12 Maternal Anxiety, Depression, and Stress During Pregnancy: Effects on the Fetus and the Child, and Underlying Mechanisms

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Abstract

There is good evidence that maternal stress, anxiety, and depression during pregnancy can have long-term effects on a variety of outcomes for the child. We need to understand how an altered emotional state in the pregnant woman affects her biology in a way that in turn affects the development of her fetus. Cortisol is one probable mediating factor, but many other systems also are likely to be important, including the pro-inflammatory cytokines. There is evidence that the function of the placenta is altered if the mother is anxious or depressed and this may control the exposure of the fetal brain to hormones including cortisol, neurotransmitters, and other factors such as brain derived neurotrophic factor that can affect brain development. Epigenetic changes are likely to underlie both changes in placental function and changes in brain structure. We know that most children are not affected by prenatal stress, and that those that are can be affected in different ways. There is evidence that this is, at least in part, because of differential genetic susceptibilities.

Keywords

Prenatal • Stress • Programming • Fetus • Cortisol • Epigenetics • Placenta

Introduction

Both animal and human studies have shown that if the mother is stressed while she is pregnant her child is more likely to have a range of neurodevelopmental problems (Talge, Neal, & Glover, 2007; Van den Bergh, Mulder, Mennes, & Glover, 2005). There is evidence that this association is, at least in part, causal and due to the phenomenon of fetal programming (Glover, 2014). This is the

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concept that the environment in utero, during specific sensitive periods for different outcomes, can affect fetal development with a long-term effect on the phenotype. Fetal programming has been studied especially in relation to fetal growth and later vulnerability to cardiovascular and related diseases (Barker, 2003, 2004). But fetal programming is equally important for the development of psychopathology. Here we will give an overview of the range of effects that prenatal stress can have on the fetus and the child, with a particular focus on neurodevelopment. These have been reviewed extensively elsewhere (Glover, 2014; Talge et al., 2007; Van den Bergh et al., 2005). We also discuss the possible underlying biological mechanisms, including the role of the placenta.

Stress in Pregnancy

Stress is a generic term and has several different definitions. Many different types of prenatal stress have been shown to be associated with altered outcome for the child. These include maternal symptoms of anxiety and depression (O'Connor, Heron, Golding, Beverage, & Glover, 2002), daily hassles (Huizink, Robles de Medina, Mulder, Visser, & Buitelaar, 2003), pregnancy specific anxiety (Hompes et al., 2013; Huizink et al., 2003) and a poor relationship with the partner (Bergman, Sarkar, O'Connor, Modi, & Glover, 2007). They also include experience of acute disasters such as an earthquake (Glynn, Wadhwa, Dunkel-Schetter, Chicz-Demet, & Sandman, 2001), a Canadian Ice storm (Laplante, Brunet, Schmitz, Ciampi, & King, 2008), a hurricane in Louisiana (Kinney, Miller, Crowley, Huang, & Gerber, 2008), Chernobyl (Huizink et al., 2007), and 9/11 (Yehuda et al., 2005). It is clear that it is not just a diagnosable mental illness or very extreme or "toxic stress" that can alter outcome. Exposures that can have an effect vary from the very severe, such as the death of an older child (Khashan et al., 2008) to quite mild stresses, such as daily hassles. We do not yet know whether different forms of stress have different effects.

Most of these studies are prospective, but those examining the effects of acute disasters are of necessity retrospective, and are less able to allow for possible confounding factors. However, they have the advantage that the effects on the child are more clearly prenatal and unlikely to be due to genetic continuity.

All these studies have shown associations. It is obviously harder to prove that these associations are, at least in part, causal. If the mother is anxious or depressed while pregnant she may be affected postnatally also, and this may affect her parenting. There may be associated factors such as smoking or alcohol consumption, lower maternal education or lower socioeconomic status. These may all affect child outcome. The evidence for thinking that there is a prenatal causal component comes from different types of evidence. First there are animal studies in which the offspring are "cross-fostered" on the first postnatal day, or in the case of primates, reared together in a nursery. These experiments show long-term effects of the prenatal stress, and provide evidence for a prenatal rather than a postnatal or other confounding effect (Weinstock, 2008). Secondly, there are large human studies which have examined associations with prenatal anxiety or depression after allowing for a wide range of potential confounders including paternal mood, postnatal maternal mood, parenting behavior, maternal education, and maternal smoking and drinking alcohol during pregnancy, and still find a clinically significant relationship between prenatal maternal mood and child outcome (O'Donnell, Glover, Barker, & O'Connor, 2014). Thirdly, there are studies which have found associations between prenatal maternal mood and aspects of child outcome at birth, thus showing effects independent of postnatal maternal mood or parenting (e.g., Hompes et al., 2013). And finally, as discussed below, there are studies that are starting to determine possible underlying biological mechanisms, such as changes in placental function.

