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The Impact of Maternal HPA Activity on Postnatal Outcomes, A Narrative Review

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Introduction

Excessive foetal exposure to maternal Hypothalamic-Pituitary-Adrenal (HPA) activity, and in particular glucocorticoids such as cortisol, can result in poor developmental outcomes for offspring [1]. The relation between HPA activity and development has been evidenced by research examining both animal and human samples [2]. In response, clinically based interventions that seek to reduce exposure to, or the impact of, foetal overexposure to HPA activity, have gained importance [3,4]. The purpose of this review is to describe the relationship between prenatal overexposure to maternal HPA activity and adverse postnatal effects in human offspring. First, we will discuss the function of the HPA axis during pregnancy and the theory underpinning its role in offspring outcomes will be described. Following this, research examining the relationship between maternal HPA activity and offspring birth and development will be outlined. We will conclude with a discussion of the implications for future research.

HPA Axis and pregnancy

Central to stress regulation in the human body is the HPA axis [5]. In response to stress eliciting stimuli, the HPA axis is activated to provide an increase in glucocorticoid concentrations [6]. Corticotrophin-releasing hormone (CRH), secreted by the paraventricular nucleus of the hypothalamus, stimulates release of adrenocorticotrophic hormone (ACTH) by the anterior pituitary gland which, in turn, stimulates peripheral secretion of cortisol by the adrenal cortex. HPA activity has been demonstrated to follow a daily diurnal pattern in which elevated levels of cortisol present in the morning decrease over the course of the day [7]. During the second and third trimesters of pregnancy, peripheral concentrations of CRH increase substantially as a result of placental activity, initiating an up to three-fold increase in peripheral cortisol [2]. Evidence suggests that by the end of gestation, this increase in peripheral cortisol results in a downregulation of CRH and a subsequent attenuation of HPA responsiveness to distress [8].

The path by which maternal glucocorticoid concentrations reach the foetus is the placenta [2]. This is supported by studies finding significant correlations between maternal cortisol levels and amniotic cortisol concentrations [5,9]. The placenta is lined with the enzyme HSD11B2 which works to protect the fetus from excessive glucocorticoid levels. Factors such as maternal psychological distress (such as anxiety), however, can weaken this enzyme and allow the fetus to be exposed to higher glucocorticoid concentrations [2].

Exposure during pregnancy to appropriate levels of glucocorticoids is important for foetal maturation [10]. For example, exposure to cortisol during the third trimester is crucial for the development of offspring's cardiovascular, pulmonary, and renal systems, as well as overall foetal growth [11]. However, when a fetus' is exposed to excessive amounts of glucocorticoid levels for a prolonged period, the development, birth, and susceptibility of the infant to physical illness may be influenced [12]. This is believed to occur through the process of foetal programming, a concept born out of the Barker hypothesis [13]. The Barker hypothesis stipulates that adult vulnerability to diseases (e.g., diabetes, and stroke) originate in the fetus and are *programmed* by the intrauterine environment [14]. Epidemiological research has increasingly supported this proposition, and both animal and human studies have backed the role of glucocorticoid overexposure in the early programming of later life disease [15,16]. From this research base, recent attention has been directed to the possible role of glucocorticoid overexposure in newborn birth and the cognitive, emotional, and behavioural development ofoffspring.

Maternal HPA activity and offspring birth

Research has considered the relationship between glucocorticoid exposure and offspring characteristics at birth, including birth-weight and size at gestation [17-19]. Overall,

studies examining both central and peripheral glucocorticoid concentrations appear to support the relationship, although findings seem to vary across study methods [2,20]. For example, Bolten *et al.* [21] examined maternal salivary cortisol levels at waking and at three time points after waking, during early (13–18 weeks) and late (35-37 weeks) gestation. Eighty-one mother-child dyads were observed, and results indicated that maternal cortisol levels at both gestational points were negatively associated with offspring birth-weight and size [21]. Additional analyses indicated that maternal cortisol levels explained 19.8% of the variance in infant birth weight and 9% of the variance in body length; these results were independent of pregnancy complications, gestational age, parity, pre-pregnancy maternal body-mass-index (BMI), smoking, and infant's sex [21].

By contrast, Goedhart *et al.* [22] examined 2810 mothers and assessed cortisol levels in maternal plasma at one time point after 20 weeks' gestation. Their results showed no association between maternal cortisol levels and offspring birth-weight or size after controlling for the same factors as Bolten *et al.* [21], plus maternal age. Similar findings have been demonstrated between other studies observing salivary cortisol and plasma cortisol [18]. It may be that the medium through which cortisol is sampled may have impacted the results of these studies.

