Review

Prenatal stress and the programming of the HPA axis

Vivette Glovera,*, T.G. O’Connorb, Kieran O’Donnell

a Institute of Reproductive and Developmental Biology, Imperial College London, Hammersmith Campus, Du Cane Road, London W12 0NN, United Kingdom
b Department of Psychiatry, University of Rochester Medical Center, 300 Crittenden Blvd, Rochester, NY 14642, USA

ARTICLE INFO

Keywords:
Prenatal stress
Programming
HPA axis
Cortisol

ABSTRACT

There are several independent prospective studies showing that a wide variety of forms of prenatal stress can have long-term effects on the behavioural and cognitive outcome for the child. Animal studies have shown that prenatal stress, as well as affecting behaviour, can also reprogram the function of the HPA axis in the offspring. However, the effects on the HPA axis are very variable depending on the nature of the stress, its timing in gestation, the genetic strain of the animal, the sex and age of the offspring and whether basal or stimulated HPA axis responses are studied. There are also several recent studies showing long-term effects of prenatal stress on basal cortisol levels, or cortisol responses to stress, in humans. The designs of these studies differ considerably, many are small, and the effects on outcome are also varied. There is little evidence, so far, that altered function of the HPA axis in the child mediates the behavioural or cognitive alterations observed to be associated with prenatal stress.

1. Introduction

Fetal programming describes the process whereby the development of a fetus is altered because of changes in its immediate environment. The effects can vary at different sensitive periods and can shape the structure and function of the brain and peripheral organ systems, with long-term or permanent effects on subsequent child and adult physiology, behaviour and health. Many studies in animals have shown that prenatal stress can have such programming effects on both neurodevelopment and the function of the hypothalamic-pituitary-adrenal (HPA) axis. In humans also there is an increasing number of prospective studies showing that various forms of prenatal stress are associated with a range of later behavioural and cognitive alterations in the child, and some limited evidence for associations with alterations in the HPA axis. It has been suggested that these fetal adaptations may have been of evolutionary value, in order to confer characteristics in the offspring that were adaptive in the context of the stressful environments in which they were developing and presumably would subsequently live (Viltart and Vanbesien-Mailliot, 2007). However, for humans in the modern world, there may often be a mismatch between characteristics of the early environment during development and subsequent environment during later stages of life. This, in turn, may result in maladaptive properties in the context of a different environment, with direct implications for increasing vulnerability for pathophysiological health outcomes (Gluckman et al., 2005).

2. Prenatal stress and programming the HPA axis-animal studies

It has been known for over five decades from animal studies that maternal stress during pregnancy can have a range of long-term effect on the offspring (Weinstock, 2001). These include...
learning deficits, more anxious behaviour, reduced attention, altered immune function, as well as altered cardiovascular responses to stress (Igosheva et al., 2007) and glucose intolerance (Lesage et al., 2004). These effects are clearly different in male and female offspring (Darnaudery and Maccari, 2008). With animals it is possible to cross-foster the prenatally stressed pups to control mothers after birth, or nursery rear in the case of monkeys (Schneider et al., 2002), and thus establish that the origin of these effects are prenatal rather than postnatal.

In the animal work much research has shown how prenatal stress can alter the function of the HPA axis in the offspring. These effects have been found in a range of species. Variation in the responsiveness of the HPA axis plays an adaptive role, and it is plausible that the prenatal reprogramming has evolutionary significance and is part of the predictive adaptive response (Love and Williams, 2008). Weinstock (2005, 2008) has reviewed this comprehensively for the rodent. She discusses the variability in results and the many parameters that may affect this: the nature and the timing of the stress exposure during pregnancy, the age of testing of the offspring, the genetic strain of rat or mouse used, the sex of the offspring, the time of day of testing the offspring HPA axis, and whether basal or stress-induced corticosterone levels were measured. Despite the variability many of the studies have found that prenatal stress did cause both an increase in basal levels and an increase in corticosterone response in the offspring. However, several others showed a decrease in the corticosterone stress response, and others still showed no change. She concludes that to have an effect the prenatal stress needs to be of sufficient intensity, be administered daily in the last week of gestation, and that female offspring are more sensitive than males. Different rat strains appear to respond in different ways. There has been little study of whether the changes in the function of the HPA axis underlie the behavioural changes induced by prenatal stress, although both have been shown to occur in the same model (Abe et al., 2009).

