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Prenatal Stress and Neurodevelopment of the Child: Focus on the HPA Axis and Role of the Placenta

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Abstract
Recent human studies have shown that a wide variety of prenatal stressors, from anxiety and partner relationship problems, to natural disasters, increase the risk for a diverse range of adverse neurodevelopmental outcomes in the child. These include impaired cognitive development and behavioral problems, autism and schizophrenia. However, many questions remain about the underlying processes. Much of the research, based on animal studies, has focussed on the maternal HPA axis, with mixed results. Maternal stress or anxiety during pregnancy has been found to be weakly associated with raised maternal cortisol, if at all. The placenta may be a more promising programming vector, because it controls fetal exposure to the maternal environment. Animal studies indicate that prenatal stress can affect the activity of the placental barrier enzyme 11-βHSD2, which metabolises cortisol. We review the evidence for a similar mechanism in humans and how maternal stress may cause other changes in the placenta which affect fetal neurodevelopment.

Prenatal Stress or Anxiety Predicts Neurodevelopmental Outcomes in the Child

There is good evidence from several independent prospective studies that maternal stress, anxiety or depression during pregnancy is associated with several types of adverse neurodevelopmental outcomes in the child. Outcomes linked so far with prenatal stress or anxiety include autism, schizophrenia, emotional/behavioral problems, and reduced cognitive abilities especially with language development. Although we still lack conclusive causal evidence, the number of studies showing effects is now sizeable; furthermore, the consistency with the experimental animal evidence makes it a powerful model for translational research on how early stress exposure may have long-term effects. We briefly review key commonalities and discrepancies in the human studies and then consider the possible mechanisms.

The range of prenatal maternal stressors that predict child outcomes is quite wide and includes minor stresses such as daily hassles, more severe traumas, and symptoms and disorders of anxiety and depression (table 1). The type and degree of stress may differ for different outcomes. For example, the increased risk for schizophrenia was associated with the very severe stress of the death of a close relative during pregnancy [1]. There may be a dose-dependent effect where certain neurodevelopmen-

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Table 1. Examples of the types of stress exposure during pregnancy, and association with a range of neurodevelopmental outcomes

Type of exposure	Prenatal timing weeks	Outcome	Age	Magnitude	Citation
Perceived stress	10	ADHD (DSM-IV)	7–8 years	23% (v) †	Rodriguez and Bohlin [57]
Anxiety (state)	12–22	ADHD (CBCL, TRF)	8–9 years	22% (v)	Van den Bergh and Marcoen [13]
		sustained attention (CPT)	15 years	–[a]	Van den Bergh et al. [58]
Anxiety (trait)	–	depression (CDI)	15 years	–[b]	Van den Bergh et al. [59]
Perceived stress	15–38	behavioral problems (CBCL)	2 years	1.12–1.17(OR)	Gutteling et al. [60]
Daily hassles	15–17	mental development (BSID-MDI)	8 months	1.1 (OR)	Huizink et al. [7]
Pregnancy-related anxiety	15–38	temperament (ICQ) attention regulation (BSID)	2 years	1.39 (OR) 1.46 (OR)	Gutteling et al. [60]
Depression	–	attentiveness (NBAS)	neonate	–	Hernandez-Reif et al. [61]
Anxiety	32	emotional and behavioral problems (SDQ)	4 and 7 years	1.9–2.2 (OR)	O'Connor et al. [5, 6]
Life events stress	15–17	memory (TOMAL)	6 years	–	Gutteling et al. [30]
Life events stress (especially relationship problems)	–	cognitive development (BSID-MDI) fear reactivity (Lab-TAB)	1.5 years	17% (v) 10% (v)	Bergman et al. [12]
Death of a close relative	0–12	schizophrenia (ICD8/ICD10)	–	1.67 (OR)	Kashan et al. [1]
Hurricane	24–40	autism (DSM-III-R/DSM-IV)	–	10.12–43.05 (OR)	Kinney et al. [2]
Ice storm	4–24	cognitive developmental (BSID-MDI)	2 years	11.4% (v)	Laplante et al. [3]
	–	language production (MCDI)		17.3% (v)	
		IQ (WISC)	5.5 years	15.3 % (v)	Laplante et al. [4]
Chernobyl	14 →	depression/MDD (C-SSAGA-A: DSM-III-R) ADHD	14 years	2.48 (OR) 2.01 (OR)	Huizink et al. [62]
9/11	–	temperament (IBQ)	9 months	–	Brand et al. [63]

