Accepted Manuscript

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PII: S0143-4004(17)30126-1

DOI: 10.1016/j.placenta.2017.01.123

Reference: YPLAC 3564

To appear in: *Placenta*

Received Date: 3 November 2016

Revised Date: 10 January 2017

Accepted Date: 20 January 2017

Please cite this article as: Meakin AS, Saif Z, Jones AR, Avilés PFV, Clifton VL, Review: Placental adaptations to the presence of maternal asthma during pregnancy, *Placenta* (2017), doi: 10.1016/j.placenta.2017.01.123.

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

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Phone 617 3443 7640

Word Count: 3358

Key words: placenta, asthma, fetus, sex, growth

Short Title: Placental adaptations to maternal asthma

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.

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, <2500g) 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 during pregnancy that may contribute to fetal growth and survival and considers the consequences of that adaptation for life long health.

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.

Sex differences in placental adaptations to maternal asthma

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.

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.

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]. Placental cytokine mRNA expression in males was not affected by the presence of maternal asthma or associated with cord blood cortisol [23].

In vitro placental explant studies also highlighted there was a sex difference in immune function between males and females. The timing of the placental response to an immune challenge *in vitro* and the regulation of the inflammatory response by cortisol differed between female and male placentae and in the presence and absence of maternal asthma [9]. Placentae from asthmatic pregnancies were more sensitive to an inflammatory stimulus than control placentae and female placentae from asthmatic pregnancies were more sensitive to glucocorticoid induced cytokine inhibition, when compared to control female placentae and male placentae overall [9]. Taken together, these studies suggest female immune gene pathways and cytokine production in pregnancies complicated by asthma are more sensitive to the suppressive regulation by cortisol while male placental immune function appears to be non-responsive to an inflammatory challenge of asthma or the suppressive effects of cortisol. Interestingly, many of the immune genes that were identified by microarray to be altered in female placentae (Table 1) are also regulated by cortisol including NFκB and CRH. Based on this data we propose that female placentae adapt to the presence of maternal asthma through suppression of their immune pathways via increased cortisol exposure. Increased exposure of the female fetus to cortisol would influence reduced growth via changes in growth factor pathways. In contrast, a reduced sensitivity to cortisol in males may be a mechanism allowing continued growth in an asthmatic environment.

Sex differences in insulin-like growth factor axis (IGF) and its regulation by cortisol

Growth factor pathways were identified by gene network analysis to change in placentae of females of pregnancies complicated by asthma [15]. There are many growth factors produced by the placenta during pregnancy but IGF-1 and IGF-2 are well characterised polypeptides that have mitogenic properties including somatic cell growth and proliferation [14]. Studies have found IGF-1 and -2 are required for placental growth and fetal survival. The bioactivity of IGF-1 and -2 are also dependent on the concentrations of the IGF binding proteins (IGFBP). The IGFBP-1 isoform has been reported to inhibit IGF-1 binding to IGF-1-cell surface receptors, resulting in decreased IGF-1 mediated growth and proliferation [24], whereas IGFBP-3 expression has been shown to be upregulated via testosterone [25, 26] and can potentiate epidermal growth factor (EGF)-induced cell proliferation and survival [27].

In pregnancies complicated by asthma, males had increased expression of IGF-1 and no change in IGFBP concentrations while females had no changes in any component of the IGF axis [28]. Both male and female birthweight centiles were positively correlated with IGF-1 and inversely associated with IGFBP-1. IGFBP-3 was positively correlated with male birthweight centile indicating this may be important in male growth relative to females [28]. This was also supported by the array data indicating IGFBP-3 was downregulated in female placentae of asthmatic pregnancies [15]. The data suggest male growth is retained in the presence of maternal asthma through an increase in the bioactivity of the IGF axis possibly via IGFBP-3 which is regulated by both cortisol and testosterone.

The female IGF axis in pregnancies complicated by asthma was closely associated with cortisol concentrations which were not observed in males. In

particular, female birthweight centile was negatively associated with cortisol while IGFBP-1 was positively related to cortisol [28]. These data suggest reduced female growth in pregnancies complicated by asthma is closely linked to the level of exposure to cortisol which subsequently influences the IGF axis. These differences in growth factors between the sexes may also be relevant to mechanisms associated with angiogenesis.