Animal studies have also identified brain structures altered by prenatal stress. For example, Coe et al. (2003), studying non-human primates, have shown that exposure to unpredictable noise, either early or late in pregnancy, resulted in reduced volume of the hippocampus in the offspring. This is a part of the brain that is important both for memory and the control of the HPA axis. In rodents prenatal stress has been shown to reduce the number of both glucocorticoid and mineralocorticoid receptors in the hippocampus (Henry et al., 1994). This could explain why the corticosterone response to a new stressor is both increased and prolonged: there is less feedback inhibition via corticosterone acting on its receptors.

Another finding in the animal research is that programming effects can last until the grandchild generation. In one experiment in which the pregnant female was treated with dexamethasone, reduced birthweight and glucose intolerance were transmitted to the second generation by both the first generation female and male offspring (Drake et al., 2005). This suggests the possibility that epigenetic changes can affect both oocyte and sperm.

Rodent experiments have shown that the effects of prenatal stress may be moderated and even reversed by positive postnatal rearing (Maccari et al., 1995). This indicates that although there can be persisting effects of prenatal stress, it is not inevitable, and that the period of sensitivity or programming extends beyond the prenatal period. Meaney and his group have shown how variation in the nature of maternal care can have long lasting effects on both the behaviour and function of the HPA axis of the offspring. Offspring of mothers showing more maternal care are both less anxious and have a less pronounced corticosterone response to a new stressor (Liu et al., 1997). This group is also uncovering some of the epigenetic changes in the brain, altered methylation in the promoter region of the glucocorticoid receptor in the hippocampus, which underlie this (Weaver et al., 2004).

Although many of the same mechanisms may well occur in humans we need to be aware that there are obviously many physiological and other differences between humans and animal models. For example, rodents are born at a much less developed stage than humans. There are differences in the nature and regulation of maternal–placental–fetal neuroendocrine processes underlying development and birth across mammals, even between non-human primates and humans (Smith and Nicholson, 2007). Nevertheless, and despite the caveats about the animal findings cited above, animal experiments have provided strong evidence that prenatal stress can have long lasting and varied effects on the offspring, including the function of the HPA axis.

3. Prenatal stress: human studies

An immediate link between prenatal maternal mood and fetal behaviour is well established from 27 to 28 weeks of pregnancy onwards (Van Den Bergh et al., 2005). The mechanisms underlying this link are not known.

In the last 10 years several independent prospective studies have examined the longer lasting effects of prenatal stress, anxiety or depression on the behavioural, emotional and cognitive outcomes during childhood. Even though these studies used a wide range of different methods, both for measuring prenatal stress or anxiety, and for assessing the child, they all support a link between prenatal mood and changes in outcome that suggest changes in neurodevelopment (Van Den Bergh et al., 2005). Different studies have examined the child at different ages, from newborn to adolescence. The newborn studies show effects that must be independent of postnatal experience; those with adolescents show the persistence of impairment (Van Den Bergh et al., 2005). In several studies these findings have been shown to be independent of potential confounding factors such as smoking or poverty, and also maternal postnatal depression and anxiety. This adds support to the effect being due to the prenatal environment, rather than genetic transmission—though no evidence directly testing the genetic mediation hypothesis has yet been presented. The studies are mainly from European and North America; none are from developing countries or countries at war, where one might predict that the effects would be even more marked.

A wide range of different outcomes have been found to be affected by prenatal stress. The most consistent adverse outcome is in symptoms of attention deficit hyperactivity disorder (ADHD) (Rodriguez and Bohlin, 2005; Van Den Bergh and Marcoen, 2004) but an increase in anxiety is also often observed (Van Den Bergh and Marcoen, 2004). Other studies have shown an effect of prenatal stress or anxiety on the cognitive development of the child, as assessed by scores on the Bayley Mental developmental Index (MDI) (Huizink et al., 2003) or language development (Laplante et al., 2004).

A recent study has shown that prenatal maternal stress, due to exposure to a Canadian Ice storm, during the fetal period of fingerprint development, in the second trimester, resulted in greater dermatoglyphic asymmetry in their children, especially in the face of greater maternal distress (King et al., 2009). This asymmetric pattern is also found in subjects with schizophrenia. The finding is of particular interest as the fingerprint pattern develops at the same time as the hippocampus, and may be a physical marker for altered development of this region, which is important in both cognition, and feedback control of the function of the HPA axis (Cottrell and Seckl, 2009).

A recent MRI study has shown that high pregnancy-specific anxiety in mid-gestation, but not later, is associated with...
decreased gray matter in children in specific brain areas, including the prefrontal cortex, which are also involved in both cognition and stress hormone regulation (Buss et al., in press). It has also been shown that women whose mothers had been exposed to a severe life event during pregnancy had longer reaction times in a working memory test, after cortisol administration (Entringer et al., 2009a). This may also reflect an impairment in prefrontal cortical functioning. These three studies provide indirect evidence that prenatal stress can affect brain development in a way that may also affect regulation of the HPA axis.