v = Amount of variance explained; OR = odds ratio; ADHD = attention deficit and hyperactivity disorder; DSM-R = diagnostic and statistical manual-revised; CBCL = child behavior checklist; TRF = teacher's report form; CPT = continuous performance task; CDI = child depression inventory; BSID = Bayley's scale of infant development; MDI = mental development index; ICQ = infant characteristics questionnaire; NBAS = Brazelton neonatal behavioral assessment scale, SDQ = strengths and difficulties questionnaire; TOMAL = test of memory and learning; Lab-TAB = laboratory temperament assessment battery; ICD = international classification of diseases; MCDI = MacArthur communicative development inventory; IQ = intelligence quotient; WPPSI = Wechsler preschool and primary scale of intelligence; MDD = major depressive disorder; C-SSAGA-A = child semistructured assessment of genetics of alcoholism; IBQ = infant behavior questionnaire; [a] in boys only; [b] in girls only; – = not reported.

tal outcomes are considered, as was shown in the case of a hurricane [2] and an ice storm [3, 4]. However, it is clear that effects on the child do not require very severe maternal distress. For example, the ALSPAC studies [5, 6] examined normative variation within a population sample in Bristol, England. The rate of emotional and behavioral problems in the children increased from about 5 to 10% in those mothers who scored in the top 15% on a measure of prenatal anxiety symptoms. Similarly, other studies predicted neurodevelopmental outcomes from daily hassles or pregnancy related anxiety [7]. Only one study found that minor stress was actually beneficial, although there was a trend for this in a second [4]. DiPietro et al. [8] suggested that mild-to-moderate levels of maternal psychological distress may enhance fetal maturation in healthy populations. This is a point that needs more investigation. Results reported so far are from Europe and North America. None are from developing countries or countries at war, where one might predict that the stressors and effects would be even more marked.

The specific impact of fetal exposure, and the phenomenon of fetal programming, is well established in animal models. These have the benefit of experimentally controlling for post-natal influences by, for example, cross-fostering [9, 10] or nursery rearing in non-human primates [11]. Human studies are obviously less able to

rule out the postnatal confounds but, insofar as that can be done by statistically modelling, the results also imply a particular effect of prenatal stress or anxiety. Thus, several of the human studies have shown that the association between prenatal maternal stress and adverse child outcome is still apparent after controlling for postnatal anxiety, depression or life events [5, 6, 12]. Alternative explanations, such as genetics, have been more difficult to control for as none of the human studies have included genetics in their research design. Nonetheless, a simple genetic transmission account does not seem satisfactory because it would not explain why prenatal stress/anxiety predicted child outcomes even after postnatal measures of maternal stress/anxiety were also included as predictors. Further support for fetal programming comes from natural experiments of somewhat better timed exposures such as an ice storm [3, 4] or hurricane [2], although even in those cases there are confounds between timing, duration, and severity of exposure.

Many studies find that prenatal stress has clinically significant effects on the child with, for example, a doubling of risk of behavioral/emotional symptoms [5, 6] or accounting for 10–20% of the variance [3, 12, 13] (table 1). Nevertheless, most children are not affected, and those that are, are not affected in the same way [12]. Thus, Bergman et al. [12] found that prenatal stress was associated with both lower cognitive ability and fear reactivity, but the minimal correlation between these infant outcomes meant that those affected in one way were not also affected in the other. These kinds of findings suggest a genotype-environment interplay, as has been shown with postnatal effects of life events on later depression [14]. Thus, in those with a particular genetic vulnerability the prenatal stress may result in one specific outcome, rather than another. This is an area which has yet to be studied, although there are a range of possible genes of interest, including, for example, that for the glucocorticoid receptor.

It may be that the gestational age of exposure is associated with greater vulnerability to a particular specific outcome, because different brain regions develop at different stages. This has been little studied, but there are some intriguing findings. The increased risk for schizophrenia was associated with exposure in the first trimester [1], rather than later. However, with autism, prevalence increased especially for cohorts exposed near the middle or end of gestation [2]. On the other hand, the data are mixed about the role of timing in relation to more common behavioral/emotional problems, with some suggesting a greater effect of late pregnancy [5, 6], whereas others suggest a stronger effect earlier in gestation [13].