However, there are also other variables which may have impacted these results. These include the different study sample sizes and the number of times cortisol was assessed over pregnancy and within each period of sampling. Unlike Goedhart *et al.* [22], Bolten *et al.* [21] accounted for the diurnal pattern of cortisol release throughout the day and throughout pregnancy. Indeed, after further analysis, Goedhart *et al.* [22] also found that the time at which cortisol was sampled moderated their results; maternal cortisol was independently related to lower birth-weight and smaller size at gestation only for mothers who provided a blood sample before 9 am. This suggests that the timing of cortisol sampling is an essential factor when examining its impact on foetal growth.

The variability across studies in this area has made it difficult to distinguish between the effects of maternal cortisol and the consequences of variable study designs [20]. Cherak *et al.* [20] recently attempted to mitigate this limitation by conducting a highly specific systematic review and meta-analysis with strict inclusion criteria [20]. Nine studies were analysed, comprising of 1606 mother-child dyads,and findings indicated that maternal salivary cortisol was negatively correlated to offspring birth-weight across all trimesters [20]. It was also observed that these factors were most strongly correlated during the third trimester and that studies examining this period of pregnancy demonstrated the lowest degree of heterogeneity. Cherak *et al.* [20] subsequently concluded that their findings highlight the third trimester of pregnancy as a possible *critical period* for foetal development and growth [23].

Similar patterns of study results and variability have also been demonstrated when examining offspring gestational age at birth [7,24]. For example, Giurgescu [25] conducted a systematic review in which 15 studies investigating the impact of cortisol overexposure and preterm birth (delivery before 37 weeks) were examined. Most findings indicated that higher levels of cortisol posed a higher risk of preterm birth [25]. However, the gestational age at which cortisol samples were collected appeared to influence study results. Specifically, studies examining maternal cortisol between 7- 24 and 27- 37 weeks' gestation were related to preterm birth. However, no such association was found when cortisol was assessed between 24- 27 weeks.

In a more recent study, Entringer *et al.* [7] observed 25 healthy pregnant women over four days and used an ecological momentary assessment (EMA) measure of salivary cortisol. EMA refers to the repeated sampling of participant's experience in real time and in their natural environment [26]. It aims to minimise recall bias and maximise ecological validity [26]. Findings from this study indicated that higher cortisol levels at awakening were related to a shorter pregnancy duration of up to one week. They also found that a one-time plasma or salivary sample of cortisol in a laboratory setting was not associated with offspring gestational age at birth. One limitation of this study was its small sample size, though the advantages of using an EMA approach were argued to outweigh this limitation as it provided 112 assessments per subject [7]. Overall, studies considering birth-related factors highlight the importance of appropriate sampling of cortisol activity during pregnancy. In the studies which better utilised this knowledge, findings suggested that glucocorticoid overexposure can lead to preterm birth, lower birth-weight, and smaller size at gestation.

In addition to newborn birth and size, research has also considered glucocorticoid effects on offspring cognition, emotionality, and temperament [27-30]. Overall, studies investigating these areas of literature are few and vulnerable to an even greater range of biological and environmental confounds than previously discussed. For example, research places an even greater emphasis on the notion of so-called *critical periods* during pregnancy in which the fetus is more susceptible to glucocorticoid impacts [1]. Additionally, studies in this area look at infant or childhood developmental outcomes which means that results are vulnerable to the influence of factors such as genetics and the postnatal environment [31]. Of importance are factors that influence the parent-child relationship, and consequently child development, such as maternal mental health [32].

During foetal life, the brain undergoes rapid development, and this makes the fetus more vulnerable to dysregulation of the maternal HPA activity [1]. Excessive exposure to cortisol and CRH, for example, have been found to reduce brain plasticity and neurotransmitter activity, and to obstruct the formation of neural connections [33]. Such impacts can have subsequent effects on foetal programming and may influence offspring cognition and neurodevelopment [33].

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Maternal HPA activity and offspring development

In research considering the cognitive development of infants in relation to HPA activity, some studies have assessed cognitive development using the Bayley Scales of Infant Development [10,34]. For example, Huizink *et al.* [34] assessed the mental development of 170 offspring at 3 and 8 months post-birth. Maternal salivary cortisol was assessed during early (15–17 weeks), mid (27–28 weeks) and late (37–38 weeks) gestation, and samples were taken seven times during each period. Results showed that early morning values of cortisol in late pregnancy were negatively related to results on the BSID at 3 months, but not at 8 months. Davis & Sandman [10] performed a similar study on 125 full-term infants. Maternal salivary cortisol was measured five times during pregnancy (at 15, 19, 25, 30, and 36 weeks) and offspring development was measured when infants were 3, 6, and 12 months of age. Findings indicated that, at 12 months, exposure to elevated cortisol during early gestation was associated with lower scoreson the BSID, while elevated cortisol in late gestation was associated with higher scores. One strength of these studies was their large sample size, longitudinal designs, and the fact that they controlled for postnatal confounding factors, such as maternal psychopathology. However, while Huizink *et al.* [34] accounted for the diurnal nature of cortisol, Davis & Sandman [10] did not. Both studies also examined low-risk samples of mothers, limiting the ability to make generalisations from their results to clinical populations. Despite these limitations, however, both studies support the role of glucocorticoid exposure in shaping offspring cognitive development, particularly during late gestation [10].