More needs to be understood about the periods of gestation which are most sensitive for all the effects described here. Different studies have found different periods of vulnerability. In the study of O'Connor et al. (2002) anxiety was measured at 18 and 32 weeks gestation, and the associations with behavioural/emotional problems in the child were stronger with the latter time point (O'Connor et al., 2002). However, in the study showing that a life event, the death of a relative, was associated with an increased risk of schizophrenia, the risk was confined to the first trimester (Khashan et al., 2008). It is likely that the gestational age of vulnerability is different for different outcomes. Brain systems underlying different aspects of cognition or behaviour mature at different stages. We still do not know why some children are affected but not others. Possible explanations include specific genetic vulnerabilities in both mother and child, timing of the prenatal exposures, and the nature of the postnatal care.

These studies show that the nature of the risk can be quite varied, and that many neurodevelopmental effects can be observed with non-clinical levels of anxiety or stress (O'Connor et al., 2002). There is evidence from one study that the effect on the child derives more from prenatal anxiety than depression (O'Connor et al., 2002); another study found that the life events most closely linked with both low scores on the Bayley Mental Developmental Index and increased fear reactivity were “separation/divorce” and “cruelty by the partner” (Bergman et al., 2007). Nevertheless, as noted, the nature of the “risk phenotype” is unclear and most studies have focused on non-diagnostic levels of anxiety and depression or life events.

In contrast to most of the findings, two studies report enhanced development following exposure to prenatal stress. In a cohort of financially and stable middle to upper class sample of women, there was a small but significant positive association between prenatal stress and both the mental and physical development of the child (Dipietro et al., 2006). A similar trend was observed by Laplante et al. (2008) on child IQ. The authors suggest that a small to moderate amount of prenatal stress may actually promote an accelerated rate of brain development, although this remains to be confirmed.

4. Prenatal stress and the function of the HPA axis-humans

Our review of the literature revealed 11 studies published in the last 10 years, that have examined in humans the association between prenatal maternal mood or stress and the function of the HPA axis (see Table 1). They all have different designs and are mostly small in terms of their sample sizes. Most are from Europe, one is from Canada, one from Australia, and three from the USA. The type of prenatal stress studied varies from self-rated anxiety (O'Connor et al., 2005; Van Den Bergh et al., 2008), anxiety diagnosed by a clinical interview (Grant et al., 2009), daily hassles and fear of bearing a handicapped child (Gutteling et al., 2004, 2005), depression (Breznau et al., 2008; Oberlander et al., 2008), to severe life events (Entringer et al., 2009b) or experience of an acute disaster, Chernobyl (Huizink et al., 2008) or 9/11 (Yehuda et al., 2005). The method of measuring outcome also varies from diurnal saliva cortisol to single basal samples, or saliva or plasma cortisol and ACTH response to a stressor. The age at which the offspring was assessed varied from 1 week to young adults.

All the studies found that there were associations between prenatal stress and some aspect of HPA axis function in the child. However, perhaps unsurprisingly, the nature of this association varied and we do not yet have any solid replications. As in the case of the studies of cognitive and behavioural outcomes, the studies on the effects on the HPA axis are not specific to one type of stress or anxiety. Further confounding the HPA axis findings is that different forms of anxiety – generalized anxiety, panic, specific phobia, and posttraumatic stress – may involve quite different, or even opposite, physiological processes. Whereas anxiety in general is associated with raised cortisol, PTSD is associated with reduced cortisol (Tsigos and Chrousos, 2002). It is notable that whereas prenatal maternal anxiety and depression have in general been found to be associated with raised cortisol in the child (Table 1), the infants of mothers exposed to the trauma of 9/11, who themselves developed symptoms of PTSD, had lower cortisol levels (Yehuda et al., 2005). The fact that the effect was particularly apparent in the children of mothers exposed in the third, rather than earlier trimesters, supports the possibility of fetal programming, rather than a shared genetic vulnerability.