There are many conceptual and methodological issues concerning the effects of prenatal stress/anxiety that remain unexamined in the human literature. Unanswered questions include the sex-dependent nature of effects, which has been widely shown in rodents [15], and the possibly moderating role of postnatal rearing. Moreover, there is little or no work translating the many accounts from the animal literature linking prenatal stress to physiological, hormonal, cardiovascular and immunological outcomes, and human studies have not yet demonstrated that there are protective effects on the infant of reducing stress/anxiety in pregnancy.

Possible Mediating Mechanisms

Role of the Maternal HPA Axis

The potentially widespread role for exposure to increased cortisol in human fetal brain development is strengthened by a microarray analysis that showed that increased cortisol exposure affects the expression of over a thousand genes in fetal brain cells [16]. The hypothesis that stress causes an increase in prenatal maternal cortisol (corticosterone in rodents), which in turn has a range of long-term effects on fetal development, is cited frequently in the programming literature. It has support from rodent and primate studies, in which the effects of prenatal stress are mimicked by administering exogenous glucocorticoids or ACTH, and abolished by adrenalectomy [17, 18]. Several animal studies have also shown an effect of prenatal stress in reprogramming the function of the HPA axis in the offspring, often resulting in a more prolonged and greater cortisol/corticosterone response to stressors later in development [19, 20].

The application of this model to humans has attracted considerable attention. One set of studies has assessed the link between maternal stress/mood symptoms in pregnancy and cortisol, a readily observed index of HPA activity. If the above model were correct, then we would find elevated levels of cortisol in anxious, depressed, and/or stressed mothers. Evidence for this is weak. Evans et al. [21] reported increased cortisol in response to a computer-based laboratory assessment only in a small group (n = 9) of women with co-morbid anxiety and depression, with no significant elevation in cortisol in those with anxiety or depression alone. Diego et al. [22] reported modest association between measures of psychological distress and a single measure of urinary cortisol in a cross-sectional study of women between 16 and 29 weeks of gestation. In our study of women awaiting amniocen-

tesis [23], we found no relationship between cortisol and trait anxiety and only a modest one with State anxiety (r = 0.18), despite high levels of State anxiety; there was no significant association between State anxiety and plasma cortisol in women for whom samples were taken after 17 weeks of gestation. The lack of association in that study may be attributed to sampling cortisol only in the morning.

Few studies have assessed diurnal variation in cortisol in pregnancy in relation to maternal stress and mood symptoms. In their study of 8 a.m. and 8 p.m. cortisol levels, Obel et al. [24] reported higher evening cortisol in late pregnancy (~30 weeks of gestation) in women who had experienced a major life event or had high levels of pregnancy-specific anxiety. Another recent study [25] found that trait anxiety was associated with a flattened afternoon decline in cortisol, which is also consistent with elevated afternoon levels.

One factor that may confound the links between maternal prenatal emotional state and cortisol is a dampening of the HPA axis responsiveness in late pregnancy. This has been demonstrated in response to a simple physical stress, the cold hand test [26], and CRH challenge [27]. Maternal cortisol increases to term under the drive of placental CRH, and the maternal adrenal cortex, already producing high levels of cortisol, may have a reduced capacity to respond to psychosocial stress or the maternal emotional state. This could be especially true in the morning when basal levels are already high [28]. It is not known at what gestational age the maternal HPA axis starts to lose its responsiveness, or how much individual variability there is in this respect. It is notable that some studies have shown that the greatest effect of prenatal stress for child development is in late pregnancy [5, 6].

It is significant that each of the above studies employed a different measurement strategy for assessing cortisol. That, along with greater attention to gestational age, is clearly a matter that requires further attention. Several groups are currently examining the links between cortisol and mood and stress in pregnancy, so there should be more definitive evidence concerning this in the near future.

However, while the link between prenatal stress/distress symptoms and maternal HPA functioning may be weak, the evidence that maternal HPA axis functioning mediates the association between prenatal stress/anxiety and child outcomes is even weaker. Thus, the few studies that measured both maternal cortisol and emotional state failed to find any evidence that maternal cortisol mediated the effects of stress or anxiety on child outcomes [29, 30]. In both studies, the authors reported that maternal cortisol predicted outcomes in the infant independently from prenatal stress/mood symptoms.

Fetal Programming and the Role of the Placenta

The placenta plays a crucial role in moderating fetal exposure to maternal factors [31], including cortisol and in preparing the fetus for the environment in which it is going to find itself [32]. Accordingly, understanding the impact of prenatal stress/anxiety and maternal HPA axis functioning on child outcomes requires a careful consideration of the role of the placenta, which has so far been largely absent. However, that is starting to change.