Sex differences in placental angiogenesis and vascular function in pregnancies complicated by asthma

Angiogenesis, controlled by VEGF and placental growth factor (PlGF) are important placental mechanisms for the establishment of a low resistance vascular network in both early and late gestation. The reported female placental bias in VEGF signalling [18], supported by the microarray data on female placentae of asthmatic pregnancies where there was no change in VEGF [15], may be important for retaining placental vascular structure in pregnancies complicated by asthma and conferring a survival advantage over males.

Stereological studies of placentae of pregnancies complicated by asthma reported reduced fetal capillary volume relative to non-asthmatic control subjects especially in moderate and severe asthmatic pregnancies [29]. The greatest reductions in capillary volume with maternal asthma were observed in male placentae [29]. In addition to structural alterations in placental vasculature of pregnancies complicated by asthma, there were functional differences in vascular responses to dilation and constriction.

Placentae of women with moderate and severe asthma had decreased vascular dilation and constriction responses relative to healthy placentae. Placental vascular responses were further reduced in asthmatic mothers who smoked cigarettes during pregnancy relative to non-smoking asthmatic women [30]. Reduced vascular function in relation to both constriction and dilation may be

indicative of an overall dysfunction in both vascular endothelium and smooth muscle of the placental circulation.

The hypovascularisation of the villous tree and reduced vascular function in placentae of asthmatic pregnancies may not be of major concern unless an acute adverse event such as exacerbation occurs when structurally and functionally the placenta does not have the capacity to cope with a sudden or extended reduction in oxygen and nutrient supply, resulting in fetal demise. The higher incidence of still birth in male fetuses of pregnancies complicated by asthma often occurred in the third trimester [4, 7]. Late gestation, in particular, is a time point of high oxygen and nutrient demand where supply to the fetus is dependent on placental capillary number and optimal vascular function. An acute adverse event combined with a poorly developed placental vascular system may be a major contributor to male demise in pregnancies complicated by asthma. Overall the data collected on placentae from asthmatic pregnancies suggests that males and females cope differently with a stress. This in part is driven by a sex specific difference in glucocorticoid biology.

Sex specific differences in placental glucocorticoid bioactivity

Pregnancy induces increased production of endogenous cortisol, with levels increasing up to four-fold during gestation progression [31]. Several studies have reported that excessive exposure of the fetus to cortisol early in gestation restricts growth [32-35]. The placenta institutes several mechanisms (P-glycoprotein, 11β-hydroxysteroid dehydrogenase type2 (11β-HSD2), and glucocorticoid receptor (GR) isoforms), collectively termed as the placental glucocorticoid barrier, to protect the fetus from increasing concentrations of maternal cortisol [36-38]. However, in pregnancies complicated by asthma the efficacy of the placental glucocorticoid barrier may be impaired.

In the presence of maternal asthma, placental 11β-HSD2 activity (a catalytic enzyme that oxidises cortisol to its innate form, cortisone) was decreased regardless of fetal sex [38, 39]. Reduced 11β-HSD2 activity in male and female placentae of pregnancies complicated by asthma resulted in the respective fetuses being exposed to comparably increased cortisol concentrations [40] and it was speculated for some time that this decrease in 11β-HSD2 function may contribute to adverse perinatal outcomes associated with growth. However only females exhibited lower birthweights from pregnancies complicated by asthma [40]. Males appeared to be unaffected by the anti-proliferative properties of cortisol inferring the male placentae may have induced a state of glucocorticoid resistance to facilitate continued fetal growth in a high glucocorticoid environment.

