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REVIEW

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Sexually dimorphic effects of maternal asthma during pregnancy on placental glucocorticoid metabolism and fetal growth

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Abstract Human pregnancy is associated with sexually dimorphic differences in mortality and morbidity of the fetus with the male fetus experiencing the poorest outcome following complications such as pre-eclampsia, pre-term delivery and infection. The physiological mechanisms that confer these differences have not been well characterised in the human. Work conducted on the effect of maternal asthma during pregnancy, combining data collected from the mother, placenta and fetus has found some significant sex-related mechanistic differences associated with fetal growth in both normal pregnancies and pregnancies complicated by asthma. Specifically, sexually dimorphic differences have been found in placental glucocorticoid metabolism in male and female fetuses of normal pregnancies. In response to the presence of maternal asthma, only the female fetus alters placental glucocorticoid metabolism resulting in decreased growth. The male fetus does not alter placental function or growth in response to maternal asthma. As a result of the alterations in glucocorticoid metabolism in the female, downstream changes occur in pathways regulated by glucocorticoids. These data suggest that the female fetus adjusts placental function and reduces growth to compensate for maternal disease. However, the male fetus continues to grow in response to maternal asthma with no changes in placental function. This response by the male fetus may partially contribute to the increased risk of morbidity and mortality in this sex.

Keywords Pregnancy · Maternal asthma · Fetal mortality/morbidity · Sexually dimorphic differences · Glucocorticoid metabolism · Human

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Introduction

In human pregnancy, sexually dimorphic differences have been found with respect to morbidity and mortality, with the male fetus being more at risk of a poor outcome than the female fetus in association with complications such as placental insufficiency, pre-eclampsia, infection, intra-uterine growth restriction and pre-term delivery (Stevenson et al. 2000). A Norwegian study of 1.7 million singleton births has clearly identified that preterm delivery and perinatal mortality are dominated by the male sex (Vatten et al. 2004). The physiological mechanisms that confer differences between male and female fetuses are unknown but their elucidation should improve both pre-natal and neonatal care. From the study of the effect of maternal asthma during pregnancy on human fetal growth, we have identified sex-specific differences in placental function that may partially contribute to the differences in fetal mortality.

Effect of asthma during pregnancy on maternal health and fetal outcome

Asthma is a respiratory disease that occurs in genetically susceptible individuals as a result of altered immune responses to commonly encountered environmental antigens. The mechanisms of asthma involve cytokine production from T-helper-2 (Th-2) effector lymphocytes that in turn orchestrate the inflammatory response. Upon recognition of an allergic antigen, Th-2 cells produce cytokines that regulate IgE synthesis, activate eosinophils and mast cells and upregulate adhesion molecule expression on endothelial and epithelial cells. Eosinophils are granulated cells that are produced in bone marrow and circulate to various tissue sites after maturation. They are a key component of chronic allergic disease and contribute to many of the pathological processes of asthma-producing molecules that stimulate vasomotor activity, bronchoconstriction and the secretion of mucus. They also produce a variety of pro-inflammatory cytokines, such as tumour necrosis factor

alpha (TNFα), interleukin (IL)-1β and IL-6 (Cohn et al. 2004; Ferreira 2004; Wenzel 2003).

The presence of an inflammatory disease that is mediated by Th-2 lymphocyte pathways may be exacerbated by pregnancy. Mammals have adapted a number of mechanisms to protect the fetus, which expresses a number of paternally derived antigens, from the maternal immune system. These include the separation of the maternal and fetal circulations, the masking of paternal antigens on the trophoblast, the endocrinological inhibition of alloreactivity and the production of immunosuppressive factors by both the mother and fetus. In 1993, Wegmann et al. proposed that a shift towards Th-2-mediated immunity, particularly at uterine sites during pregnancy, inhibits Th-1 immune responses and prevents the rejection of the fetus by the maternal immune system. The upregulation of Th-2 immune function may exacerbate maternal allergic diseases such as asthma and rhinitis. Interestingly, not all asthmatic women experience a worsening of their asthma during pregnancy.