Placental 11β-Hydroxy Steroid Dehydrogenase Type II in Animal Models

The developing fetus is normally protected from the high levels of circulating maternal cortisol by the placental barrier enzyme 11β-hydroxy steroid dehydrogenase Type II (11β-HSD2), which converts cortisol to the inactive cortisone [33]. Localised to the syncytiotrophoblast, the placental interface with the maternal circulation, this enzyme normally excludes the large majority of maternal cortisol from the fetus [34]. This is supported by the finding that fetal blood has a 13-fold lower cortisol concentration than maternal blood [35].

Several animal studies support downregulation of placental 11β-HSD2, and thus a greater fetal exposure to maternal cortisol/corticosterone, as a possible component of programming mechanisms. For example, pharmacological blockage of 11β-HSD2 by carbenoxolone during pregnancy caused an upregulation of glucocorticoid receptors in basolateral, central and medial nuclei of the amygdala in adult offspring, together with increased basal corticosterone [36]. A more direct targeting of enzyme activity has been achieved by a pregnant 11β-HSD2 mouse knock-out model, which affected the fetus/placenta rather than the mother [36]. The adult offspring in this model were more anxious than controls; their adrenals were also smaller, but basal and stress-induced corticosterone levels were unaffected [36].

Maternal diet may also affect 11β-HSD2 activity. Reducing protein intake by 50% in pregnant rats decreased placental 11β-HSD2 activity by 33% [37]; there was also a reduction in birth weight and increased blood pressure at 7 weeks in both male and female offspring. These effects were abolished by blocking maternal corticosterone production by metyrapone [38], and restoring corticosterone

to physiological levels caused the re-emergence of the low-protein phenotype in females only, perhaps suggestive of a sexually dimorphic sensitivity to this manipulation. However, the role of fetal sex, which controls the sex of the placenta, remains largely unexplored.

Prenatal stress has also been shown to influence placental 11β-HSD2 activity in rats. In one study, placental 11β-HSD2 activity was unchanged relative to controls in the chronic stress condition, but markedly increased in the acute stress condition [39]. However, when the chronically stressed animals were exposed to an acute stressor this potentially protective upregulation of 11β-HSD2 activity was absent [39]. In contrast, another study has found markedly reduced both placental 11β-HSD2 mRNA expression and activity in rats subjected to stress in the last week of pregnancy [40]. The fetuses of these pregnancies were smaller and, as in the knock out mice, had reduced adrenal size. Circulating fetal corticosterone levels were similar to controls, despite lower fetal ACTH [40]. Further, a recent study has shown that Wistar rats selectively bred for high anxiety and exposed to prenatal stress, had significantly lower placental 11β-HSD2 activity than prenatally stressed low anxiety animals [41]. This finding suggests that the response of placental 11β-HSD2 activity to stress may also depend on the genetic vulnerability of the mother.

In summary, rodent studies have shown that placental 11β-HSD2 activity is sensitive to a range of manipulations, including maternal prenatal stress. Reducing enzyme activity can alter the neuroendocrine, structural and behavioral phenotype of the offspring.

11β-HSD2 in the Human Placenta

In general, human 11β-HSD2 mRNA increases to term and remains relatively stable in late gestation [42–45]. However, reduced placental 11β-HSD2 activity has been found in a range of pathological conditions, which may involve fetal exposure to elevated cortisol. These include pre-eclampsia [46], maternal asthma [47], preterm birth [48] and intrauterine growth restriction [34, 49]. Lower enzyme activity has also been associated with poorer clinical outcome, and symptoms of adrenal insufficiency, in extremely low birthweight neonates [48]. Additionally a congenital deficiency of 11β-HSD2 has been reported to result in reduced birthweight and increased susceptibility to hypertension in later life [50].

An interesting feature of human placental 11β-HSD2 activity is its apparent sexual dimorphism. Female fetuses from normal healthy pregnancies have been reported to have higher enzyme activity [47]. In response to maternal asthma, female fetuses demonstrated decreased placental enzyme activity than males, whose levels remained unchanged. Despite these differences in activity levels, cortisol concentrations in cord blood were similar in males and females [47]. This is in agreement with work by Kajantie et al. [48, 51] who also failed to find an association between enzyme activity and cortisol concentration in cord blood.

