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Maternal prenatal anxiety and downregulation of placental 11β-HSD2

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Summary
Background: Raised maternal anxiety during pregnancy is associated with increased risk of adverse neurodevelopmental outcomes for her child. The mechanisms underlying this are not known but animal studies suggest prenatal stress may alter the function of the placenta. Here we determined whether maternal prenatal anxiety was associated with a downregulation of placental 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), the enzyme which metabolises cortisol.
Methods: We recruited mothers the day before delivery by elective caesarean, and gave them the Spielberger Trait and State anxiety and Edinburgh Depression self-rating scales. Placentae were collected and aliquots stored for later analysis.
Results: Prenatal Trait anxiety was negatively correlated with placental 11β-HSD2 mRNA expression ($r = -0.40$, $p < 0.01$, $n = 56$). Results were similar with male and female fetuses ($r = -0.39$, $p = 0.04$, $n = 28$; $r = -0.40$, $p = 0.03$, $n = 28$) respectively. Results were also significant with State anxiety ($r = -0.27$, $p = 0.05$, $n = 56$) but somewhat weaker for depression ($r = -0.20$, $p = 0.13$, $n = 56$). Preliminary analyses on a subset of cases ($n = 25$) suggested parallel results for enzyme activity.
Conclusions: These findings provide evidence for an association between prenatal maternal mood and downregulation of placental 11β-HSD2. Results are consistent with raised maternal anxiety being associated with increased fetal exposure to maternal cortisol, and support the hypothesis that this may be one mechanism underlying fetal programming by prenatal stress.

1. Introduction

The developmental origins hypothesis proposes that fetal programming can permanently affect the phenotype of the fetus resulting in an altered risk of disease in adult life

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(Gluckman et al., 2005). The mother's emotional state during pregnancy may be one factor which can predispose the child to a range of psychiatric, behavioural and cognitive problems in later life.

It is now well established in animal models (see Weinstock, 2001, 2005), and increasingly in humans, that stress experienced by the mother during pregnancy is associated with increased risk for many adverse long-term effects on the child (Talge et al., 2007; O'Donnell et al., 2009; Glover, 2011). These can include an increased risk of anxiety (Phillips et al., 2005), ADHD (Motlagh et al., 2010), conduct problems (Barker and Maughan, 2009), and cognitive deficits (Bergman et al., 2010; Davis and Sandman, 2010). A wide range of stressors have been found in different studies to be associated with altered child outcome, ranging from daily hassles (Huizink et al., 2003), symptoms of anxiety (O'Connor et al., 2003, 2005) or depression (Davis et al., 2007), life events (Bergman et al., 2007, 2010) and natural disasters (King and Laplante, 2005; King et al., 2009).

In animal models it has been established by cross-fostering in rodents, or nursery rearing in monkeys, that prenatal stress effects can be independent of later mothering (Schneider et al., 2002; Del Cerro et al., 2010). It has also been shown that these effects are at least partly mediated by increased exposure to glucocorticoids (Seckl and Holmes, 2007). Little is understood about the mechanisms which may underlie fetal programming by prenatal stress in humans. One possible mediating factor is increased exposure of the fetus to cortisol. The potential for cortisol to alter neurodevelopment is demonstrated by a microanalysis of fetal brain explants. Cortisol treatment affected the expression of over a thousand genes, most notably those involved in cell growth and metabolism (Salaria et al., 2006).

Elevated fetal exposure to glucocorticoids could occur through increases in maternal cortisol associated with anxiety and during periods of stress, which then crosses the placenta into the fetal environment (Mairesse et al., 2007). Administration of adrenocorticotropic hormone (ACTH) to pregnant rhesus monkeys resulted in increased maternal cortisol production and adverse neurodevelopmental outcomes in the offspring, similar to those seen in response to prenatal stress (Schneider et al., 1992). The effects of prenatal stress in rats have been shown to be prevented by adrenalectomy and reinstated by corticosterone administration (Barbazanges et al., 1996). However, the human hypothalamic pituitary adrenal (HPA) axis functions differently in pregnancy from most animal models, because of the placental production of corticotrophin releasing hormone (CRH), which in turn causes an increase in maternal cortisol (Petraglia et al., 1987). The maternal HPA axis becomes gradually less responsive to stress as pregnancy progresses (Kammerer et al., 2002), and there is only a weak, if any, association between maternal mood and her cortisol level, especially later in pregnancy (Obel et al., 2005; Sarkar et al., 2006). Instead, changes in maternal mood during pregnancy could affect other systems, independently of increases in maternal cortisol.

Another mechanism which could increase fetal cortisol exposure is by prenatal anxiety or stress impairing the function of 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), the barrier enzyme which converts cortisol to the inactive cortisone (Brown et al., 1993; O'Donnell et al., 2009). Within the placenta, 11β-HSD2 is primarily expressed in the syncytiotrophoblast (Sun et al., 1997) where it acts to prevent the majority of maternal cortisol from crossing the placenta, resulting in circulating cortisol concentrations in the fetus being approximately 13-fold lower than those in the mother (Gitau et al., 1998). If there is less of this barrier enzyme then the fetus will be exposed to more maternal cortisol, independently of any change in the maternal cortisol level. Clinical studies of intrauterine growth restriction and preterm birth, reporting reduced placental 11β-HSD2 gene expression, highlight the clinical relevance of cortisol metabolism in pregnancy (McTernan et al., 2001; Schoof et al., 2001; Causevic and Mohaupt, 2007; Wächter et al., 2009).

There is some evidence in rat models that prenatal stress can inhibit placental 11β-HSD2. Restraint stress of pregnant rats in the last week of pregnancy is associated with decreased placental 11β-HSD2 expression and enzyme activity (Mairesse et al., 2007), although Welberg et al. (2005) found more complex effects. There is also evidence that reduced 11β-HSD2 causes an alteration in the behaviour of the offspring. Administration of the 11β-HSD2 inhibitor carbenoxolone, a synthetic derivative of glycyrrhizinic acid, in rodent models resulted in an increase in anxiety (Welberg et al., 2000), mirroring the phenotype of offspring exposed prenatal stress. Also, 11β-HSD2 knockout mice, generated from heterozygote breeding, show increased anxiety-like behaviour as adults (Holmes et al., 2006). Thus, animal studies suggest that at least some of the effects of prenatal stress may be mediated through decreased placental 11β-HSD2 activity.

Indirect evidence in humans also suggests that maternal anxiety may be associated with a decreased function of this enzyme. Glover et al. (2009) reported that the correlation between maternal and amniotic fluid cortisol levels was greater in women with elevated anxiety compared to less anxious women (Glover et al., 2009). This suggests that prenatal anxiety in humans can increase the placental permeability to cortisol. A potentially significant feature of this model is that it might provide an account of how prenatal anxiety or stress might lead to increased fetal exposure to glucocorticoids, even in the absence of elevated maternal prenatal cortisol. Further indirect support for this hypothesis was provided by Räikkönen et al. (2009, 2010) who found impaired cognitive and behavioural development as well as raised saliva cortisol in the children of women who consumed high levels of liquorice during pregnancy. Liquorice contains glycyrrhizin an inhibitor of 11β-HSD2.

In this study we have investigated the association between maternal prenatal anxiety and human placental 11β-HSD2 in women who had an elective caesarean. Our hypothesis was that the more anxious women would have a lower gene expression of placental 11β-HSD2.

2. Materials and methods

2.1. Participants

Study participants were recruited one day prior to elective caesarean section at Queen Charlottes and Chelsea Hospital, London, UK. Women scheduled for singleton deliveries, with