At least two studies using older child samples have also considered cortisol overexposure and childhood intellectual functioning [28]. For example, LeWinn *et al.* [31] compared IQ scores at 7 years of age between 74 sibling pairs. Siblings were born at different times and exposed to different amounts of prenatal cortisol during late gestation (31- 36 weeks). IQ was assessed using the Wechsler IntelligenceScale for Children (WISC; edition not specified) and maternal cortisol was collected from plasma. Within sibling pairs, maternal cortisol was negatively associated with verbal IQ, independent of prenatal and postnatal confounding factors. Similar findings were also observed in a more recent study by Aizer *et al.* [28]. However, neither of these studies controlled for post-natal maternal mental health. This is significant because studies such as Bergman *et al.* [35] suggest that the mother-child relationshipmay mediate the association between in utero cortisol exposure and offspring cognitive development. Such results, however, suggest that cortisol can have an impact on offspring cognition without postnatal intervention.

In addition to cognitive development, some studies have also examined the role of cortisol overexposure on offspring temperament [12,36]. For example, De Weerth *et al.* [37] examined cortisol in 17 mothers at 36 weeks' + gestation and infant behaviour in full-term 5-month-old offspring. Infant behaviour was videotaped during a bath at 1, 3, 5, 7,18 and 20 weeks of age and mothers rated infant temperament when their offspring were 7 and 18 weeks old. Findings indicated that infants of mothers with high cortisol levels at 36+ weeks' gestation demonstrated greater displays of crying, fussing and negative facial expressions and scored higher on scales indicating more difficult behaviours [37]. In another study Davis *et al.* [30] assessed the temperament of 247 full-term infants on a measure of negative reactivity rated by their mothers. Maternal salivary cortisolwas assessed at 18-20, 24-26, and 30-32 weeks of gestation. Results showed that elevated maternal cortisol only at 30-32 weeks' gestation was significantly associated with greater maternal reports of infant negative reactivity. The strength of Davis *et al.* [30] is the longitudinal nature of their results, and together, these studies support the vulnerability of fetus' to maternal cortisol during late gestation [38].

However, while cortisol overexposure appears to impact offspring temperament, this relationship may be more complicated than initially thought [2]. For Example, Braithwaite *et al.* [39] examined 216 5-week-old infants exposed to high concentrations of cortisol at 32 weeks' gestation and found sex differences in offspring temperament. Specifically, females tended to show greater reactivity and anxiety towards challenging tasks while males showed less reactivity and greater aggression. Such sex-dependent findings have also been supported in other recent studies [40-42]. Additionally, research has suggested that the impact of glucocorticoid exposure in utero may be mediated by factors such as low birth weight [5] and foetal brain development [43].

Indeed, studies examining prenatal glucocorticoid exposure, brain development, and offspring emotionality support the claim by Gutteling *et al.* [43,45,38]. For example, Davis *et al.* [38] studied the impact of synthetic glucocorticoid exposure on brain development and affective problems in 54 full-term children aged 6- 10-years-old. Results indicated that children who were exposed to synthetic glucocorticoid treatment between 24-34 weeks' gestation had significantly thinner cortices in areas associated with stress and emotion regulation. Interestingly, thinner cortices, but not glucocorticoid treatment, was associated with affective problems. In other child studies, however, thinner cortices have been associated with depressive symptomatology [45]. Consequently, these findings suggest that glucocorticoid treatment may make children more vulnerable to affective problems through the impact it has on their brain development. This is supported by Buss *et al.* [44] longitudinal study in which higher cortisol levels during early gestation (15 weeks) were associated with greater affective problems in girls, and this appeared to be mediated by amygdala volume. Together, these studies support the notion that there are areas of the foetal brain that are vulnerable to maternal HPA activity and have subsequent impacts on offspring emotionality [1]. Buss *et al.* [44] study also support the notion of sex- specific effects.

