disease is also associated with a predominance of Th2 T cells via a similar mechanism [18].

The identification of pregnancy-derived and asthma-derived factors involved in the induction of worsening asthma during pregnancy is in the preliminary stages of investigation. Proteomic analysis of pregnant sera from women with and without asthma indicate that there are a number of circulating proteins that are specific to the presence of maternal asthma and change with gestational age [19[•]]. When examining placental and cord blood protein profiles from the same group of women, it was found that there were 14 placental proteins altered in the presence of maternal asthma and 10 proteins altered in cord blood [20[•]]. These data suggest that maternal asthma induces dynamic protein changes during gestation that may influence both worsening asthma during pregnancy and fetal growth and development.

Pregnancy-related factors may also influence maternal asthma. Using fetal and maternal sera from the same population used in the proteomic analysis [19[•],20[•]], Osei-Kumah *et al.* [21[•]] demonstrated that sera of normal pregnancies and pregnancies complicated by asthma induced protein production of the chemokines RANTES, eotaxin and IL-8, the inflammatory cytokine IL-6, and the adhesion factor soluble intercellular adhesion molecule-1 by human bronchial smooth muscle cells *in vitro* [21[•]]. These data indicate pregnancy-derived factors alone can activate asthma-associated pathways, potentially exacerbating the disease in genetically susceptible individuals.

Effect of pregnancy on susceptibility to infection in women with asthma

Changes in maternal immune function during pregnancy may contribute to an increased susceptibility to parasitic [22], bacterial [23] and viral infections [24^{••}]. Women with asthma appear to be more susceptible to respiratory tract infection during pregnancy. A population-based study with an asthma prevalence of 4% reported 50% of respiratory-related hospitalizations of pregnant women had a comorbidity of asthma, suggesting increased susceptibility to respiratory tract infections [25]. Pregnant women with asthma also have an increased risk of community-acquired pneumonia [23].

There is no scientific information relating to why pregnant women with asthma are more at risk from infection. Mechanistic studies conducted in nonpregnant women with asthma, however, provide some clues.

Viral RNA expression and release in airway epithelial cells *in vitro* were significantly increased in cells derived from individuals with asthma when compared with cells derived from women without asthma [24^{••}]. Viral-induced exacerbations in nonpregnant women with asthma are promoted by airway neutrophil influx and increased IL-10 expression [26]. Both neutrophil concentrations [27] and placental IL-10 levels [28] are upregulated with pregnancy. These studies suggest the combination of asthma and pregnancy-induced immunosuppression may significantly increase the risk of infection and result in acute asthma exacerbations during pregnancy.

Preventive measures against infection for women with asthma during pregnancy may need to be considered. There has been a recent recommendation for vaccination during the influenza season of pregnant, high-risk women, including those with severe asthma [29]. Retrospective studies suggest influenza vaccination is safe during the second and third trimesters of pregnancy [30].

Effect of fetal sex on maternal asthma

Since 1930 there have been anecdotal and scientific reports that indicate the sex of the fetus influences maternal asthma severity, with asthma worsening in the presence of a female fetus [31,32]. More recently, there have been reports supporting this observation [33–35,36[•]]. The most recent study has shown that in a population-based prospective cohort study, peak expiratory flow liability was greater in women with asthma pregnant with a female fetus relative to those with a male fetus [36[•]]. Clinically, this observation may be of no use, as the sex of the fetus is often not known until later in gestation and even then it may be requested by the parents not to be divulged. The information, however, does provide scientific clues of the mechanisms influencing maternal asthma and in broader terms it indicates that fetal sex can influence maternal physiology.

Sex-specific factors derived from the fetus that may influence maternal asthma have not been identified. Male-derived testosterone, however, was proposed to exert antiinflammatory and bronchodilator effects in the pregnant maternal system, resulting in improved lung function of women with asthma during pregnancy [36[•]]. The sex-related difference in asthma severity may also be due to increased inflammation in the presence of female sex steroids and sex-specific placental proteins [20[•]]. In women with asthma who did not use inhaled glucocorticoids and were pregnant with a female fetus, there was a significant increase in circulating monocytes and no change in circulating eosinophils [35]. These data suggest that worsening asthma in the presence of a female fetus may be mediated by noneosinophilic pathways during pregnancy.