The general concept is that 33% of asthmatic women experience an increase in the severity of their asthma during pregnancy; this is based on evidence collected by questionnaire either antenatally or post-partum (Schatz 1999; Lao and Huengsburg 1990; Kurinczuk et al. 1999). At present, no prospective studies have determined the prevalence of worsening asthma during pregnancy by using objective measurements of lung function or inhaled glucocorticoid intake during pregnancy. The sex of the fetus may be one factor contributing to worsening asthma during pregnancy. A number of recent studies have reported that the presence of a female fetus is associated with worsening maternal asthma and increased requirement for inhaled steroid treatment (Dodds et al. 1999; Beecroft et al. 1998; Murphy et al. 2003). Murphy et al. (2003) have reported that circulating monocyte concentrations increase in asthmatic women who avoid the use of inhaled glucocorticoids during pregnancy and are pregnant with a female fetus. These data suggest that fetal sex influences maternal immune function and may contribute to worsening asthma during pregnancy.

Epidemiological studies have indicated that maternal asthma during pregnancy is associated with a number of poor outcomes for the fetus and neonate, including intrauterine growth restriction, preterm birth, stillbirth and neonatal sepsis (Gordon et al. 1970; Schatz et al. 1995; Liu et al. 2001; Dombrowski et al. 2004). The effects of asthma on fetal outcome are related to the asthma severity and the intensity of treatment (Schatz 1999; Schatz et al. 2003; Bracken et al. 2003). Studies of women with well-controlled asthma, which involves the use of inhaled glucocorticoids to inhibit inflammatory mechanisms at a systemic level, seldom demonstrate adverse effects on fetal outcome (Schatz et al. 1995; Bracken et al. 2003). However, the regular use of oral glucocorticoids for the treatment of asthma during pregnancy is known to be associated with an increased incidence of low birthweight babies and preterm births (Bracken et al. 2003; McDonald and Burdon 1996; Fitzsimons et al. 1986; Perlow et al. 1992). Inhaled glucocorticoid treatment has a number of known systemic effects, including adrenal suppression and reduced bone density in non-pregnant adults (Kos-Kudla and Pluskiewicz 1997; Lipworth 1996). We initially proposed that, if inhaled glucocorticoids can alter maternal systemic function, they might also affect the fetus systemically. Research in a number of animal models including the human suggests that fetal exposure to excess maternal glucocorticoid results in intrauterine growth retardation (Wintour et al. 1994; Tangalakis et al. 1994; Lindsay et al. 1996; Jobe et al. 1998; Quinlivan et al. 1998; French et al. 1999). Our research has prospectively examined the effect of maternal asthma during pregnancy in the presence and absence of inhaled glucocorticoid treatment on placental function and fetal development (Murphy et al. 2002, 2003; Clifton and Murphy 2004). We have found that inhaled glucocorticoid use for the treatment of asthma is not associated with alterations in fetal growth and that maternal asthma without treatment has the most significant effect upon placental function and fetal growth (Murphy et al. 2002, 2003).

Placental 11β-hydroxysteroid dehydrogenase type 2 and fetal growth

Fetal exposure to maternal glucocorticoids is known to be regulated by the placenta. Baseline maternal cortisol is positively correlated with fetal cortisol at mid-gestation in human pregnancy (Gitau et al. 2001) suggesting that changes in maternal hypothalamic–pituitary–adrenal (HPA) function affect fetal HPA function as measured by circulating fetal cortisol concentrations. One mechanism that is central to controlling fetal exposure to maternal glucocorticoids is the placental 11β-hydroxysteroid dehydrogenase enzyme (11β-HSD; Benediktsson et al. 1997). This enzyme has two isoforms; the type 2 isoform (11β-HSD 2) converts active cortisol to inactive cortisone and the type 1 isoform (11β-HSD 1) interconverts cortisol and cortisone in either direction. Physiologically, the type 2 isoform protects the mineralocoroticoid receptor (MR) from cortisol allowing it to be available for aldosterone (Hirasawa et al. 2000; Odermatt et al. 2001), whereas the type 1 isoform promotes cortisol availability to the glucocorticoid receptor (GR; Seckl and Walker 2001). Under normal conditions, the human fetus is protected from 85% of maternal glucocorticoids through the action of placental 11β-HSD 2 (Benediktsson et al. 1997). Furthermore, 11β-HSD 2 has been localised to many sites within the human fetus, such as bone, adipose tissue and pituitary (Condon et al. 1998), possibly to protect the fetus from the anti-proliferative effects of glucocorticoids (Rabbitt et al. 2003). Placental 11β-HSD 2 activity and birth weight are positively correlated (Kajantie et al. 2003) suggesting that the activity of this enzyme is important in normal fetal growth.