Other studies considering offspring brain maturation have investigated offspring HPA development [43,44]. Recently, for example, Davis *et al.* [47] examined prenatal maternal cortisol

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levels and infant behavioural responses to stress. Plasma cortisol was assessed in 116 mothersat 15, 19, 25, 31 and 36 + weeks' gestation and infant stress reactivity was assessed at 24 hours' post-birth in a heel-prick scenario. Statistical analyses showed that infants who were exposed to higher levels of maternal cortisol in mid-late gestation were more reactive to the stressful procedure. Elevated maternal cortisol levels during early pregnancy was also a predictor of a slower behavioural recovery rate. All findings were independent of delivery type, prenatal medical history, socioeconomic status or child race, sex or birth order.Findings from studies considering exogenous administrations of glucocorticoids also support these findings [48]. At least one of these studies has also suggested that increased cortisol reactivity in offspring can continue into childhood, though again, results may be more pronounced for girls than boys [19].

Overall, studies suggest that prenatal overexposure to maternal glucocorticoid concentrations can influence foetal brain development and subsequent offspring emotionality and stress reactivity. Most of the studies in this area are longitudinal, account for the possible *critical period* of later gestation, use various means of measuring cortisol, and consider additional mediating factors such as offspring sex. This is a great strength in this literature. The primary limitation, however, is the low-risk sample frequently used in research. Again, such samples limit the ability for research to generalise their results to clinical populations of pregnant women.

In summary, foetal overexposure to maternal HPA activity can have implications for offspring birth and subsequent development. Specifically, excessive exposure during late gestation can lead to preterm birth, low birth-weight, and smaller size at gestation. Similar trends in exposure can also lead to unfavourable offspring cognitive functioning, temperament, and emotionality. Recent research further proposes that these relationships are largely mediated by foetal brain development and dependent on offspring sex. An alternative mediumthrough which offspring development may be impacted is low birth weight. Both preterm birth and low birth weight have been associated with increased risk of later behavioural and psychological concerns [48]. However, newborns born prematurely or at a lower birth weight also demonstrate underdeveloped brains [49]. Consequently, the mediating role of low birth weight may again be better attributed to foetal brain development.

Implications for future research

The present review leads to several implications for future research. First, more research is required to further clarify the impact of foetal overexposure to glucocorticoids. Some of this research needs to take an exploratory approach to identify additional factors that have potential to confound study findings. For example, studies could further examine the role of foetal brain development in mediating prenatal cortisol exposure and postnatal cognitive, emotional, and behavioural difficulties [43]. Other research should continue to build upon current findings using improved study methods which account for the natural patterns of HPA activity. They should use approaches that have greater ecological validity than measuring one-off samples of cortisol, such as EMA [7]. To prevent confounding results research should also account for prenatal and postnatal factors such as genetics, offspring sex and maternal mental health. Longitudinal research methods will also add to current findings by allowing researchers to consider the impact of *critical periods* in foetal development.

Second, research should use larger samples of mother-child dyads and direct their attention towards populations that may exhibit clinically elevated prenatal cortisol concentrations [10]. Currently, research has focused more on healthy, low-risk samples of mothers. However, this has limited the potential for studies to generalise their findings to clinical populations. There is some evidence suggesting that prenatal maternal depression and anxiety may increase prenatal maternal cortisol levels [2]. Consequently, research may benefit from using samples of pregnant women with clinical presentation of psychopathology [10]. At the same time, other research suggests that there is no correlation between maternal anxiety and depression and cortisol levels during pregnancy [2]. Further research is therefore required to bring greater clarity to this area of literature.

Finally, research needs to investigate ways of limiting the impact of foetal overexposure to maternal glucocorticoid concentrations. Given the results across studies this implication appears imperative, and there are at least two ways of addressing this. For example, psychological interventions could aim to reduce prenatal maternal distress. Some researchershave begun considering such interventions out of the understanding that prenatal psychopathology can lead to increases in maternal cortisol levels [4]. As previously mentioned, while some studies support this correlation, others do not [2]. Consequently, it may be more appropriate for interventions to address the HSD11B2 enzyme and aim to prevent it from weakening. Another method of intervening may be to focus on the parent-child relationship post-birth [32]. As previously mentioned, this relationship can mediate the adverse effects of foetal overexposure to cortisol [35]. Currently, research investigating interventions during the post-natal period show promising results and suggest that increasing parental warmth and responsiveness are useful in mitigating the adverse effects of foetal glucocorticoid overexposure [32].

To conclude, excessive foetal exposure to maternal HPA activity can result in unfavourable birth and development outcomes in offspring. Further research is required toclarify this relationship in human samples, however findings to date indicate that interventions aimed at minimising the effects of this relationship are crucial.

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