O'Connor et al. (2005) and Van Den Bergh et al. (2008) both examined diurnal cortisol levels and found increased basal levels in the child associated with prenatal anxiety. O'Connor et al. (2005) found raised morning and afternoon levels, whereas Van Den Bergh et al. (2008) found raised evening levels and a flatter curve. Gutteling et al. (2004) studying children of mothers reporting more daily hassles and Huizink et al. (2008) studying children born to mothers exposed to Chernobyl, had raised baseline cortisol levels. Gutteling et al. (2005) also showed that prenatal fear of bearing a handicapped child was associated with raised diurnal cortisol in the 4-year-old child. Entringer et al. (2009b) carried out the most comprehensive study to date. They retrospectively identified pregnant women who had been exposed to a severe life event such as the death of someone close or had experienced severe relationship problems, and recruited the young adult offspring of these mothers for their study (prenatal stress group) and a matched non-exposed comparison group. They examined both the diurnal cortisol pattern and the response to the Trier Social Stress Test and to a pharmacological challenge of ACTH\textsubscript{1–24} stimulation in the young adult offspring. They found no differences in the diurnal patterns. However, the exposed group had a lower plasma cortisol pre-stress test level and, perhaps relatedly, a lower cortisol but higher ACTH stress response. Exposed subjects also showed significantly lower cortisol levels during the ACTH challenge. A recent study by Grant et al. (2009) found that prenatal anxiety was associated with an increased cortisol after the stressor of the “still face” procedure in 7-month-old infants. Interestingly they also found that this was moderated by the sensitivity of the mother infant interaction. This was a small study, with quite complex analyses, and certainly warrants replication.

Our group is currently carrying out the largest study in this area to date (O'Donnell, O'Connor and Glover in preparation). We are examining the diurnal cortisol pattern in approximately 1000 15 year olds from the ALS PAC cohort for whom we have prospective maternal self-report data on depression and anxiety at both 18 and 32 weeks gestation. We will later be able to investigate any association with current psychopathology, and also with different genetic vulnerabilities such as polymorphisms in the glucocorticoid receptor gene.

Van Den Bergh et al. (2008) have provided the only evidence that an altered cortisol diurnal profile associated with prenatal anxiety was also associated with an altered behavioural phenotype, depressive symptoms in adolescent girls. It is unlikely that alterations in the function of the HPA axis underlie all, or even
Table 1
Prenatal stress and effects on the HPA axis of the child.