These findings suggest that human placental 11β-HSD2 activity may be sensitive to certain medical disorders, and that reduction in its activity may affect fetal development. It is thus plausible that human placental 11β-HSD2 activity may also be affected by the maternal emotional state and affect fetal neurodevelopment.

Recent results from our laboratory suggest that maternal anxiety may indeed increase the permeability of the placenta to cortisol [52]. We tested this hypothesis by measuring the correlation between maternal plasma and amniotic fluid cortisol in relation to maternal anxiety. We found a strong positive correlation ($r(62) = 0.59$, $p < 0.001$) between maternal plasma and fetal amniotic cortisol in women with the highest quartile state anxiety; no relationship was found in women with the lowest levels of anxiety ($r(60) = 0.05$, $p = NS$). Similar differences were found with trait anxiety.

Despite this stronger correlation in women with highest anxiety, there was no difference in the absolute levels of amniotic fluid cortisol between groups of anxious women. This possibly surprising finding is similar to that of Kajantie et al. [48, 51] who found no association between cord blood cortisol and placental 11β-HSD2 activity, and that of Mairesse et al. [40] who found no difference in cord blood corticosterone associated with prenatal stress-induced reduction of placental 11β-HSD2 activity in the rat.

Thus, prenatal stress may cause a downregulation of placental 11β-HSD2 activity, as shown by Mairesse et al. [40] in rats and suggested by Glover et al. [52] in humans. This may allow more cortisol to cross from the maternal to fetal blood and cause a decrease of fetal ACTH and impede fetal adrenal growth and maturation. A smaller, or less mature, fetal adrenal development has been shown by Holmes et al. [36] using a knockout mouse model and suggested by Kajantie et al. [48] in extremely low birth weight neonates. Thus, while the maternal contribution to circulating fetal cortisol may be increased, the fetal contribution may be decreased. This could explain the finding of unchanged cortisol in fetal blood despite de-

creased placental 11β-HSD2 activity [48, 51, 52]. However, the net effect may vary at different gestational ages. It is important to note that the study of cord blood or amniotic fluid cortisol is a very crude index of fetal exposure to cortisol in specific tissues, although it is the best currently available. Studies of fetal levels have been conducted during brief time windows, either early in gestation at time of amniocentesis, or at term.

For this to help explain the mediating mechanism between prenatal stress and child neurodevelopmental outcome one would need to establish that the proposed increases in exposure to maternal cortisol, or changes in the function of the fetal HPA axis, have long-term effects on the function of the HPA axis and behavior of the child. Specifically, it remains to be seen if the results of Holmes et al. [36] using the knock out mouse model, which showed increased anxiety in the offspring, translate to human development.

Other Placental Factors

Reduction in 11β-HSD2 activity may affect other aspects of placental structure and function, which in turn affect fetal development. The 11β-HSD2 knock-out mice demonstrated significant placental pathology [36]. These animals were found to have a smaller placenta with significantly reduced capillary surface area, volume and density, and a 53% decrease in glucose transport [53].

The emotional state of the mother may also alter the function of the placenta in other ways, independent of cortisol. There is some evidence for effects on uterine blood supply and nutrient transport, which could affect the neurodevelopment of the fetus. For example, some studies have shown that maternal prenatal anxiety in late pregnancy is associated with reduced blood flow in umbilical or uterine arteries [54, 55], and altered fetal cerebral circulation [55], although others have not found this earlier in gestation [e.g. 56]. A direct effect of maternal stress on placental nutrient transport has been observed in the rat [40].

Conclusions

The evidence for an association between maternal stress, depression or anxiety in pregnancy and an adverse neurodevelopmental outcome for the child is now substantial. The search for the underlying mechanisms is much less advanced. Here, we have discussed the current evidence for the possible role of the maternal HPA axis and changes in the placenta, including activity of 11β-HSD2. These are promising and largely undeveloped areas for future study. If, for example, there is a down-regulation of placental 11β-HSD2, then work is needed to understand these processes. And it is almost certain that other systems are also involved. We know little of how the maternal sympathetic system responds to stress and anxiety during pregnancy. We need to know more about what types of stress are most detrimental, the gestational ages of sensitivity, gene-environment interactions, and the nature of the mediating mechanisms. This will help us to target appropriate interventions to reduce maternal emotional distress during pregnancy and improve the neurodevelopmental outcome for the child.

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