Current findings suggest the sex specific difference in glucocorticoid sensitivity may be controlled by differences in the expression of placental GR isoforms. Female placentae remain sensitive to glucocorticoids in pregnancies complicated by asthma due to the expression of GRα A, C and D3 isoforms [36, 41], while male placentae expressed the glucocorticoid antagonistic isoform GR-β and a low trans-activational isoform, GRα D1. Indeed, glucocorticoid resistance has been well characterised to be mediated through GR-β expression [42-44], and suggests continued growth of the male fetus may be via the induction of glucocorticoid resistance. The physiological impact of these GR isoforms on downstream signalling remain to be clarified but based on the array data [15] and other studies conducted in this laboratory [9, 23, 28], it is likely that immune and growth factor pathways are centrally regulated by the differential expression of GR translation isoforms and splice variants. Although numerous gene changes in the female placenta of pregnancies complicated by asthma appear to be driven by cortisol, the factors that regulate continued male growth are yet to be defined.

The role of androgens in fetal growth and development

Sex specific placental adaptations that drive continued male growth in a high glucocorticoid environment may be via the male sex hormones, androgens. Androgens including testosterone and dihydrotestosterone (DHT) interact with the androgen receptor (AR) to regulate transcriptional activity of downstream AR target genes attributed to cellular growth, angiogenesis, and proliferation [45, 46]. Previous studies have shown that increased cord blood levels of cortisol were associated with increases in cord blood testosterone. Furthermore males have increased levels of this androgen derivative compared to females [47, 48]. Testosterone is synthesised in the adrenal gland, testes, and ovaries, however studies have reported human syncytiotrophoblast cells are able to synthesise androgens. Escobar *et al*. [49] identified syncytiotrophoblast expresses 17α-hydroxy/17,20-lyase (CYP17), a metabolising enzyme that converts C21 steroids (such as progesterone) to C19 steroids (such as testosterone). These placental derived androgens may have physiological effects including increasing growth in high stress environments such as pregnancies complicated by asthma.

The human placenta reduces testosterone via 5α-reductase activity which leads to DHT, a potent metabolite that exhibits higher binding affinity towards the AR [50]. The human placenta expresses two 5α-reductase isoforms and previous studies identified that 5α-reductase I expression was increased in male placentae at term, with no sex specific difference in preterm placentae [51]. There was no sex specific difference in 5α-reductase II expression in preterm or term placentae. This data suggests 5α-reductase I may increase testosterone bioactivity in male placentae and lead to the activation of AR regulated pathways.

Interestingly, recent findings in cancer biology suggest glucocorticoids and androgens may interact to regulate cellular proliferation and growth via an interaction between AR and GR-β [52, 53]. Inhibition of GR-β *in vitro* resulted in decreased growth and proliferation of AR positive cancer cells [54] and these results suggest that GR-β may affect AR signalling pathways attributed to cellular growth, however the exact interaction between these steroid receptors remains undefined. Drawing parallels between cancer and developmental biology [55] our lab investigated the relationship between AR isoforms and GR-β in male and female placentae from asthmatic and non-asthmatic pregnancies. It was found that the placenta expresses several different AR isoforms, some of which may be regulated by GR-β, thereby optimising cellular conditions for increased or continued male growth (unpublished data), however further studies focussed on identifying and characterising the exact signalling pathways involved in AR and GR-β interactions, within the placenta, are needed.

Taken together, the current findings suggests male placentae have higher bioactive androgen derivatives than females, facilitated by increased 5 α-reductase I expression. The physiological relevance of these findings remain unclear, however recent work from our lab has identified sex specific changes in placental AR expression may modify activity of downstream signalling pathways attributed to growth including IGF axis and angiogenesis via VEGF. The known *in utero* mechanisms underlying pathogenic programming of the fetus include alterations in growth trajectory, organ and tissue development and changes in homeostasis control systems [56]. This review has provided evidence to suggest that maternal asthma during pregnancy contributes to pathogenic programming of the fetus in a sex specific manner [1, 14, 57]. Specifically, there are reported alterations in growth trajectory in the presence of maternal asthma, especially in females and adjustments in glucocorticoid regulated homeostatic control of placental immune and growth pathways for

both sexes. Female adjustments in placental function and growth appear to be essential for survival *in utero* if the supply of oxygen and nutrients are restricted following a secondary event. Male placentae and fetuses also adjust homeostatic cortisol control by inducing a state of glucocorticoid resistance to maintain normal immune function and growth. This modification in males appears appropriate for coping with one adverse event but not a secondary event.