Effect of maternal asthma on fetal outcome

Detrimental fetal outcomes in the presence of maternal asthma include intrauterine growth restriction and stillbirth [3[•],6[•]]. The mechanisms contributing to altered growth and survival of the fetus appear to be sexually dimorphic [6[•],35,37[•]]. In response to maternal asthma and in the absence of inhaled steroid use, the female fetus had reduced growth and reduced adrenal function due to decreased placental glucocorticoid metabolism [35,37[•]]. Placental function, hypothalamic–pituitary–adrenal axis activity and growth of the male fetus appeared to be unaffected by asthma or inhaled steroid use [35,37[•]]. In the presence of a second stress, however – an acute, severe asthma exacerbation – male neonates had reduced growth and an increased incidence of stillbirth and preterm delivery while the female fetus appeared unaffected [6[•]]. These data suggest that the female fetus responds to maternal asthma by downregulating placental and fetal pathways associated with glucocorticoid regulation, reducing growth and increasing the chances of survival. In contrast, the male fetus continues to grow normally in the presence of maternal asthma, but with the addition of a severe exacerbation, the male fetus then experiences reduced growth and has an increased risk of in-utero death [6[•]]. These findings could change how we assess the wellbeing of a fetus in pregnancies complicated by asthma. A female fetus may appear to have IUGR in late gestation in pregnancies complicated by asthma, raising significant obstetric concerns, but will ultimately survive the pregnancy. A male fetus, however, may be growing normally in the presence of maternal asthma but is at risk of stillbirth in the presence of another stressful event such as an exacerbation or infection.

Solutions for a healthy outcome

The deterioration of asthma during pregnancy and adverse perinatal outcomes can be avoided with maternal asthma education, joint respiratory and obstetric care and compliance with the use of inhaled glucocorticoids [38^{••}]. If persistent asthma during pregnancy is related to the influence of noneosinophilic mechanisms, then treatment regimes may be reconsidered – from the use of inhaled glucocorticoids to the use of long-acting β_2 -agonists [39] or anti-immunoglobulin E (IgE) therapies [40]. There are no reports of anti-IgE therapy use during pregnancy. One publication has examined the effect of the long-acting β_2 -agonist, salmeterol, on placental function and neonatal birthweight [41]. The treatment of severe asthma during pregnancy with salmeterol and fluticasone propionate was associated with reduced neonatal birthweight [41]. The study numbers were small and further investigation is required [41]. The Salmeterol Multicentre Asthma Research Trial (SMART) did not provide reassuring evidence for the use of salmeterol, as asthma-related deaths were increased with its use [42^{••}]. These findings indicate that inhaled steroid long-acting

β_2 -agonist pharmacotherapy during pregnancy must be used with caution.

There are a number of recent population-based studies that report the benefits of inhaled corticosteroid use during pregnancy on perinatal outcomes [35,43, 44,45**]. Inhaled budesonide has no effect on fetal outcome in pregnant women with asthma and is presently the recommended inhaled glucocorticoid treatment during pregnancy [45**,46]. The ideal scenario for women with asthma would be a combined respiratory/antenatal clinic which includes an education program for the management of their disease during pregnancy. It has already been reported that this type of care can significantly improve the health of pregnant women with asthma and their offspring [38**].

Conclusion

There are many factors that may influence increased maternal asthma severity during pregnancy, including fetal sex, noncompliance with medication, susceptibility to infection, pregnancy-induced immunosuppression and prepregnancy asthma severity. Each of these components are interlinked and all of them can influence maternal health and neonatal outcome. Interestingly, it seems that worsening asthma during pregnancy may be attributable to noneosinophilic mechanisms and could have implications in how women with asthma are treated during pregnancy. Not all women have worsening asthma during pregnancy, however, and more attention needs to be given to this group of women to understand why their asthma does not change. It could be due to prepregnancy asthma status or related to the presence of a male fetus but definitive answers need to be found. Most importantly, prospective cohort studies need to be conducted in the future to examine mechanisms associated with asthma exacerbations and infection during pregnancy, with the goal of developing effective treatment regimes. The study of asthma during pregnancy provides an important paradigm for studying fetal and maternal physiology and how each system interacts for an optimal outcome. These findings may be applicable to other inflammatory complications during pregnancy, including preeclampsia, connective tissue diseases and inflammatory bowel disease.

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