It has been suggested that mild to moderate stress may actually improve some outcomes. Mild prenatal stress has been shown to be associated with accelerated motor development and cognitive ability for example (DiPietro, Novak, Costigan, Atella, & Reusing, 2006). It is an interesting idea that the pattern of child outcome response to prenatal stress is not linear, with mild

stress causing an acceleration of development and more severe stress an impairment of development. However, other studies have found a linear dose response between prenatal maternal anxiety and emotional/behavioral problems in the child (O'Connor et al., 2002). Thus, it is possible that prenatal stress has different patterns and direction of effect for different outcomes. It would be compatible with this evidence if mild to moderate stress improves physical maturation and cognitive function while also increasing symptoms of anxiety.

Stress also is associated with activation of the hypothalamic-pituitary-adrenal (HPA) axis, which produces cortisol (corticosterone in rodents) and the sympathetic adrenal system, which produces adrenaline and noradrenaline. However, the association between maternal psychological symptoms, maternal exposures to stressors, and activation of these biological systems is complex, and can depend on the type and length of exposure. Pregnancy also affects these biological responses, especially those of the HPA axis. Several studies have found little, or a complex association between maternal symptoms of anxiety and depression and cortisol levels during pregnancy (Kane, Dunkel-Schetter, Glynn, Hobel, & Sandman, 2014; Sarkar, Bergman, Fisk, & Glover, 2006). As human pregnancy progresses the placenta produces increasing quantities of corticotrophin releasing hormone (CRH), which in turn stimulates maternal production of cortisol. Cortisol itself stimulates the production of placental CRH by a positive feedback mechanism. By the end of a normal human pregnancy levels of plasma cortisol are double to treble those in the nonpregnant state and as high as those that can be found in depression (Kammerer, Taylor, & Glover, 2006). The HPA axis becomes less responsive to stressors as gestation increases (Kammerer, Adams, von Castelberg, & Glover, 2002), although evening levels (but not morning) have been found to be raised in depressed pregnant women (O'Keane et al., 2011), and pregnant women with material deprivation (Thayer & Kuzawa, 2014). Social support has been shown to buffer increases in HPA axis function during pregnancy (Giesbrecht, Poole, Letourneau, Campbell, & Kaplan, 2013).

Effects on the Child

Many different outcomes have been shown to be changed in association with various types of prenatal stress. The effects can be quite subtle, and often have been measured on continuous scales, rather than by diagnostic categories. However, they also are often of clinical significance (O'Donnell, Glover, Barker, et al., 2014). Here we do not give a comprehensive review of the literature but give selective examples to show the range of outcomes found to be altered. The studies almost all date from the last 10–15 years. Although this type of research has been conducted in animals since the 1950s, it is relatively recently that similar research has been carried out in humans. Some studies have examined large population cohorts such as the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort in Bristol, UK (Glover, O'Connor, Heron, & Golding, 2004; O'Connor et al., 2002, 2007), and used maternal reports of offspring outcome. Other studies have been smaller observational cohorts, such as those of Van den Bergh and her colleagues (Mennes, Van den Bergh, Lagae, & Stiers, 2009; Van den Bergh & Marcoen, 2004) and that of Bergman and colleagues (2007)

The wide range of outcomes which have been found to be altered, include those from birth until adulthood. At birth, an increase in congenital malformations has been found to be associated with very severe stress in the first trimester, such as the death of an older child (Hansen, Lou, & Olsen, 2000). Many studies have shown that less severe stress is associated with somewhat lower birth weight and reduced gestational age (e.g., Rice et al., 2010; Wadhwa, Sandman, Porto, Dunkel-Schetter, & Garite, 1993). Another finding at birth is an altered sex ratio, with fewer males to females being born than in an unstressed population (Obel, Henriksen, Secher, Eskenazi, & Hedegaard, 2007; Peterka, Peterkova, & Likovsky, 2004).

