Associations between biological markers of prenatal stress and infant negative emotionality are specific to sex

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\textbf{A R T I C L E  I N F O}

\textbf{Keywords:}
Prenatal stress
Glucocorticoids
Fetal programming
Alpha-amylase

\textbf{A B S T R A C T}

\textbf{Purpose:} Fetal programming is the idea that environmental stimuli can alter the development of the fetus, which may have a long-term effect on the child. We have recently reported that maternal prenatal cortisol predicts infant negative emotionality in a sex-dependent manner: high prenatal cortisol was associated with increased negative emotionality in females, and decreased negative emotionality in males. This study aims to test for this sex-specific effect in a different cohort, and investigate whether sex differences in fetal programming may be specific to glucocorticoid mechanisms by also examining a maternal salivary alpha-amylase (sAA) by sex interaction.

\textbf{Methods:} 88 pregnant women (mean gestational age = 27.4 weeks, SD = 7.4) collected saliva samples at home over two working days to be assayed for the hormone cortisol (range = 0.13–88.22 nmol/l) and the enzyme alpha-amylase (range = 4.57–554.8 units/ml). Samples were collected at waking, 30-min post-waking and 12 h post-waking. Two months after birth participants reported infant negative emotionality using the distress to limits subscale of the Infant Behavior Questionnaire.

\textbf{Results:} The interaction between maternal prenatal cortisol and infant sex to predict distress to limits approached significance (\(p = 0.067\)). In line with our previous finding there was a positive association between prenatal cortisol and negative emotionality in females, and a negative association in males. The interaction between sAA and sex to predict distress was significant (\(p = 0.025\)), and the direction of effect was the same as for the cortisol data; high sAA associated with increased negative emotionality in females and reduced negative emotionality in males.

\textbf{Conclusions:} In line with our previous findings, this research adds to an emerging body of literature, which suggests that fetal programming mechanisms may be sex-dependent. This is the first study to demonstrate that maternal prenatal sAA may be an important biomarker for infant behavior, and the findings have implications for understanding sex differences in developmental psychopathology.

\section{1. Introduction}

Prenatal psychological stress, which includes depression and anxiety, increases risk for adverse offspring outcomes, such as: preterm birth (Class et al., 2011), low birth weight (Zhu et al., 2010), behavioral difficulties (O’Connor et al., 2002, 2003; Connor et al., 2002, 2003), and psychiatric problems (Pearson et al., 2013; Van den Bergh et al., 2008). The prevailing mechanistic theory in perinatal psychiatry is that prenatal stress exerts influence on fetal developmental trajectories via glucocorticoid mechanisms. The animal literature has consistently supported this hypothesis (Barbazanges et al., 1996; Koehl et al., 1999; Lemaire et al., 2000; Maccari et al., 1995), however human studies have been less consistent. For example, evidence that prenatal stress is associated with increased maternal cortisol is mixed, with some studies supporting this association (Giesbrecht et al., 2012; Murphy et al., 2014; O’Connor et al., 2013; Obel et al., 2005) and others not (Braithwaite et al., 2016; Hellgren et al., 2013; Pluess et al., 2010). Similarly, evidence for associations between prenatal cortisol and offspring negative emotionality has been mixed, with evidence both for (Baibazarova et al., 2013; Davis et al., 2007) and against (Gutteling et al., 2005a) an association. Furthermore, there is a lack of evidence supporting a mediating role of maternal cortisol in associations...
between prenatal stress and adverse offspring outcomes; often only maternal cortisol or mood is reported to be associated with offspring outcomes (Davis and Sandman, 2010; Gutting et al., 2005b; Sarkar et al., 2008).

One possible explanation for the disparate literature is that effects of prenatal stress may be sex-dependent. Sex differences in offspring outcomes following exposure to prenatal risks have been described in the animal and human literature. In animal studies, prenatal stress is associated with offspring depression and anxiety behaviors (Frye and Wawrzyncki, 2003; Schulz et al., 2011; Zagron and Weinstock, 2006). Notably, these behaviors are present in the female, but not male, offspring. Interestingly, adrenoregulatory patterns of pregnant dams eliminated effects of prenatal stress on adverse female behavior (Zagron and Weinstock, 2006), further supporting sex-dependent effects mediated by glucocorticoid mechanisms. There is accumulating evidence in the human literature that prenatal risks for developmental psycho-pathology may be sex-dependent. For example, a range of prenatal risks, such as; stress, smoking and low birth weight, are associated with internalizing symptoms in females (Costello et al., 2007; Van den Bergh et al., 2008; Van Lieshout and Boylan, 2010) and externalizing symptoms in males (Li et al., 2010; Rodriguez and Bohlin, 2005). Prenatal anxiety has been linked to dampened diurnal cortisol release and depression in female offspring (Van den Bergh et al., 2008), and also gender-specific effects on vagal withdrawal during childhood (Tibu et al., 2014). Further, heightened cortisol in pregnancy has been linked with a range of other effects in female, but not male, offspring, including; a more difficult temperament (Sandman et al., 2013); increased amygdala volume (Buss et al., 2012); and anxiety and affective problems (Buss et al., 2012; Sandman et al., 2013). In addition, we have recently shown that heightened prenatal cortisol was associated with increased negative emotionality in female infants, but decreased negative emotionality in male infants at 5 weeks of age (Braithwaite et al., 2017). This literature supports an emerging concept that there may be sex-dependent processes underpinning effects of prenatal stress on developmental trajectories, whereby females become more reactive to challenge and more anxious, and males become less reactive and more aggressive (Glover and Hill, 2012; Sandman et al., 2013).