Alterations in placental 11β-HSD 2 expression and activity are known to be associated with reduced fetal growth. Significant reductions in 11β-HSD 2 mRNA and activity have previously been observed in placentae of

human pregnancies complicated by intrauterine growth restriction (Shams et al. 1998) or pre-eclampsia (Heilmann et al. 2001; Schoof et al. 2001; McTernan et al. 2001). In a number of animal models, inhibition of 11β-HSD 2 activity with carbenoxolone or infusion of synthetic steroids that are not metabolised by 11β-HSD 2, such as betamethasone or dexamethasone, results in decreased fetal growth (Lindsay et al. 1996; Jobe et al. 1998; Smith and Waddell 2000; Sloboda et al. 2000).

Several interesting results have been obtained by studying the effect of maternal asthma on placental 11β-HSD 2 activity during pregnancy. First, the data have revealed sex-specific differences in placental glucocorticoid metabolism in the human fetus. In normal non-asthmatic pregnancies, placental 11β-HSD 2 activity is significantly higher in female than male fetuses (Murphy et al. 2003). This suggests that, in the placenta, intracellular cortisol concentrations are lower in the female than the male during normal pregnancy, with possible implications in terms of the sensitivity or the response to glucocorticoids between males and females.

When examining placentae collected from women with asthma, a sex-specific effect of asthma and its treatment was noted on placental 11β-HSD 2 activity. Asthmatic women who did not use inhaled glucocorticoids during pregnancy for the treatment of their asthma and were pregnant with a female had significantly decreased placental 11β-HSD 2 activity when compared with non-asthmatic controls (Murphy et al. 2003). Conversely, asthmatic women who did use inhaled glucocorticoids during pregnancy and were pregnant with a female had significantly increased placental 11β-HSD 2 activity (Murphy et al. 2003). No changes were observed in placental 11β-HSD 2 activity in asthmatic women pregnant with a male fetus, regardless of the presence or absence of treatment, when they were compared with non-asthmatic control subjects carrying a male fetus. The difference in activity could not be accounted for by a change in placental 11β-HSD 2 mRNA or protein in any of the groups suggesting that placental 11β-HSD 2 activity is regulated in a sex-specific manner at a post-translational level. These data indicate that the placenta of a female fetus adjusts its capacity to metabolise glucocorticoids in response to a change in the maternal environment. On the other hand, the placenta of the male fetus does not change its 11β-HSD 2 activity in response to asthma or its treatment. Similar sex-specific changes have been found in the rat in which maternal exposure to alcohol in late gestation is associated with a decrease of placental 11β-HSD 2 mRNA in only the female fetus (Wilcoxon et al. 2003). These changes in placental 11β-HSD 2 are associated with significant sex-specific changes in birthweight (Murphy et al. 2003; Wilcoxon et al. 2003).

Glucocorticoid effects on fetal growth

Changes in fetal growth velocity may be mediated by exposure to endogenous or exogenous glucocorticoids and the anti-mitogenic effects of these steroids. Fowden et al. (1996) have described that the cortisol surge towards late gestation in fetal sheep is coincident with the slowing down of growth, reflected by a decrease in the increment crown–rump length. Multiple doses of betamethasone, a steroid that is not metabolised by the placenta, administered to women at risk of preterm delivery, has been shown to result in a 9% reduction in neonatal birth weight and 4% reduction in neonatal head circumference (French et al. 1999). In pregnancies complicated by maternal asthma, a slight increase in cortisol concentrations in circulating cord blood was associated with a 12% reduction in female birth weight; this equated to an approximately 500 g mean difference in size compared with female neonates from non-asthmatic mothers (Murphy et al. 2003). Conversely, the growth of the male fetus was unchanged by maternal asthma, even though cortisol concentrations in cord blood were the same as levels found in growth-reduced female fetuses of asthmatic women (Murphy et al. 2003). No effect of maternal inhaled glucocorticoid use for the treatment of asthma during pregnancy was seen on male fetal growth or neonatal birthweight. These data indicate that increased circulating concentrations of bioactive cortisol contribute to reduced growth in a sex-specific manner.