Many studies have looked at neurodevelopmental and psychopathological development. Some investigators have examined the newborn and found a poorer performance on the Neonatal Behavioral Assessment Scale (Field et al., 2003; Rieger et al., 2004), showing that adverse

behavioral outcomes are observable from birth. Studies of infants and toddlers have shown more difficult temperament (e.g., Buitelaar et al., 2003; Davis et al., 2007), more sleep problems (O'Connor et al., 2007), and lower cognitive performance and increased fearfulness (Bergman et al., 2007). More recent studies have shown that effects can be persistent, at least until adolescence and early adulthood (Betts, Williams, Najman, & Alati, 2014; Glasheen et al., 2013; O'Donnell, Glover, Barker, et al., 2014; Pearson et al., 2013).

Others have examined the association between prenatal stress and neurodevelopmental outcomes in children, rather than babies, infants, or adults. Many independent groups have shown increases in child emotional problems, especially anxiety and depression, and symptoms of attention deficit hyperactivity disorder (ADHD) and conduct disorder (e.g., Huizink et al., 2007; O'Connor et al., 2002; O'Connor, Heron, Golding, Glover, & ALSPAC Study Team, 2003; Rice et al., 2010; Rodriguez & Bohlin, 2005; Van den Bergh & Marcoen, 2004), as well as increased vulnerability to victimization (Lereya & Wolke, 2013; Pawlby, Hay, Sharp, Waters, & Pariante, 2011). Others have shown a reduction in cognitive performance (e.g., Laplante et al., 2008; Mennes, Stiers, Lagae, & Van den Bergh, 2006) and differences in learning strategies in adulthood (Schwabe, Bohbot, & Wolf, 2012).

Several studies have found an association between prenatal stress and increased risk of autism or autistic traits (Beversdorf et al., 2005; Kinney et al., 2008; Walder et al., 2014), although one population study failed to replicate this finding (Li, Liu, & Odouli, 2009). Two studies have found an increased risk of schizophrenia in adults. Both showed associations with severe stress, the death of a relative (Khashan et al., 2008) or exposure to extreme adversity, the invasion of the Netherlands in 1940 (Van Os & Selten, 1998), and both showed that the sensitive period of exposure was during the first trimester.

Associations also have been found between prenatal stress and a range of altered physical and physiological outcomes in children. Alterations in brain structure have been observed, reduced brain grey matter density (Buss, Davis, Muftuler, Head, & Sandman, 2010; Sandman, Buss, Head, & Davis, 2014) and altered limbic-prefrontal white matter circuitry (Sarkar et al., 2014). An altered fingerprint pattern (King et al., 2009), and more mixed handedness (Glover et al., 2004; Obel, Hedegaard, Henriksen, Secher, & Olsen, 2003; Rodriguez & Waldenström, 2008) are physical changes observed to be associated with prenatal stress, and are known to be determined in utero. Prenatal stress also has been shown to be associated with an altered diurnal pattern or altered function of the HPA axis, although the pattern of alteration is quite complex (Glover, O'Connor, & O'Donnell, 2010; O'Donnell et al., 2013). Finally, recent studies have shown prenatal stress is associated with reduced telomere length in cord blood cells (Entringer et al., 2013). This is an intriguing finding, as well as of concern, as reduced telomere length is associated with a reduced life span.

Animal studies have consistently found sex differences in the effects of prenatal stress on offspring outcome (e.g., Van den Hove et al., 2013). Female offspring are more vulnerable to increases in anxiety and males to cognitive problems (Weinstock, 2007). In humans, there also is increasing evidence that there may be sex differences in the nature of some of the effects, although the picture is more complex (Glover & Hill, 2012; Glynn & Sandman, 2012; Tibu et al., 2014).

