



Maternal prenatal cortisol predicts infant negative emotionality in a sex-dependent manner



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HIGHLIGHTS

- Prenatal cortisol was associated with infant negative emotionality in a sex dependent manner.
- Females exposed to high prenatal cortisol were more negatively emotional, but males were less negatively emotional.
- There may therefore be sex differences in fetal programming mechanisms.
- There are implications for understanding sex differences in developmental psychopathology.

ARTICLE INFO

Article history:

Received 12 December 2016

Received in revised form 16 January 2017

Accepted 14 March 2017

Available online 16 March 2017

Keywords:

Prenatal stress

Cortisol

Fetal programming

Sex differences

Infant behaviour

ABSTRACT

Objective: Prenatal stress influences fetal developmental trajectories, which may implicate glucocorticoid mechanisms. There is also emerging evidence that effects of prenatal stress on offspring development are sex-dependent. However, little is known about the prospective relationship between maternal prenatal cortisol levels and infant behaviour, and whether it may be different in male and female infants. We sought to address this question using data from a prospective longitudinal cohort, stratified by risk.

Method: The Wirral Child Health and Development Study (WCHADS) cohort ($n = 1233$) included a stratified random sub-sample ($n = 216$) who provided maternal saliva samples, assayed for cortisol, at home over two days at 32 weeks of pregnancy (on waking, 30-min post-waking and during the evening) and a measure of infant negative emotionality from the Neonatal Behavioural Assessment Scale (NBAS) at five weeks-of-age. General population estimates of associations among measures were obtained using inverse probability weights.

Results: Maternal prenatal cortisol sampled on waking predicted infant negative emotionality in a sex-dependent manner (interaction term, $p = 0.005$); female infants exposed to high levels of prenatal cortisol were more negative (Beta = 0.440, $p = 0.042$), whereas male infants were less negative (Beta = -0.407 , $p = 0.045$). There was no effect of the 30-min post-waking measure or evening cortisol.

Discussion: Our findings add to an emerging body of work that has highlighted sex differences in fetal programming, whereby females become more reactive following prenatal stress, and males less reactive. A more complete understanding of sex-specific developmental trajectories in the context of prenatal stress is essential for the development of targeted prevention strategies.

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1. Introduction

Maternal prenatal depression and anxiety are associated with increased risk for adverse offspring outcomes, including: poor obstetric outcomes [1,2], behavioural difficulties in childhood [3], and mental health disorders in adolescence [4,5]. Notably, these effects appear to

be independent of maternal postnatal mood [4,6]. Although most studies are unable to rule out possible genetic confounds, results from an *in vitro* fertilisation study suggest that some effects of prenatal mood on fetal development are also independent of shared risk genes between mother and infant [7], highlighting potential *in utero* mechanisms as mediating processes.

Animal studies implicate alterations of the hypothalamic pituitary-adrenal (HPA) axis as a potential mediating mechanism in associations between prenatal stress and adverse offspring development [8,9], however evidence from the human literature has been less consistent. The theory is that disturbances in maternal mood during pregnancy results in higher levels of circulating glucocorticoids, namely cortisol, which cross the placental barrier and alter fetal development. Indeed, a number of studies have demonstrated associations between heightened cortisol in pregnancy and adverse obstetric outcomes, including reduced birth weight and shortened gestational length [10–15]. There have also been reports of associations between heightened maternal prenatal cortisol and negative emotionality and behaviour problems in children. In the largest study to date (N = 247), maternal salivary cortisol in late pregnancy was associated with maternal reports of more negative infant reactivity at 2 months of age [16]. Although this study assessed maternal salivary cortisol during each trimester, only cortisol in late pregnancy predicted infant reactivity. In a sample of 135 infants whose mothers underwent an amniocentesis during mid pregnancy, amniotic fluid cortisol was not associated with maternal reports of temperament at 3 months of age [14]. These two studies highlight that cortisol in late, but not mid pregnancy, may be a particularly important marker for offspring behaviour. Alternatively, in a study that assessed maternal reports of temperament and behavioural problems in older children (27 months), there was no association between maternal salivary cortisol sampled during each trimester and behavioural outcomes [17]. Thus, prenatal cortisol may be a salient predictor of early infant, but not childhood, behaviour. It is also plausible that variation in study methodologies, including different sample sizes, cortisol sampling procedures and measures of infant behaviour, could explain the disparate findings.