Maternally derived glucocorticoids appear to exert the most significant effect on fetal growth. Wilcoxon et al. (2003) reported that increased maternal corticosterone in pregnant rats treated with alcohol resulted in growth restriction of female pups only and that this effect was reversed in the presence of maternal adrenalectomy. Jobe et al. (2003) has described the effect of maternal or fetal betamethasone or cortisol administration on the growth and lung maturation of the sheep fetus. Maternal administration of cortisol had no effect on fetal birthweight or lung function, although betamethasone administration was associated with a 16% reduction in fetal birthweight and induced lung maturation (Jobe et al. 2003). When cortisol or betamethasone was administered directly to the fetus, no change occurred in birthweight but lung maturation was observed (Jobe et al. 2003). These data indicate that glucocorticoids derived from the maternal compartment have indirect effects on fetal growth by altering placental function.

The data from the study of pregnancies complicated by asthma suggest that alterations in placental 11β-HSD 2 result in an increase of fetal glucocorticoid exposure; these alterations may represent one of the placental factors that are affected by changes within the maternal environment that influences human fetal growth and development. However, factors initiating a sex-specific decrease in placental 11β-HSD 2 activity in association with maternal asthma have yet to be identified. Based on the evidence that we have collected, we speculate that a maternal systemic inflammatory factor induced by asthma, which can be inhibited by inhaled glucocorticoid use, may alter placental 11β-HSD 2 activity. Previous work on human 11β-HSD in vitro indicates that cytokines and prostaglandins down-regulate 11β-HSD gene expression (Alfaidy et al. 2001; Cooper et al. 2001; Evagelatou et al. 1997) thereby increasing intracellular cortisol concentrations and mod-

ulating the inflammatory response. One question arising from these data is whether the changes observed in placental 11β-HSD 2 activity in female placentae result in an alteration of intracellular cortisol concentrations. Because of the impossiblility of accurately measuring the levels of intracellular cortisol, we have examined placental pathways known to be regulated by glucocorticoids, such as the placental T-helper-1 (Th-1) and Th-2 cytokines, placental GR mRNA and markers of fetal HPA function, to determine whether a sex-specific difference exists in these pathways in both normal pregnancies and pregnancies complicated by asthma.

HPA function

The HPA axis plays a central role in the regulation of glucocorticoid release and the response to stress. Hypothalamic corticotrophin-releasing hormone stimulates the release of adrenocorticotropin (ACTH) from the pituitary; the ACTH subsequently activates cortisol release from the adrenal. Cortisol then negatively feeds back upon the hypothalamus and hippocampus to modulate the HPA response (Harbuz et al. 1990). Experimental animal models have revealed differences in HPA function in relation to sex. Basal and stressed-induced activation of the HPA axis are associated with a greater ACTH and corticosterone response in female rats relative to male rats (Le Mevel et al. 1978). Prenatal stress is associated with alterations in HPA function with greater effects on the female relative to the male (McCormick et al. 1995; Weinstock et al. 1992). In human adults, sex hormone differences are central to differences in HPA function and responses to stress (Kirschbaum et al. 1999). These data indicate the probability of differences in human fetal HPA function based on sex but the evidence supporting this concept is presently deficient.

In the human fetus, significant alterations occur in HPA function in pregnancies complicated by maternal undernutrition (Warnes et al. 1998), maternal alcohol consumption (Wilcoxon et al. 2003), maternal infection (Gravett et al. 2000), fetal asphyixia (Procianoy et al. 1988), intra-uterine growth restriction (Goland et al. 1993) and pre-eclampsia (Procianoy and Cecin 1986). These changes in HPA function are predominantly defined by an increase in cord blood cortisol and a decrease in cord blood dihydroepiandrosterone sulphate (DHEAS).

Maternal administration of synthetic glucocorticoids during pregnancy has been documented to have an effect on fetal HPA function in both animals and humans (Sloboda et al. 2000; Parker et al. 1996). Parker et al. (1996) reported that both human cord blood cortisol and DHEAS concentrations were significantly reduced in women administered betamethasone and remained low in their offspring for 4 days after delivery relative to control infants (Parker et al. 1996). Oestriol, a derivative of fetal adrenal DHEAS (Siiteri and MacDonald 1966) can be measured in the maternal and fetal circulation during pregnancy as an indicator of fetal HPA function (Troisi et al. 2003b). Troisi et al. (2003a, 2003b) have demonstrated that maternal oestriol concentrations are positively correlated with fetal DHEAS concentrations. Maternal oestriol concentrations are negatively associated with maternal cortisol concentrations. Maternal oestriol levels vary diurnally with maternal cortisol during gestation (Patrick et al. 1979). Oestriol concentrations are suppressed by maternal dexamethasone administration (Egerman et al. 1998) and by the maternal stress response to labour during which endogenous cortisol levels are increased (Maltau et al. 1979). These findings indicate that maternal and fetal HPA are closely linked and that maternal oestriol can be used as an indirect measure of fetal HPA function.