<table>
<thead>
<tr>
<th>Country</th>
<th>Type of stress</th>
<th>N</th>
<th>Age tested</th>
<th>Outcome measure</th>
<th>Results</th>
<th>Comments</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germany</td>
<td>Severe prenatal life events</td>
<td>N=31 prenatal stress N=30 controls</td>
<td>Young adults</td>
<td>Venous cortisol after ACTH1–24 challenge and TSST Diurnal saliva cortisol</td>
<td>Prenatal stress predicted lower cortisol pre-TSST and lower cortisol but higher ACTH response to TSST. Cortisol response to ACTH was lower in PS subjects. No difference in diurnal levels subjects.</td>
<td>Mainly females studied</td>
<td>Entringer et al. (2009b)</td>
</tr>
<tr>
<td>Finland</td>
<td>Effect of Chernobyl</td>
<td>N=121 twins exposed N=157 not exposed</td>
<td>14 years</td>
<td>Baseline salivas</td>
<td>Cortisol raised in those exposed from second trimester onwards</td>
<td>Stress not measured directly</td>
<td>Huizink et al. (2008)</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>Self-rated maternal anxiety at 12–22, 23–32, 32–40 weeks gestation</td>
<td>N=58</td>
<td>14–15 years</td>
<td>Diurnal saliva cortisol</td>
<td>Maternal trait anxiety at 12–22 weeks associated with flattened diurnal profile (lower in morning/higher in evening). This profile was associated with depressive symptoms in girls</td>
<td></td>
<td>Van Den Bergh et al. (2008)</td>
</tr>
<tr>
<td>UK</td>
<td>Self-rated anxiety 18 and 32 weeks gestation</td>
<td>N=74</td>
<td>10 years</td>
<td>Diurnal salivas</td>
<td>Basal waking and afternoon cortisol raised in children of mothers in top 15% anxiety at 32 weeks Maternal daily hassles and fear of bearing a handicapped child predicted raised cortisol in the child</td>
<td>Co-varied alcohol, smoking, etc. and postnatal anxiety No cortisol response to the inoculation</td>
<td>O'Connor et al. (2005)</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>Daily hassles, pregnancy related anxiety, perceived stress at 16 weeks gestation</td>
<td>N=24</td>
<td>4–6 years</td>
<td>Saliva cortisol pre- and post-inoculation</td>
<td>Maternal trait anxiety at 12–22 weeks associated with flattened diurnal profile (lower in morning/higher in evening). This profile was associated with depressive symptoms in girls</td>
<td></td>
<td>Gutteling et al. (2004)</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>Range of prenatal stress indices</td>
<td>N=29</td>
<td>4 years</td>
<td>Diurnal salivas on first day of school and weekend</td>
<td>Prenatal fear of bearing a handicapped child predicted raised diurnal cortisol Maternal prenatal cortisol also showed an association with child cortisol</td>
<td></td>
<td>Gutteling et al. (2005)</td>
</tr>
<tr>
<td>USA</td>
<td>Exposure to 9/11</td>
<td>N=38</td>
<td>9 months</td>
<td>Saliva cortisol awakening and at bedtime</td>
<td>Low infant cortisol in mothers with PTSD. Effect greatest with exposure in the third trimester</td>
<td></td>
<td>Yehuda et al. (2005)</td>
</tr>
<tr>
<td>Australia</td>
<td>Anxiety (diagnostic clinical interview)</td>
<td>N=104</td>
<td>7 months</td>
<td>Saliva cortisol pre- and post-still face procedure</td>
<td>Prenatal anxiety group showed higher cortisol at 40 min post-procedure</td>
<td>Shows moderating effect of caregiving</td>
<td>Grant et al. (2009)</td>
</tr>
<tr>
<td>USA</td>
<td>Depression and anxiety (Lifetime diagnostic interview)</td>
<td>N=189</td>
<td>6 months</td>
<td>Saliva cortisol at baseline and following stress tests</td>
<td>Maternal perinatal depression associated with raised baseline cortisol; comorbid anxiety associated with increased reactivity. No clear distinction of prenatal as opposed to postnatal effects</td>
<td>Maternal medication during pregnancy offset effects of perinatal mood on infant cortisol</td>
<td>Brennan et al. (2008)</td>
</tr>
<tr>
<td>Canada</td>
<td>Depression</td>
<td>N=82 (33 depressed and treated with SSRI, 13 depressed untreated, and 36 non-depressed)</td>
<td>3 months</td>
<td>Saliva cortisol pre- and post-infant stress test</td>
<td>Prenatal depressed mood predicted methylation status of the promoter region of GR (NR3C1) in the newborn. This methylation status predicted infant cortisol stress response</td>
<td>No direct analysis of relationship between prenatal mood and cortisol stress reactivity</td>
<td>Oberlander et al. (2008)</td>
</tr>
<tr>
<td>USA</td>
<td>Depression 26 weeks gestational age</td>
<td>N=71</td>
<td>1 week</td>
<td>Urine cortisol</td>
<td>Perinatal depression associated with raised newborn cortisol</td>
<td></td>
<td>Diego et al. (2004)</td>
</tr>
</tbody>
</table>
most, of the neurodevelopmental outcomes found to be affected by prenatal stress, but more studies of this type are needed. It is important to note that studies have often found little correlation between various psychological measures and cortisol levels (e.g., Teixeira et al., 2005).

Oberlander et al. (2008) have conducted the only prospective prenatal study exploring a possible underlying epigenetic mechanism. They showed that prenatal depressed mood predicted the methylation status of the promoter region of the glucocorticoid receptor (NR3C1) in lymphocytes in the newborn. This methylation status in turn predicted infant cortisol stress response. The finding is indeed intriguing. However, there are a number of conceptual and methodological questions about assessing epigenetics in peripheral tissue as markers of CNS processes that need to be resolved before it is possible to interpret this finding. More recently Meaney and colleagues have translated their work in rodents and report epigenetic changes in brain samples from newborns. This suggests that there is indeed a possibility that epigenetic changes may be associated with an altered cortisol response in the offspring. Future work needs to take account of many more potentially relevant variables including timing and nature of the prenatal exposure, method of delivery, birth weight, genetic vulnerabilities in mother and offspring, sex of offspring, age at testing and nature of the postnatal care; as well as trying to understand more about the underlying mechanisms, such as the epigenetic changes in relevant genes.

Acknowledgement

Thanks to Dr Pathik Wadhwa for helpful comments and suggestions.

References


5. Conclusion

The animal literature shows convincingly that prenatal stress can have a long-term effect on the function of the HPA axis in the offspring; but it also shows the variability and complexity of the possible effects. Equivalent work in humans is only just starting, but there is suggestive evidence that there may be equivalent reprogramming effects. These are also very variable, but mostly suggest that prenatal stress or anxiety is associated with raised basal cortisol or raised cortisol reactivity in the offspring. Future work needs to take account of many more potentially relevant variables including timing and nature of the prenatal exposure, method of delivery, birth weight, genetic vulnerabilities in mother