From the few existing studies, we can conclude that effects of maternal prenatal cortisol on early measures of infant behaviour are currently unclear. It is possible that associations between prenatal cortisol and infant behaviour may be sex-dependent. Indeed, sex differences in postnatal outcomes following exposure to prenatal risk have been described in the human and animal literature. For example, a number of studies have exposed pregnant dams to random daily stress, and have tested behaviour in the adult offspring. Many of these studies report elevated anxiety and depression-like behaviours in offspring exposed to maternal prenatal stress [18], including reduced exploration of the open arms of an elevated maze test [19] and increased length of immobility in the forced swim test, in females but not in males [20]. Further, adrenalectomy of the pregnant dams eliminated effects of prenatal stress on female offspring behaviour [19], consistent with a sex-dependent effect mediated *via* glucocorticoid mechanisms.

Accumulating evidence from the human literature also suggests that prenatal risks for offspring psychopathology may be sex-dependent. For example, prenatal risks have been reported to be associated with increased internalising symptoms in females but not males [5,21,22], and externalising behaviours in males but not females [23,24]. Elevated cortisol in pregnancy has been shown to predict fearful temperament in girls at 2 months, and to predict pre-adolescent anxiety in girls. This effect was not seen in boys [25]. Elevated maternal cortisol predicts increased amygdala volume and more affective problems in girls but not boys [26]. Similarly, high prenatal anxiety has been related to a flattened diurnal cortisol profile and depressive symptoms in adolescent daughters [5]. Previous research from our group has found that maternal prenatal anxiety is associated with autonomic reactivity to challenge in a sex-dependent manner. High prenatal anxiety was associated with lower vagal withdrawal in response to the still face procedure at

29 weeks of age in boys, but higher vagal withdrawal in girls [27]. We also found that low birth weight was associated with vagal withdrawal in the same sex-dependent manner. This literature supports the emerging idea that processes underpinning fetal programming in the context of prenatal stress may be sex-dependent [25]; whereby females may become more reactive to challenge and anxious, and males become less reactive and more aggressive [25,28].

However, more evidence is needed to support this idea, and key questions remain regarding effects of prenatal cortisol on early measures of infant behaviour. Critically, a more complete understanding of mechanisms by which prenatal stress impacts on development during early infancy is essential for the design of intervention and prevention strategies to avert the onset of later mental health difficulties. It is also critical to understand whether such pathways of effect may be different in male and female infants, so that intervention/prevention strategies may be targeted more effectively. Thus, the aims of the current study were to investigate effects of prenatal cortisol on early infant behaviour in a longitudinal cohort. Consistent with our previous vagal reactivity findings, we hypothesised that prenatal cortisol would predict infant irritability in a sex-dependent manner, whereby females exposed to high levels of prenatal cortisol become more behaviourally reactive (*i.e.* show more negative emotionality) and males show less negative emotionality.

2. Materials and methods

2.1. Design

Participants were members of the Wirral Child Health and Development Study (WCHADS), a prospective epidemiological longitudinal study of first-time mothers starting in pregnancy and with multiple follow-up assessments after birth. For some phases requiring more detailed and expensive measurement, data collection was restricted to a randomly drawn stratified sub-sample. The stratified design allows general population estimates of means and associations to be derived for measures from all phases. Recruitment of the cohort has been described in detail previously [29,30]. Approval for the procedures was obtained from the Cheshire North and West Research Ethics Committee (UK).

2.2. Sample

The cohort consists of 1233 mothers, with a mean age at recruitment of 26.8 years (SD = 8.5, range = 18–51). Using the revised English Index of Multiple Deprivation (IMD) [31] based on data collected from the UK census in 2001, 41.8% fell in the most deprived UK quintile, consistent with high levels of deprivation in some parts of the Wirral. Only 48 women (3.9%) described themselves as other than White British.

The measures used in this report were obtained for the whole cohort from questionnaires at 20 weeks gestation and administrative records at birth, and the stratified sub-sample of mothers (n = 316) who provided interviews and saliva at 32 weeks gestation (mean 32.1, SD = 2.0) and additional questionnaires and the Neonatal Behavioural Assessment Scale (NBAS) (n = 282) of their infants at 5 weeks-of-age (mean 37 days, SD = 9).

2.3. Measures

2.3.1. Maternal cortisol

At 32 weeks gestation, mothers collected saliva samples at home over two consecutive working days. Saliva was collected on waking, 30 min post-waking, and during the evening (approx. 12 h after waking (mean = 12h 10min, SD = 1 h 15 min)). Participants stored the samples in their freezer until a research assistant collected them 1–2 weeks later. Samples were then stored at –20 °C before transportation to Imperial College London on dry ice for analysis. All samples were assayed for salivary cortisol using a commercially available

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