The presence of sex-specific differences with respect to human fetal HPA function in normal or complicated pregnancies is controversial possibly because sex differences have not been consistently factored into the experimental design, unless testosterone was one of the measurable parameters (Troisi et al. 2003a; Haning et al. 1989; Edwards and McMillen 2002). Most papers report that cord blood cortisol, oestriol and DHEAS are not significantly different between male and female fetuses (Haning et al. 1989; Simmons et al. 1994; Hercz et al. 1989; Furuhashi et al. 1982; Bremme and Eneroth 1983; Bremme et al. 1990; McDowell et al. 1988; Lagerstrom et al. 1990; Bazzett et al. 1998; Ficicioglu and Kutlu 2003) with only one article indicating that cord blood oestriol was higher in females than males (Troisi et al. 2003b). Direct measurements of cord blood concentrations may not provide informative details of whether there are sex-specific differences in fetal HPA function and more information may be obtained by relating HPA function to outcome. For example, when maternal oestriol was examined in relation to birthweight, head circumference and length, a positive correlation was noted with oestriol (Troisi et al. 2003b). When maternal and fetal oestriol were examined in relation to fetal sex and birthweight, oestriol was inversely associated with birthweight in male fetuses (Troisi et al. 2003a; Simmons et al. 1994). These data suggest that differences in human male and female fetal HPA function are associated with alterations in growth but this area of research lacks definitive evidence.

A study conducted on pregnancies complicated by asthma has shown sex-specific differences in cord blood oestriol levels at delivery of male and female fetuses; in normal pregnancies, no significant differences were detected in the level of cord blood cortisol between male and female fetuses, with oestriol concentrations only being slightly higher in females than in males (Murphy et al. 2003). One weakness of this study was that the control numbers were small, a feature that might have contributed to the non-significant differences. In asthmatic mothers who did not treat their asthma with inhaled steroids, placental 11β HSD 2 activity was the same in male and female fetuses, with equivalent concentrations of cord blood cortisol in both sexes (Murphy et al. 2003). However, oestriol was significantly reduced only in the female fetuses of asthmatic mothers and this was associated with reduced growth (Murphy et al. 2003). These data suggest that, even

though the male and female fetuses from this group are exposed to similar concentrations of cortisol, the female fetus is more sensitive to any change in concentration as reflected by a change in HPA function. Further investigations with larger sample sizes should be conducted to clarify differences in human fetal HPA function based on sex. This information will assist with the determination of the way that male and female fetuses cope with prenatal stress and may provide clues as to why the risk of perinatal mortality is greater in males.

Sex-specific differences of fetal immunity

The activation of the immune system is associated with the activation of the HPA axis resulting in glucocorticoid production for the modulation of the inflammatory response (Bornstein and Rutkowski 2002). Sex differences in immune function have previously been observed in neonatal animal models and adult humans (Hodgson et al. 2001; McCormick et al. 2002; Schuurs and Verheul 1990; Hodgson and Knott 2002). Shanks et al. (1994) have reported that 1-day-old female rat pups have a more enhanced immune and HPA response to endotoxin challenge than age-matched male pups. Further investigations have suggested that the enhanced immune and HPA response is mediated via the sex-steroid regulation of corticosterone-binding globulin (CBG) concentrations and the bioavailabilty of corticosterone. Female pups have higher circulating concentrations of CBG resulting in decreased corticosterone negative feedback upon immune and HPA function relative to male pups (McCormick et al. 2002; Shanks et al. 1994). In the human placenta, cortisol bioavailability is probably controlled by 11β-HSD 2 activity (Patel et al. 1999) and possibly CBG (Dancis et al. 1978; Misao et al. 1999; Benassayag et al. 2001). However, no sex-specific differences are known in placental CBG. Sexually dimorphic differences in 11β-HSD 2 activity have been identified in the human placenta (Murphy et al. 2003) and this enzyme may be the central regulator of cortisol bioavailablity that confers differences in fetal-placental immune function.