Overall it appears a placenta can cope and adequately adapt to one adverse event in pregnancy but a second hit appears to be the deciding factor on growth, delivery and survival of the fetusAlthough these adjustments promote survival *in utero* they may result in adverse consequences in both early childhood and later life.

Long term implications of the fetal exposure to asthma *in utero*

Several reports have shown that uncontrolled asthma during pregnancy was associated with alterations in childhood neurodevelopment [58], lung function [59, 60] and an increased risk of endocrine and metabolic disorders based on Danish epidemiological analyses.

We have observed altered growth trajectories in children whose mothers had asthma during pregnancy [57]. While children of non–asthmatic mothers did not deviate from their birth growth trajectory, as projected from their birthweight centile, 40% of children of asthmatic mothers had already deviated from this trajectory at 18 months of age, with 78% demonstrating accelerated growth from birth to 18 months. Interestingly there was a sex difference in the children that were 2 standard deviations away from the predicted growth trajectory with 60% of females displaying accelerated growth relative to 40% of males. Human and animal studies have provided evidence that low birthweight followed by rapid postnatal weight gain are associated with adult cardiovascular disease and premature mortality [61]. Most of the weight gain is in the form of adipose

tissue rather than lean tissue with numerous studies reporting deposition predominantly in the abdomen though usually total body fat is increased overall [61]. Adults who were IUGR still had a greater abdominal fat content relative to adults of similar height, weight, age and sex [61]. Increased abdominal fat predisposes individuals to increased risk of hypertension with aging. The presence of abdominal fat increases sympathetic nervous system activity stimulating activation of the kidney renin-angiotensin system and causing peripheral vasoconstriction and hypertension [62]. It is possible that the accelerated growth postpartum of children whose mothers had asthma during pregnancy may predispose them to cardiovascular disease, and endocrine and metabolic disorders. The long term follow up of these children will be important to establish the risk of metabolic disease in later life.

More recent studies suggest there are epigenetic modifications in children whose mothers had asthma [63]. Blood immune cells from a cohort of 12 month old children whose mothers were enrolled in the MAP trial [64] had 67 autosomal genes that were differentially methylated relative to children of non-asthmatic mothers. In particular Aurora Kinase A (AURKA) gene was hypermethylated and correlated with child height and weight [63]. This gene plays a role in mitosis and is known to be hypermethylated in obese individuals [65] which may in part contribute to the accelerated growth pattern observed in children of mothers with asthma [57]. Investigations such as these will be essential in determining the long term impact of maternal asthma on offspring health.

Overall these data indicate that the presence of maternal asthma during pregnancy results in a placental adaptation that ensures continued growth of the fetus and survival as long as asthma does not worsen as pregnancy progresses. Numerous studies have reported that the appropriate management and treatment

of asthma during pregnancy can prevent growth restriction and prevent the development of bronchiolitis in early childhood. It is likely that pre-pregnancy interventions for the management of maternal asthma will be significant in allowing the placenta and fetus to develop in a manner equivalent to a non-asthmatic pregnancy.

Conclusion

It is evident from the body of work reviewed that placental alterations to: gene expression related to the inflammatory and immune pathways; steroid responsivity; growth factor pathways; and placental vasculature structure and function can result in sex specific perinatal outcomes associated with growth and survival from pregnancies complicated by asthma (summarised in Figure 1). Females remain responsive to cortisol throughout pregnancy and it is postulated the continued sensitivity to cortisol may modulate placental immune pathways to potentially protect the female fetus from any secondary event that may include infection. Increased activation of immune pathways can increase oxidative stress which the placenta again controls via increased anti-oxidant enzyme activity. However the activation of pro-inflammatory cytokines may also increase apoptosis to influence reduced female growth. The continued sensitivity to cortisol was associated with an increase in IGFBP-1 which again contributes to reduced female growth but may confer a survival advantage. Although males have increased risk of *in utero* morbidity and mortality, glucocorticoid insensitivity, minimal alterations in placental function and modulated androgen bioactivity may result in unimpaired growth in pregnancies complicated by asthma however the exact molecular mechanisms underlying these sex specific growth and survival differences still remain undefined. Indeed, understanding the complexity of placental adaptations, in the event of maternal asthma, may provide some insight into: the mechanisms that facilitate

414 fetal growth and survival in other inflammatory events of pregnancy such as
415 pre-eclampsia, infection, autoimmune disease and preterm delivery; as well as
416 the developmental origins of chronic diseases.