An explanation for difficulties in characterizing the role of glucocorticoids in associations between prenatal stress and adverse offspring outcomes is that other mechanisms may also be important. For example, changes in maternal sympathetic nervous system (SNS) activity may be an alternative pathway by which prenatal mood impacts fetal development (Braithwaite et al., 2014; Talge et al., 2007). The SNS is activated during psychological distress, resulting in increased noradrenaline levels. Noradrenaline does not cross the placental barrier (Giannakoulopoulos et al., 1999), however could indirectly influence fetal development by initiating vasoconstriction and reducing uterine blood flow. This mechanism could contribute to reduced birth weight or premature birth, both of which are associated with prenatal stress. Fluctuating oxygen and nutrient supplies to the developing fetus could also increase risk for psychological difficulties (Morsing et al., 2011). Animal studies show that both acute stress and intravenous noradrenaline induce decreased uterine blood flow (Shnider et al., 1979; Stevens and Lumbers, 1995). Initial human studies mirrored these findings (Sjostrom et al., 1997; Teixeira et al., 1999); however there have been a number of non-replications (Harville et al., 2008; Kent et al., 2002; Mendelson et al., 2011; Monk et al., 2012). The disparate findings could be attributable to difficulties in assessing uterine blood flow in a controlled laboratory setting, or could be explained by fetal sex-differences. An alternative method to assess SNS function is via the salivary biomarker, alpha-amylase. Salivary alpha amylase (sAA) is an enzyme produced by the salivary glands, which is controlled by SNS innervation. Increased sAA concentrations are evident during periods of psychological distress (Bosch et al., 1996; Chatterton et al., 1997; Skosnik et al., 2000), and sAA levels are inflated in people with depression (Ishitobi et al., 2010; Tanaka et al., 2012; Veen et al., 2013).

Pregnant populations, heightened sAA has been associated with anxiety (Giesbrecht et al., 2013) and depression (Braithwaite et al., 2015b). It is currently unknown, however, whether prenatal sAA is an important biomarker for offspring development, and whether any effects may be gender-specific.

The primary aim of this study is to test if our recent finding, that high prenatal cortisol predicts increased negative emotionality in females, and decreased emotionality in males, is evident in a different cohort. A second aim is to investigate whether sex-dependent associations of the same kind may be specific to glucocorticoid mechanisms, by also testing for a SNS effect (sAA by gender interaction). Data used in this analysis has been previously published (Braithwaite et al., 2016, 2015b), however in this manuscript we present a reanalysis of the data to specifically address the question of fetal sex.

2. Methods

2.1. Participants

Participants were a community sample of 103 first-time mothers and their infants participating in a longitudinal study based in Oxford, UK, designed to investigate the effects of prenatal mood disturbance on maternal and infant stress responses (Braithwaite et al., 2016, 2015b). All participants were primiparous, more than 14 weeks pregnant, had a singleton pregnancy, were over the age of 18, had no medical complications associated with their pregnancy and were not currently taking any steroid-based medications. 10 participants reported medication use during pregnancy. The medications included: tri-cyclic anti-depressants (n = 2), selective serotonin re-uptake inhibitors (n = 1), ranitidine hydrochloride (n = 2) and omeprazole (n = 1) to treat gastro-esophageal reflux, antibiotics (n = 1), lactulose (n = 2) and thyroxine (n = 1). This research study was reviewed and approved by the Research Ethics Committee South Central Oxford B (REF: 12/SC/0473), and all participants provided informed consent for themselves and their infants to be included in the study. Complete prenatal and postnatal data was available for 88 mothers and their infants (39 males and 49 females), who comprise the sample for this analysis.

2.2. Procedure

This study comprised one prenatal and one postnatal assessment, which are detailed below.

2.2.1. Prenatal assessment

At the time of the prenatal assessment participants were in either the second or third trimester of pregnancy (range = 106–281 days gestation, mean = 191.4 days, SD = 50.6). Participants were invited to a prenatal test session, which took place either at the Department of Psychiatry, University of Oxford, or at the participants’ home. This session took place between the hours of 1pm and 7pm, and lasted for approximately 90 min. Participants were asked to complete a questionnaire, which included questions about their demographic characteristics and current levels of depressive symptoms, and participated in a task, which has been described previously (Braithwaite et al., 2016). Participants were then asked to collect six saliva samples at home over two working days (3 per day), to be assayed for the hormone cortisol and the enzyme alpha-amylase. Samples were collected using the passive drool method, and participants were provided with six 2 ml cryovials and six saliva collection aids, as well as a stamped-addressed envelope to return the samples. On each day, samples were collected immediately after awakening, and 30 min and 12 h post-awakening. Participants were asked to refrain from eating, drinking, smoking and exercising for 30 min before each sample was collected. Participants stored the samples in their home fridges at −4 °C, before returning them to the Department of Psychiatry. Samples were shipped at room temperature, and remained at room temperature for a maximum of 24 h.
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