A role for the placenta in programming maternal mood and childhood behavioural disorders.

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Abstract

Substantial data demonstrate that the early life environment, including *in utero*, plays a key role in later life disease. In particular, maternal stress during pregnancy has been linked to adverse behavioural and emotional outcomes in children. Data from human cohort studies and experimental animal models suggest that modulation of

the developing epigenome in the fetus by maternal stress may contribute to the fetal programming of disease. Here, we summarise insights gained from recent studies that may advance our understanding of the role of the placenta in mediating the association between maternal mood disorders and offspring outcomes. Firstly, the placenta provides a record of exposures during pregnancy, which can be evidenced by changes in the placental trancriptome and epigenome. Secondly, prenatal maternal mood may alter placental function to adversely impact fetal and child development. Finally, we discuss the less well established but interesting possibility that altered placental function, more specifically changes in placental hormones, may adversely affect maternal mood and later maternal behaviour, which can also have consequence for offspring wellbeing.

Introduction

Pregnancy can be a challenging time in a woman's life where she may experience many changes in her circumstances. Pregnancy can also be a time of vulnerability to perinatal mental illnesses including depression, stress and postnatal psychosis [1]. In the UK, it is estimated that maternal mood disorders, either prenatally or in the immediate period after birth, affect approximately 1 in 5 women, and is therefore one of the most common conditions of pregnancy. These disorders affect women of all ethnicities, nationalities and social strata [2]. In addition to the distress this causes women and their families, mental health disorders are one of the leading causes of death during pregnancy and the year after birth [1]. Of equal concern is an additional consequence for her child's wellbeing, with an increased risk of adverse behavioural and metabolic outcomes following exposure to maternal prenatal stress [3]. Thus, a

greater understanding of both the causes and the consequences of prenatal maternal stress and mood disorders is imperative.

Fetal programming by maternal stress

Prenatal stress at its broadest level includes major life event stress, catastrophic disasters, chronic stress, daily hassles, perceived stress or pregnancy-specific anxiety along with related symptoms of depression or general anxiety during pregnancy [4]. Both animal and human studies indicate that maternal prenatal stress is associated with an increased risk of adverse emotional, behavioural and cognitive outcomes in the offspring, a subject that has been extensively reviewed (for example [5, 6]). Several studies, including the large Avon Longitudinal Study of Parents and Children (ALSPAC) cohort, allow for multiple confounders, including prenatal paternal and postnatal maternal mood. The findings from such studies indicate that the increased risk for adverse outcomes in the offspring are programmed *in utero* by the maternal emotional state, in least in part [7]. If the mother is in the top 15% of a normal population for prenatal symptoms of anxiety or depression, her child has double the risk of a probable mental disorder, raised from about 6% to 12% at the age of 13 years [7]. However, it is also clear that not all children are affected equally by exposure to maternal stress, and also the effects of prenatal stress on child development are inconsistent. Recent data suggests that this may be, in part, due to gene/environment interplay, including the interaction between prenatal maternal anxiety with the child *brain-derived neurotrophic factor* (*BDNF*) [8] and *catechol-O-methyltransferase* (*COMT*) (O'Donnell *et al.*, in preparation) genotypes, in the development of emotional and cognitive outcomes, respectively.

The role of the placenta in mediating fetal programming

Placental function is important both for optimal fetal growth and maternal health [9]. The placenta is a transient organ of pregnancy that transports nutrients and oxygen to the growing fetus and removes waste products. Additionally, the placenta functions to mitigate the mother's immune response to her semi-allogeneic fetus and manufactures large quantities of hormones that flood the maternal system to induce the adaptations required for a successful pregnancy [10]. An optimally functioning placenta can provide protection to the fetus against some forms of prenatal adversity. For example, the placental enzyme 11β-hydroxysteroid dehydrogenase 2 (HSD11B2) regulates fetal exposure to maternal cortisol by converting it to inactive cortisone. Thus the placenta is able to partially protect the fetus against elevated maternal cortisol levels. However, there is evidence that placental function may be affected by prenatal stress [11-15]. Both endogenous and synthetic glucocorticoids have been shown to impact a variety of placental functions, including vascularisation, apoptosis and nutrient transport, in a range on animal models and human studies [16-20]. Moreover, there is evidence that other maternal factors, such as catecholamines [21], may transfer the effects of maternal stress to the fetus by altering placental function. Consequently, suboptimal placental function, induced by the maternal state may contribute to altered, and in our environment, poorer outcomes for children [22]. Prenatal anxiety is associated with both lower expression and activity of placental *HSD11B2* [14], potentially mitigating the protective role this enzyme usually plays, and theoretically exposing the fetus to higher cortisol levels. Fetal glucocorticoid exposure is also regulated by the placental glucocorticoid (GR; NR3C1) and mineralocorticoid (MR; NR3C2) receptors. Placental *NR3C1* and *NR3C2* expression is higher among depressed compared to non-depressed new