There is little consistency in the literature as to the most sensitive time in gestation for the influence of prenatal stress. It is likely that there are different periods of sensitivity dependent on the outcome studied, and the stage of development of the relevant brain structures. The two studies of schizophrenia found the most sensitive period was in the first trimester (Khashan et al., 2008; Van Os & Selten, 1998). This is when neuronal cells are migrating to their eventual site in brain, a process previously suggested to be disrupted in schizophrenia. In contrast, one study of conduct disorder found the greatest association with stress was in late pregnancy (Rice et al., 2010), as did a study on the risk for autism (Kinney et al., 2008). However, there is inconsistency in the literature even when the same outcome is being considered.

Understanding the times of sensitivity for different outcomes is an area where much more research is needed.

Fetal Stress Responses

There is evidence for continuity from fetal behavior and neurological maturation into early childhood (DiPietro, Bornstein, Hahn, Costigan, & Achy-Brou, 2007). There also is good evidence for an association between the mother's emotional state and the behavior or heart rate of her fetus in later pregnancy (DiPietro, Hilton, Hawkins, Costigan, & Pressman, 2002; Monk, 2001; Van den Bergh et al., 2005). Catherine Monk and her colleagues have conducted studies in which a pregnant mother is asked to carry out a stressful computer task, while the fetal heart rate is monitored (Monk, Myers, Sloan, Ellman, & Fifer, 2003), and shown a correlation between fetal heart rate changes and the mother's self-rated anxiety. Thus, even before birth the fetus can show an immediate response to the maternal emotional state, although we do not know what the mechanism is; the effects are too fast to be due to cortisol, which takes 10–20 min to rise. And noradrenaline does not cross the placenta (Giannakoulopoulos, Teixeira, Fisk, & Glover, 1999).

The fetus can mount its own stress responses from around mid-gestation, independently from any maternal stress response. If a blood transfusion is carried out through the fetal abdomen the fetus shows an increase in β-endorphin and noradrenaline from 18 weeks gestation, and in cortisol from 20 weeks gestation (Giannakoulopoulos et al., 1999; Gitau, Fisk, Teixeira, Cameron, & Glover, 2001).

Underlying Mechanisms

Much remains to be understood about the mechanisms which underlie fetal programming by prenatal stress in humans. One early suggestion was a decrease in blood flow to the fetus (Teixeira, Fisk, & Glover, 1999). However, it is not clear if the decrease observed in that study would be clinically significant, and others have failed to replicate the original finding (Kent, Hughes, Ormerod, Jones, & Thilaganathan, 2002; Mendelson, Dipietro, Costigan, Chen, & Henderson, 2011; Monk et al., 2012).

Another possible mediating factor is increased exposure of the fetus to cortisol (Mina & Reynolds, 2014). Glucocorticoids (cortisol in humans and primates, corticosterone in rodents) are known to have a range of effects on the developing fetus, including on the brain (Herbert et al., 2006). Whilst they are essential for fetal development and tissue maturation, overexposure of the fetus to glucocorticoids may have effects which predispose the child to ill health in later life (Harris & Seckl, 2010). The potentially widespread role for exposure to increased cortisol in human fetal brain development is demonstrated by a study using microarray analysis, which showed that increasing cortisol exposure affected the expression of over a 1000 genes in fetal brain cells (Salaria et al., 2006). A recent study has shown that babies exposed to synthetic glucocorticoids in the womb, because of threatened preterm labour, had more mental health problems than matched controls (Khalife et al., 2013). Davis and colleagues (2013) have shown that babies exposed to synthetic glucocorticoids in utero have altered brain structure, including a thinner cortex, as shown by magnetic resonance imaging scans (Davis, Sandman, Buss, Wing, & Head, 2013). Also, the children of mothers who had consumed high levels of liquorice during pregnancy, (which contains a natural inhibitor of 11β-hydroxysteroid dehydrogenase type II (11β-HSD2), the enzyme which converts cortisol to its inactive form cortisone in the placenta), and were thus exposed to higher levels of cortisol in utero, were more likely to have emotional and cognitive problems in childhood (Räikkönen et al., 2009).