The fetal-placental immune system has been recognised to play a significant role in the implantation, growth and delivery of the fetus (Wegmann et al. 1993; Wegmann and Guilbert 1992; Hunt 1989). The placental immune system is partially regulated by glucocorticoids via the transcriptional regulation of cytokine production (Rosen et al. 1998; Lappas et al. 2002). Placental basal cytokine mRNA expression, which includes TNFα, IL-1β and IL-10, has been measured in placentae of male and female fetuses of normal pregnancies. All of these cytokines are more strongly expressed in females than males in normal pregnancies (Clifton and Murphy 2004) suggesting that, at an intracellular level, the placenta of the female fetus is exposed to less cortisol than that of a male fetus during normal pregnancy.

In the presence of maternal asthma, no inhaled glucocorticoid use and a female fetus, placental basal cytokine mRNA expression is reduced and an increase in the ratio of Th-2:Th-1 cytokines has been measured that is negatively correlated to placental 11β-HSD 2 activity (Clifton and Murphy 2004). These data indicate that, in the presence of a maternal inflammatory environment, the female fetus responds by activating anti-inflammatory pathways in the placenta thereby increasing exposure to cortisol and pushing placental cytokine expression towards an anti-inflammatory Th-2 phenotype. No such changes have been observed in the same group of women pregnant with a male fetus; both the basal cytokine expression and the ratio of Th-2:Th-1 cytokines in placentae of male fetuses of asthmatic mothers who did not use inhaled steroids were comparable with placentae of male fetuses of non-asthmatic women. Women using inhaled steroids during pregnancy for the treatment of their asthma and pregnant with either a male or female fetus exhibited no changes in placental cytokine mRNA levels or Th-2:Th-1 ratios when compared with placentae of non-asthmatic control subjects. These data indicate that a change in placental 11β-HSD 2 activity alters immune pathways regulated by glucocorticoids (Clifton and Murphy 2004). Furthermore, we have reported that both male and female fetuses of asthmatic mothers are exposed to equivalent concentrations of glucocorticoid but that a change in immune pathways is only observed in the female fetus suggesting a sex-specific difference in glucocorticoid sensitivity.

Previous work examining lung maturation has identified a significant difference in sensitivity to glucocorticoid administration between male and female fetuses. Clinical data have demonstrated that human female fetuses have a greater response to glucocorticoid treatment for lung maturation than male fetuses at risk of preterm delivery (Papageorgiou et al. 1981). Kovar et al. (2001) report that prenatal glucocorticoid therapy is less effective in promoting improved lung function in male fetal sheep than in females and propose that androgens competitively inhibit glucocorticoid binding to the GR in male fetuses. In the fetal rat lung, maternal administration of glucocorticoids increases fetal lung GR expression and maternal administration of testosterone inhibits fetal lung GR expression in both male and female fetuses (Sweezey et al. 1998). In vitro studies of fetal lung fibroblasts indicate that androgens oppose the effects of glucocorticoids on triglyceride uptake (Rodriquez et al. 2001). These data indicate that differences between male and female fetuses in the response to glucocorticoids may be related to the regulation of GR by sex steroids.

Fetal GRs and MRs

Central to the regulation of cortisol activity is the presence of low and high affinity MRs and GRs, respectively. These receptors mediate the effects of cortisol both centrally and peripherally. Sexually dimorphic changes in GR and MR expression in the brain and central nervous system in the presence of increased pre-natal glucocorticoid have previously been reported in a number of animal models (Banjanin

et al. 2004; Lingas et al. 1999; Halasz et al. 1997). Maternal administration of glucocorticoid during late gestation in the guinea-pig results in an increase in GR and MR mRNA of the central nervous system in only male offspring, as shown by Banjanin et al. (2004). Other studies by this group have indicated that short-term maternal nutrient restriction during guinea-pig pregnancy is associated with an increase in circulating cortisol in both male and female fetuses but that only the female fetus has decreased hypothalamic and hippocampal GR mRNA and no change in MR mRNA (Lingas et al. 1999). Maternal adrenalectomy during pregnancy in the rat results in a sex-specific response in the neonates with the female offspring having increased hypothalamic GR mRNA at birth and the male neonates having decreased GR mRNA (Halasz et al. 1997).