mothers, providing another mechanism for programming of adverse offspring outcomes [15]. Alterations in the expression of *placental cortiticotropin releasing hormone* (*pCRH*; stimulates the production of cortisol via the HPA axis), *monoamine oxidase A* (*MAOA*; metabolises serotonin into 5-hydroxyindoleacetic acid) and *placental serotonin transporter* (*SLC6A4*; transports the neurotransmitter serotonin) and *P-glycoprotein* have also been linked to prenatal stress [11, 23-25]. Interestingly, very recent evidence suggests that the associations between prenatal maternal mood and placental gene expression may be different in Caucasian and non-Caucasian populations (Capron et al., in preparation). Thus, alterations in the expression of a number of genes in the placenta may mediate aspects of fetal programming associated with prenatal stress (Figure 1), however these findings may have ethnic specificities.

Maternal stress and epigenetic changes in the placenta

Although it is clear that there are changes in the expression of genes in the placenta in relation to prenatal stress exposure, the mechanisms underpinning these changes are unclear. One possibility is epigenetic deregulation of gene expression. Epigenetics describes the marks or tags that are added or removed from DNA sequence and histones that regulate gene expression in a manner that is heritable through cell division. Such marks may be altered by exposure to stress during prenatal development, a period when the epigenome is rapidly changing [26]. Animal research demonstrates that maternal stress can induce epigenetic changes in the placenta; DNA methylation changes have been reported in the promoter region of *Hsd11B2* [12] and altered chromatin methylation linked to *O-linked*-N-*acetylglucosamine transferase* (*Ogt*) [27]. Such alterations may be mediated by sex-

specific changes in the placental epigenetic machinery [28]. In humans, maternal anxiety has been linked to greater placental methylation of *HSD11B2,* while maternal depression (but not anxiety) has been associated with increased placental methylation of *NR3C1* [29]. Recent research with mothers in a conflict-ridden region of the Democratic Republic of Congo has reported that higher levels of war trauma and chronic stress were associated with DNA methylation levels in multiple placental genes involved in HPA axis regulation, including: *CRH, CRHBP, NR3C1*, and *FKBP5* [30]. Stress-linked variation in DNA methylation was observed in placental tissue as well as maternal and umbilical cord blood. However, similar to Pena *et al.*, (2012), the effects at individual CpG sites differed between tissues. The majority of CpG sites identified were situated in transcription factor binding regions, and several were associated with offspring birth weight [30]. Similar effects of maternal war trauma and chronic stress have been observed with placental *BDNF* methylation [31]. The observation that many affected CpG sites bind transcription factors, along with observed associations with mRNA levels or offspring birth weight suggests that stress-linked variation in placental methylation may have functional consequences for offspring outcomes.

Maternal stress and epigenetic changes in offspring

Experimental animal models have demonstrated that early life stress can leave a mark on the offspring epigenome, with alterations reported in offspring exposed to prenatal stress [28], maternal separation [32], and low levels of maternal postnatal care [33]. In humans, variation in CpG methylation in umbilical cord blood at *NR3C1* has been associated with prenatal maternal anxiety [34] and depressive symptoms [29, 35]. Also in cord blood, CpG methylation at both *NR3C1* and *CRH* is associated

with maternal experiences of war trauma and chronic stress [30]. The *NR3C1* and *CRH* CpG sites identified in these studies are the same as those linked with pre-eclampsia in cord blood [36] or prenatal exposure to inter-partner violence in offspring venous blood [37]. In animal models, methylation at the *NR3C1* sites affects NGFI-A binding [38]. These may be sites for which DNA methylation is particularly sensitive to several stress-linked phenotypes. Prenatal maternal chronic stress and war trauma is associated with *BDNF* methylation in cord blood at birth [31] and prenatal depression has been associated with DNA methylation at the *BDNF* promoter region in buccal cells at two months of age [39]. BDNF plays an essential role in brain development and has been linked to psychiatric risk [40], thus suggesting that *BDNF* DNA methylation may be an important target for future investigation. Maternal cortisol and self-reported depressive and anxiety symptoms has also been associated with altered DNA methylation of the imprinted genes *IGF2* and *GNASXL* [41]. However, it is important to note that across both rodent and human studies, there are tissue specific associations of prenatal stress and DNA methylation. These differences may reflect the different physiologic functions of each tissue or differences in the epigenetic status of certain tissues at the time of exposure. Nonetheless, it seems clear that the maternal stress can impact both the placental and the fetal epigenomes to alter gene expression.