Fetal overexposure to glucocorticoids could occur through increases in maternal cortisol associated with anxiety and during periods of stress, which then crosses the placenta into the fetal environment. In animal models, this has been shown to be one possible mechanism. Administration of adrenocorticotropic hormone

(ACTH) to pregnant rhesus monkeys resulted in increased maternal cortisol production and adverse offspring neurodevelopmental outcomes similar to those seen in response to prenatal stress (Schneider, Moore, Kraemer, Roberts, & DeJesus, 2002). The effects of prenatal stress in rats have been shown to be prevented by adrenalectomy and reinstated by corticosterone administration (Barbazanges, Piazza, Le Moal, & Maccari, 1996). However, the human HPA axis functions differently in pregnancy from most animal models, because of the placental production of CRH, which in turn causes an increase in maternal cortisol. The maternal HPA axis becomes gradually less responsive to stress as pregnancy progresses (Kammerer et al., 2002), and as discussed earlier, there is only a weak, if any, association between maternal mood and her cortisol level, especially later in pregnancy (Kammerer et al., 2006; O'Donnell, O'Connor, & Glover, 2009; O'Keane et al., 2011; Sarkar et al., 2006; Voegtline et al., 2013).

It is possible that fetal programming, caused by prenatal stress, may be mediated by raised fetal exposure to cortisol without increases in maternal levels. Maternal prenatal depression and maternal prenatal cortisol levels have been found to be independent predictors of infant temperament (Davis et al., 2007). Stress or anxiety may cause increased transplacental transfer of maternal cortisol to the fetal compartment without a rise in maternal levels. The placenta clearly plays a crucial role in moderating fetal exposure to maternal factors, and presumably in preparing the fetus for the environment in which it is going to find itself (McKay, 2011; O'Donnell et al., 2009) as part of the predictive adaptive response (Gluckman, Hanson, & Spencer, 2005). Thus, another mechanism by which the fetus could become overexposed to glucocorticoids is through changes in placental function, especially in a down regulation of the enzyme 11β-HSD2, the barrier enzyme which converts cortisol to the inactive cortisone (Togher et al., 2014). If there is less of this barrier enzyme in the placenta then the fetus will be exposed to more maternal cortisol, independently of any change in the maternal cortisol level. If the mother has higher basal levels of cortisol also then the amount of fetal exposure will be higher too, as there is a strong correlation between maternal and fetal cortisol levels (Gitau, Cameron, Fisk, & Glover, 1998). There is evidence in rat models that prenatal stress can affect placental 11β-HSD2. Restraint stress of pregnant rats in the last week of pregnancy has been shown to result in decreased placental 11β-HSD2 expression and activity (Mairesse et al., 2007). Additionally, there is evidence that reduced 11β-HSD2 causes an alteration in the behavior of the offspring. Administration of the 11β-HSD2 inhibitor carbenoxolone in rodent models resulted in an increase in anxiety, mirroring the phenotype of offspring exposed to prenatal stress. Glover, Bergman, Sarkar, and O'Connor (2009) reported that the correlation between maternal and amniotic fluid cortisol levels was greater in women with high anxiety compared to less anxious women. This suggests that prenatal anxiety in humans can increase the placental permeability to cortisol. Our laboratory has found direct evidence that maternal prenatal trait anxiety is associated with a down regulation of 11β-HSD2 in placenta taken from women who underwent an elective caesarean section (O'Donnell et al., 2012).

In utero cortisol has been shown to be inversely correlated with infant cognitive development at about 18 months old (Bergman, Sarkar, Glover, & O'Connor, 2010). This study also measured attachment using the Strange Situation test, and found that this inverse correlation was strong in insecurely attached infants but absent in the securely attached. This suggests that the quality of attachment may be able to buffer against, at least in part, this effect of raised in utero cortisol.

The timing of fetal exposure to raised cortisol also may be important for its effect on cognitive development. Elevated concentrations of maternal cortisol early in gestation has been shown to be associated with a slower rate of development over the first year and lower mental development scores at 12 months of age. However, elevated levels of maternal cortisol late in gestation, were associated with accelerated cognitive development and higher scores at 12 months of age (Davis & Sandman, 2010).