GR and MR protein amount, affinity and binding are also altered in relation to sex. In neonatal rats exposed to alcohol in utero, greater receptor concentrations and a lower affinity of GR have been measured in the hippocampus of female rats when compared with males (Weinberg and Petersen 1991). Conversely, in the sheep fetus following exposure to maternal betamethasone, no sex-specific differences have been detected in lung GR affinity or amount between male and female fetuses (Kovar et al. 2001). Administration of betamethasone to the guinea-pig during gestation results in decreased hippocampal MR protein in the male fetus and has no effect on GR protein in males or females (Owen and Matthews 2003). These studies highlight the presence of sex-specific differences in GR and MR regulation and expression but their relevance to the human fetus has yet to be defined.

Human placental GRα and MR mRNA expression were measured in male and female fetuses of normal and asthmatic pregnancies (Clifton and Murphy 2004). In normal pregnancies, female placental GR and MR mRNA expression were significantly greater than that that observed in males (Clifton and Murphy 2004). In the presence of maternal asthma and no treatment, female placental GRα and MR mRNA expression were significantly reduced (Clifton and Murphy 2004). Interestingly, placental GRα and MR mRNA expression was significantly increased in the male fetus under the same conditions (Clifton and Murphy 2004). These data suggest there are sex-specific differences in GR expression and regulation in the placenta of both normal pregnancies and pregnancies complicated by asthma.

The differences in GR and MR regulation in the placentae of male and female fetuses may be attributable to differences in the promoter regions of these receptors. Breslin and Vedeckis (1998) have reported multiple promoters in the human GR gene, with exon 1A being alternatively spliced into multiple transcripts. One particular transcript known as 1A3 is expressed in leukaemic cell lines and, when present, can up regulate GR expression in response to glucocorticoids (Breslin and Vedeckis 1998). The various splice variants of the GR promoter region have not been examined in the human placenta but may explain the sexually dimorphic difference in receptor expression in response to glucocorticoid.

Implications of a sex-specific difference in glucocorticoid pathways

The recent literature concerning fetal physiology indicates that increased exposure of the fetus to maternally derived glucocorticoids at particular time points during gestation has significant effects upon fetal growth and organ maturation thereby influencing neonatal development and adult health (Seckl 2004). The organ mediating the physiological changes between mother and fetus is the placenta, which appears to act in a sex-specific manner in the human. Under normal physiological conditions of pregnancy, the female fetal–placental unit may be exposed to less bioactive cortisol because of increased placental 11β-HSD 2 activity. Decreased intracellular concentrations of cortisol affect the placental immune function and increase sensitivity to glucocorticoids, possibly because of increased GR and MR expression in the female. The enhanced immune response in the female fetus may be protective against bacterial infection and promote lung maturation under conditions of intrauterine infection (Moss et al. 2002). These adaptations may explain why the female neonate has a higher survival rate following pregnancies complicated by chorioamnionitis (Stevenson et al. 2000).

In the presence of a maternal stress such as asthma, the female fetus responds by increasing exposure to glucocorticoid and reducing growth. The male fetus continues to grow in the presence of maternal asthma and appears insensitive to glucocorticoids as demonstrated by increased placental GR mRNA but no identifiable changes in placental pathways regulated by glucocorticoids. This has been supported by the finding that male and female cord blood cortisol concentrations are the same in the maternal asthma group but only the female fetus has altered HPA function and growth. These data lead us to speculate that, from an evolutionary perspective, it may be important for male survival ex utero to be as large as possible and therefore, to achieve that goal, the male fetus continues to grow under conditions of maternal stress by exhibiting a degree of glucocorticoid insensitivity. Conversely, the size of a female is not as important for ex utero life and therefore the female adjusts the intrauterine environment to compensate for maternal stress and promote her chance of survival. Interestingly, a North American study of fetal sex and pre-term birth reports that pre-term female fetuses are more likely to be growth-restricted than pre-term male fetuses (McGregor et al. 1992). More research needs to be conducted in this area, although these studies emphasise that the sex of the human fetus or neonate needs to be considered as part of the physiological interpretation of research data and might be a consideration in clinical care.

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