417 **Acknowledgements**

418 This review was generated as part of the Queensland Perinatal Consortium
419 Inaugural Conference held on July 15th 2016 in Brisbane, Queensland
420 Australia. The conference was supported by an Intra-Faculty Collaborative
421 Workshop grant from the Faculty of Medicine, The University of Queensland.

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604 **Table 1: Sex specific placental genes altered by maternal asthma during**
605 **pregnancy** (adapted from [15, 23, 28])

606

	Female genes altered by maternal asthma	**Expression relative to non-asthmatics**	**Male genes altered by maternal asthma**	**Expression relative to non-asthmatics**
Inflammatory genes	Apoptosis inhibitor 5 (API5)	down	Coagulation Factor 8 (F8)	up
	Complement regulatory protein (CD59)	down	Heat shock protein 70 1A (Hsp70)	up
	Complement Factor B (CFB)	up		
	Chemokine Receptor 1 (CCR1)	down		
	Corticotrophin releasing hormone (CRH)	up		
	Dystroglycan 1 (DAG1)	up		
	Furin (FURIN)	up		
	Keratin 1 (KRT1)	up		
	Major Histocompatability complex class II DR	up		

	beta 1 (HLA_DRB1)			
	Matrix metalloproteinase 11 (MMP-11)	down		
	Mitogen activated protein kinase 10 (MAPK10)	down		
	Nuclear Factor Kappa B (NFKB)	down		
	Plasminogen activator, urokinase receptor (PLAUR)	down		
	Spermidine/spermine N1 aceytransferase 1 (SAT1)	down		
	Syndecan 1 (SDC1)	up		
Cytokines	TNFα, IL-1β, IL-6, IL-8, IL-5	up		
Growth factor genes	Insulin –like growth factor 3 (IGFBP3)	down	No genes	
	Placental Growth Factor (PlGF)	down		
Anti-oxidant Enzymes	Glutathione Peroxidase (GPX)	up		
	Malate Dehydrogenase 2 (MDH2)	down		

607

608 **Figure legend**

609 **Figure 1: Summary of key sex specific placental mechanisms that alter fetal survival and growth.**
610 Maternal asthma results in increasing levels of cortisol, testosterone, and oxidative stress, however
611 the placenta institutes multiple adaptations that can facilitate growth and survival for the developing
612 fetus. Both female (pink boxes, dashed lines) and male (blue boxes, solid lines) placentae are able to
613 adequately regulate oxidative stress via increased activity of anti-oxidant enzymes. The female
614 placenta confers survival for the developing fetus via: modulation of immune function facilitated by
615 increased expression of glucocorticoid receptor (GR)-αA, C, and D3; and reduced placental blood
616 flow but retained angiogenesis via vascular endothelial growth factor (VEGF). In contrast, the male
617 placenta is unable to regulate inflammation due to a state of glucocorticoid receptor (GR)-β induced
618 glucocorticoid resistance, which results in no change in placental immune function and decreased
619 angiogenesis, ultimately resulting in decreased survival in the presence of a second hit. Increased
620 GR-β expression, however, is proposed to increase growth in the developing male fetus via androgen
621 regulated pathways to elicit increased transcription of *IGF-1*, increased expression of IGFBP-3 and
622 transcription factors associated with mTOR signalling. The female placenta, however, limits growth
623 of the developing fetus via increased expression of insulin like growth factor binding protein (IGFBP)-
624 1 and through cortisol's anti-proliferative properties.

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