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Review: Placental adaptations to the presence of maternal asthma during pregnancy

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ABSTRACT

Asthma is a highly prevalent chronic medical condition affecting an estimated 12% of pregnant, women each year, with prevalence of asthma greatest (up to 16%) among the socially disadvantaged. Maternal asthma is associated with significant perinatal morbidity and mortality including preterm births, neonatal hospitalisations and low birthweight outcomes each year. We have identified that the placenta adapts to the presence of chronic, maternal asthma during pregnancy in a sex specific manner that may confer sex differences in fetal outcome. The male fetus was at greater risk of a poor outcome than a female fetus in the presence of maternal asthma and an acute inflammatory event such as an asthma exacerbation. This review will examine the role of sex specific differences in placental function on fetal growth and survival.

Contents

1. Introduction 00
2. Asthma and pregnancy 00
3. Sex differences in placental adaptations to maternal asthma 00
3.1. Global gene expression 00
4. No sex differences in placental oxidative stress pathways 00
5. Sex differences in placental immune responses to maternal asthma in pregnancy and its regulation by cortisol 00
6. Sex differences in insulin-like growth factor axis (IGF) and its regulation by cortisol 00
7. Sex differences in placental angiogenesis and vascular function in pregnancies complicated by asthma 00
8. Sex specific differences in placental glucocorticoid bioactivity 00
9. The role of androgens in fetal growth and development 00
10. Long term implications of the fetal exposure to asthma *in utero* 00
11. Conclusion 00
Acknowledgements 00
References 00

1. Introduction

There are known sex specific differences in fetal growth and survival in pregnancies complicated by asthma which include females being more susceptible to low birthweight (LBW, <2500 g) and small for gestational age (SGA, <10th birthweight centile), and males more likely to deliver preterm (<37 weeks gestation) and at higher risk of stillbirth especially as asthma worsens with increasing gestation [1–3]. These sex specific differences may be conferred by the placenta which adapts to reduce female growth but as a result increases female survival relative to males in pregnancies complicated by asthma. The current review assesses sex specific placental adaptations, in the presence of maternal asthma

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during pregnancy that may contribute to fetal growth and survival and considers the consequences of that adaptation for life long health.

2. Asthma and pregnancy

Asthma is a common co-morbidity to affect women during pregnancy. Its prevalence is particularly high in Australia affecting 12% of pregnant women [4] and 3–12% of women worldwide [5]. Asthma has been identified to worsen as gestation progresses with recurrent uncontrolled asthma [6] and asthma exacerbations [7] contributing to poor outcomes for the fetus.

The presence of asthma during pregnancy can result in increased maternal systemic inflammation [8,9], increased oxidative stress [10,11], and reduced levels of maternal oxygen especially when asthma is recurrently uncontrolled or when women experience an acute exacerbation of asthma [6,12]. Asthma exacerbations can result in maternal alkalosis, which can lead to reductions in the uterine blood flow and fetal oxygenation leading to fetal hypoxia, hypercapnia, or acidosis under extreme conditions [13]. These maternal factors may lead to adverse perinatal outcomes with complications of asthma occurring early in gestation potentially contributing to preterm delivery and growth restriction and late gestation exacerbations resulting in stillbirth.

Current research indicates maternal asthma in pregnancy is associated with sex specific differences in fetal growth which may be mediated by sex specific differences in placental function [14]. It has been observed that the female fetus reduces her growth trajectory in response to maternal asthma by 12% which confers a survival advantage in the presence of a secondary event such as an acute exacerbation. The male fetus continues to grow normally in response to maternal asthma but is at higher risk of a poor outcome following an acute exacerbation. The placental mechanisms that likely confer these sex specific fetal differences will be discussed in this review.