The programming of maternal mood by the placenta

While considerable data from both animal models and human studies support changes in the placenta and fetus in response to maternal stress, which may then contribute to the programming of neurodevelopmental changes in offspring, few studies have explored a placental origin for maternal mood disorders. Pituitary

prolactin and the placental lactogens are a group of evolutionarily and functionally related hormones important in pregnancy. Human placental lactogen (hPL) is produced by the placental syncytiotrophoblast and secreted into the maternal circulation, replacing prolactin as the main lactogenic hormone during pregnancy [42]. Numerous studies highlight a functional role for these hormones and their shared receptor (prolactin receptor; PRLR) in the onset of maternal behaviours in rodents and, in the case of prolactin and PRLR, also maternal neurogenesis [43-53]. In humans, these hormones may contribute to suppression of anxiety related behaviours during pregnancy [54]. Decreased serum prolactin levels have been reported in human mothers with postnatal depression [55, 56] while increased levels of prolactin have been associated with low anxiety scores during pregnancy [57]. Impaired human placental lactogen (hPL) production has also been associated with adverse infant outcomes such as fetal growth restriction [58, 59]. Thus the altered placental expression of *placental lactogen* could contribute to both maternal mood disorders and adverse outcomes (Figure 1).

Imprinted genes, fetal programming and maternal mood disorders.

Imprinted genes are expressed from one parental allele through epigenetic marking in the germline [60]. Imprinted genes are known to regulate fetal growth, placental development, adult behaviour and metabolism [61]. These multifunctional roles and the flexibility of epigenetic marks has led to the suggestion that imprinted genes may contribute to the fetal programming of adverse outcomes [62]. Numerous studies have reported the aberrant expression of imprinted genes in the placenta in relation to fetal growth restriction and low birth weight [63]. Altered expression of imprinted genes in the placenta has also been linked to infant neurobehavioral developmental

outcomes [64, 65]. Recently, imprinted genes have been highlighted as key regulators of the endocrine lineages that express placental hormones in rodents [66]. This newly defined function suggests that the aberrant expression of imprinted genes in the placenta could contribute to the mispriming of maternal behaviour, at least in rodents, by modulating exposure of the maternal brain to key placental hormones such as the placental lactogens. If the function of imprinted genes in regulating the endocrine lineage of the human placenta was conserved across species, aberrant imprinting could help to explain the co-occurrence of low birth weight with prenatal mood disorders, which has been reported in a number of studies [67-73]. Epigenetic changes in cord blood DNA at imprinted loci have been associated with depressed maternal mood during pregnancy [74] and with maternal stress [41, 75]. One study reported changes in DNA methylation in both cord blood DNA and placental DNA at an imprinted locus [76]. While it is generally presumed that such changes occur in response to prenatal adversity with the focus primarily concerning offspring outcomes, it is possible that such changes contribute to altered maternal mood by changing the endocrine function of the placenta (Figure 1). Consistent with this hypothesis, recent data identifies a significant association between both symptoms of prenatal depression and clinically diagnosed depression with placental expression of both an imprinted gene and also *placental lactogen*, a hormone predicted to be regulated by this gene (Jannsen *et al.*, under review). Determining cause and effect relationships in human studies of pregnancy is challenging. However, very recent work utilising a novel rodent model suggests that imprinted genes in the placenta can influence both the maternal neural transcriptome during pregnancy and maternal behaviour in the early postnatal period (Creeth *et al*, in prep), data that supports a causal relationship.

Summary and outlook

In summary, the placenta plays a key role in supporting a successful healthy pregnancy. The placenta can provide a record of prenatal adversity, including maternal stress. Changes in placental function, potentially driven by epigenetic processes, may impact neurodevelopmental outcomes for children and both mental and metabolic health into adulthood. Importantly, placental dysfunction may also contribute to maternal mood disorders, either during pregnancy and/or in the immediate postnatal period, by exposing the mother to abnormal levels of placental hormones. At present most women experiencing heightened levels of prenatal depression, stress and anxiety are undetected and untreated. The potential clinical implications of maternal prenatal mood on fetal and child neurodevelopment are substantial. Better emotional care for all pregnant women and the enhanced identification and support for women at particularly high risk of maternal mood disorders will help not only them but also their children, and potentially subsequent generations.

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Figure 1. The role of the placenta in prenatal stress

Prenatal stress can influence the placental and fetal transcriptomes and epigenomes, which may contribute to adverse outcomes for children. Dysfunctional placental signaling may also influence maternal mood during pregnancy and maternal behaviour in the postnatal period further contributing to adverse outcomes.