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Influence of prenatal maternal stress, maternal plasma cortisol and cortisol in the amniotic fluid on birth outcomes and child temperament at 3 months

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Summary This prospective, longitudinal study aimed to investigate relationships between indicators of maternal prenatal stress, infant birth outcomes and early temperament. We examined the pattern of associations and postulated pathways between physiological (cortisol plasma concentrations) and self-report indices (stress, anxiety) of maternal prenatal stress, cortisol in the amniotic fluid, birth outcomes and infant temperament at 3 months. The sample consisted of 158 women undergoing amniocentesis in the 2nd trimester of pregnancy. Questionnaire measures of maternal stress and anxiety were found to be unrelated to cortisol in plasma or amniotic fluid. Maternal cortisol was related to amniotic cortisol, which in turn was associated with lower birth weight. Birth weight predicted infant fear and distress to limitation at 3 months old. We found trend-like indirect effects of amniotic fluid on infant distress to limitation and fear via birth weight. This is one of the few studies to simultaneously assess the role of maternal and amniotic fluid cortisol on birth outcomes and infant emotional development. The results suggest that foetal cortisol may be an important predictor of infant outcomes and shed light on the mechanisms through which prenatal maternal stress affects infant psychological health.

1. Introduction

An increasing amount of research suggests that the prenatal environment can have a profound effect on child outcomes. Animal studies provide good evidence that prenatal stress can have long-lasting effects on the offspring (e.g. Weinstock, 1997; 2005). There is accumulating evidence that in

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humans, prenatal stress and anxiety can influence infant birth outcomes and the development of temperament and cognition (e.g. Huizink et al., 2004; Talge et al., 2007).

Various studies report a link between prenatal stress and child outcomes, with higher levels of stress having a negative impact on temperament, cognitive and motor development of the child. For example, prenatal stress and feelings of general anxiety have been linked to lower birth weight (Lobel et al., 1992; Wadhwa et al., 1993), difficult temperament and behavioural problems (Huizink et al., 2002; Buitelaar et al., 2003; O'Connor et al., 2003; Gutteling et al., 2005; Rothenberger et al., 2011). It has also been proposed that pregnancy-related anxiety specifically may be more closely linked to child outcomes than general feelings of anxiety (Huizink et al., 2004). Indeed, Buitelaar et al. (2003) found pregnancy-related anxiety (fear of having a handicapped child and fear of giving birth) to be uniquely associated with various infant temperament outcomes at age 8 months. More recently, Blair et al. (2011) found pregnancy-specific anxiety between 13 and 17 weeks of gestation to be a unique predictor of negative child temperament at 2 years.

However, the mechanisms through which prenatal maternal stress and anxiety influence subsequent child outcomes are not fully understood, with few studies investigating the possible mediating factors that might be important in linking prenatal stress and child postnatal outcome. Some of the effects of prenatal stress on child emotional development may be due to genetic inheritance. Rice et al. (2010) disentangled the influence of genetic factors and prenatal environment by examining the influence of prenatal stress in women pregnant with a genetically related child and women pregnant with a genetically unrelated child (either through egg or embryo donation through in vitro fertilization). The association between prenatal stress and child outcome (i.e., gestational age, anxiety and antisocial behaviour) was confirmed in both genetically related and unrelated mother—child pairs. This study provides evidence that maternal stress does not influence the child only through genetic factors, but also through other factors, one of which could be maternal stress hormonal activity.

The hypothalamic-pituitary-adrenal (HPA) axis is one of the major systems involved in stress response and its regulation. The HPA system is activated during stress and threat (Weinstock, 2005), and studies have looked at the concentrations of its end product, cortisol, as an endocrinological marker of stress and anxiety (Weinstock, 2008). It has been suggested that the activation of the HPA axis is one of the main biological mechanisms underlying the effects of prenatal stress (Huizink et al., 2004; Talge et al., 2007). Various studies have included measures of maternal cortisol concentrations during pregnancy in addition to, or instead of, psychosocial assessments of stress and anxiety (e.g. Buitelaar et al., 2003; Bergman et al., 2010a,b; Davis and Sandman, 2010; Rothenberger et al., 2011).

The mechanisms through which maternal HPA axis activity can influence foetal development in humans are not yet fully understood (Talge et al., 2007). A study by Radke et al. (2011) showed that prenatal stress linked to domestic violence in pregnancy was associated with glucocorticoid receptor (GR) gene methylation in children in their early teens. Increased GR methylation is associated with stronger cortisol responses to stress. These results suggest that prenatal stress can adversely influence gene expression in the HPA-axis.

It has also been proposed that maternal cortisol can pass through the placenta and affect foetal cortisol concentration and HPA axis development. The activity of placental enzyme 11 β-hydroxysteroid-dehydrogenase type 2 protects the foetus from maternal cortisol (e.g. Benediktsson and Seckl, 1998) by converting it into inactive cortisone. However, evidence from animal studies suggests that prenatal stress can affect the function of the placenta and the expression of 11 β-hydroxysteroid-dehydrogenase enzyme (Welberg et al., 2005). Furthermore, Gitau et al. (1998) compared maternal and foetal cortisol concentrations in women undergoing clinically-indicated foetal testing, and found them to be linearly related (r = .62). They also found that maternal cortisol accounted for about 40% of the variance in amniotic cortisol concentrations in high stress conditions. Glover et al. (2009) looked at maternal and amniotic fluid cortisol in a sample of women undergoing amniocentesis. They also found that maternal and amniotic cortisol concentrations were significantly correlated (r = .32), and that in the sub-sample of more anxious women the correlation was even higher (r = .59). These studies support the claim that elevations in maternal cortisol can have an impact on concentrations of cortisol in the amniotic fluid. It should be noted however, that there are other possible sources of amniotic cortisol apart from maternal cortisol, such as cortisol from the fetal adrenal and the fetal membrane. In addition, Sarkar et al. (2001) have shown that 11 β-hydroxysteroid-dehydrogenase can be downregulated by norepinephrine and epinephrine. Hence, the relationship between maternal and amniotic fluid cortisol may partly be dependent on norepinephrine and epinephrine.

The question of whether amniotic fluid cortisol could explain variation in child temperament arises because concentrations of stress hormones in the amniotic fluid could affect foetal brain development. Salaria et al. (2006) found that increased prenatal cortisol exposure influenced the expression of over a thousand genes in foetal brain cells. A study by Bergman et al. (2010a) was the first to investigate the influence of amniotic fluid cortisol on child outcome. It was found that higher levels of amniotic cortisol were associated with lower cognitive scores at 17 months, but in a different paper Bergman et al. (2010b) reported no relationship with child temperament (i.e., fear reactivity at 17 months). These findings call for more research to be carried out to investigate the association between amniotic fluid cortisol and a wide range of outcomes, such as birth outcomes and temperament. Specifically, cortisol concentration in the amniotic fluid could function as a mediator of the relationship between maternal cortisol and child outcomes.

The current study combined psychosocial and hormonal assessments of maternal prenatal stress together with amniotic cortisol levels in a normal sample of healthy women undergoing amniocentesis early in pregnancy to better capture prenatal stress experience to investigate how different indices of prenatal stress are associated with birth outcomes (i.e. gestational age and birth weight) and early infant temperament. Foetal gestational age and infant birth weight are important markers of subsequent infant development. Low birth weight has been linked to lower IQ scores (Breslau, 1995) and to hyperactivity and inattention (Breslau et al.,