3. Sex differences in placental adaptations to maternal asthma

3.1. Global gene expression

Several studies report that there are sex specific global gene differences in the human placenta [15,16] which include genes on both the autosomal and sex chromosomes. Sood et al. [17] reported increased gene expression related to immune and inflammatory pathways (JAK1, IL2RB, Clusterin, LTBP, CXCL1, IL1RL1 and TNF) in female placentae compared to males. Buckberry et al. [18] reported there were 142 sex-biased human placental genes of which 75 were expressed higher in female placentae and 67 were expressed higher in male placentae. Buckberry et al. [18] identified transcription factor genes associated with mTOR and vascular endothelial growth factor (VEGF) signalling pathways were sex specifically biased. mTOR signalling is an important nutrient sensor in the placenta and a regulator of growth and cellular proliferation [19] while VEGF is a growth factor involved in placental angiogenesis [20]. In particular, there was a male bias in the numbers of expressed transcription factors associated with the mTOR pathway which included a number of ribosomal proteins (RPS4Y1, RPS4Y2, RPS6KA6) and a protein phosphatase (PPP2R3B). In female placentae there was a bias towards transcription factors associated with VEGF signalling which included eukaryotic translation initiation factors (EIF1AX, EIF2S3). Sex differences in immune gene expression and growth factor pathways were also identified in placentae of pregnancies complicated by asthma and suggest it may be these particular biological functions that influence sex differences in fetal growth and survival.

Placental global gene microarray was conducted on placentae from non-asthmatic and asthmatic pregnancies [15]. The presence of maternal asthma resulted in 59 gene changes in female placentae, whereas only six gene changes were identified in male placentae. Using gene network analysis; immune genes, oxidative stress genes and growth factor genes were significantly altered in female placentae of pregnancies complicated by asthma (Table 1) [15]. Alterations in males were primarily associated with acute phase response signalling and oxidative stress (Table 1). This analysis infers female placentae of asthmatic pregnancies undergo gene adaptations associated with the suppression of both immune and growth factor pathways that may contribute to decreased growth in the presence of maternal asthma and secure a survival advantage. In contrast, conserved male placental gene expression may promote continued growth in an adverse maternal environment which results in a survival disadvantage with further complications. In both sexes oxidative stress pathways were comparable suggesting some fundamental mechanisms essential for survival remain constant.

4. No sex differences in placental oxidative stress pathways

Asthma itself is associated with increased activation of oxidative stress related pathways in association with the systemic and chronic presence of inflammation [10]. Oxidative stress is an imbalance between the cellular generation of reactive oxygen species (ROS) and the capacity of anti-oxidants to prevent oxidative damage, and has been reported to affect placental function in a number of pregnancy complications [10,11,21]. ROS are generated by enzymatic processes in the mitochondrial membrane where a series of oxidations, changes in protein conformation and activity often leads to pro-apoptotic events. ROS are sequestered by anti-oxidant enzymes and optimal function of these anti-oxidants regulates mitochondrial homeostasis. In normal pregnancies placental anti-oxidant enzymes and associated factors increase as gestation progresses to compensate for an increase in the generation of ROS. In placentae from pregnancies complicated by asthma, markers of oxidative stress were increased [10]. However, anti-oxidant enzyme activity mediated by superoxide dismutase and thioredoxin reductase also increased in placentae from pregnancies complicated by asthma as markers of oxidative stress increased. This compensatory activity by anti-oxidant enzymes did not vary between the sexes in healthy or asthmatic pregnancies and suggests some fundamental mechanisms such as the regulation of ROS generation may be essential for the survival of both sexes. This data along with the microarray data suggests that the placenta adapts to the presence of maternal asthma by increasing anti-oxidant activity to counteract the increasing production of ROS protecting the fetus from maternal asthma-induced oxidative stress. This may also counteract the effects of asthma-induced inflammation driving the generation of ROS.

5. Sex differences in placental immune responses to maternal asthma in pregnancy and its regulation by cortisol

Placental immune pathways and inflammatory responses were examined in more detail in pregnancies complicated by asthma. Similar to the global immune gene bias observed in female placentae of pregnancies complicated by asthma [22], baseline placental cytokine mRNA expression including TNF-α, IL-1β, IL-6, IL-5 and IL-8 was increased compared to female controls [23]. Female immune gene expression was negatively correlated with cord blood cortisol concentrations suggesting cortisol may be an important regulator of immune function in the placenta [23].

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