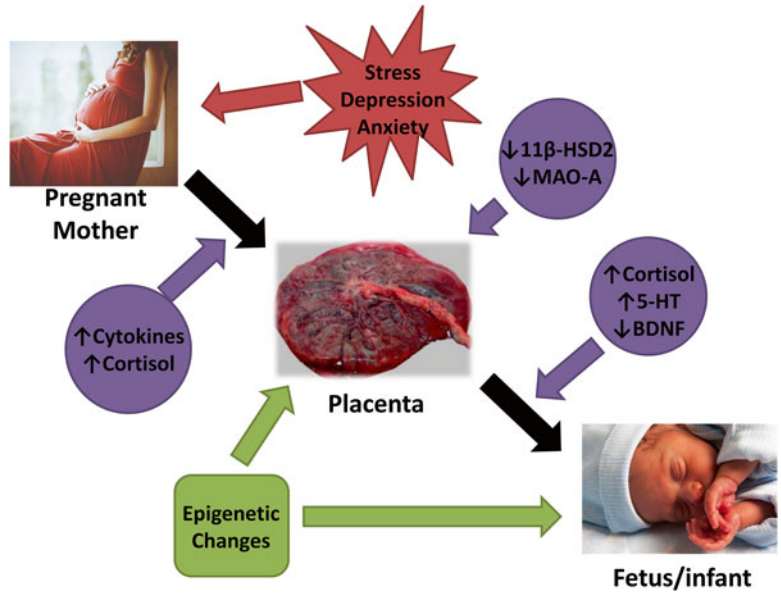

Fig. 12.1 Possible mechanisms by which maternal stress in pregnancy many alter fetal neurodevelopment

Many other systems are likely to be involved as well as the HPA axis and cortisol (Beijers, Buitelaar, & de Weerth, 2014). 5-Hydroxytryptamine (5-HT) is another possible mediator of prenatal stress induced programming effects on offspring neurocognitive and behavioral development. During gestation 5-HT acts as a trophic factor regulating cell division, differentiation and synaptogenesis in the fetal brain (Oberlander, 2012). Animal studies have shown that increased brain 5-HT exposure during gestation is associated with alterations in many neuronal processes and subsequent changes in offspring behavior. Recent work has identified an endogenous 5-HT biosynthetic pathway in the human placenta (Bonnin et al., 2011), suggesting a possible role for alterations in placental 5-HT in human fetal programmming. Prenatal depression has been found to be associated with a down regulation of the expression of placental monoamine oxidase A, the enzyme which metabolizes 5-HT to its inactive metabolite (5-HIAA) (Blakeley et al., 2013). Thus, if the mother is depressed prenatally, the placenta may produce more 5-HT which in turn may result in the brain of her fetus being exposed to more 5-HT, with altered neurodevelopment.

Another potentially interesting mediating factor is brain derived neurotrophic factor (BDNF). This is a trophic factor known to be important in the perinatal period and in synapse formation (e.g., Chikahisa et al., 2006). It is decreased in depression and raised by antidepressants. Prenatal stress in a rat model has been shown to inhibit the formation of mature BDNF in the offspring brain (Yeh, Huang, & Hsu, 2012). A recent study has shown that cord blood levels of BDNF in neonates born to mothers with general anxiety disorder were about half those in controls (Uguz et al., 2013).

Thus, maternal stress, anxiety or depression may be associated with altered placental function, which results in fetal increased exposure to cortisol, 5-HT or decreased BDNF, among other possible factors, and these in turn may change fetal neurodevelopment (Fig. 12.1). These causal pathways all still need to be shown directly. This hypothesis also raises the question as to what biological changes take place in the mother during prenatal stress, anxiety or depression which in turn alters the function of the placenta. As discussed above, the maternal changes in cortisol are not of sufficient magnitude to be a likely sole mediator. And prenatal maternal cortisol levels can be a predictor of child outcome independent of maternal mood (Davis & Sandman, 2010). The maternal mediator, or mediators, between prenatal stress, anxiety and depression and altered child outcome is currently not known.

One possible group of biological maternal mediators could be those associated with the immune system and inflammation, including the pro-inflammatory cytokines, such as interleukin-6 (IL-6) (Buss, Entringer, & Wadhwa, 2013). A mouse model has shown an association between prenatal stress and alterations of immune pathways within the placenta, specifically in male offspring (Bronson & Bale, 2014). Treating the pregnant mice with nonsteroidal anti-inflammatory drugs both reduced the placental cytokine levels and hyperactive locomotion in the male offspring.

There is a growing literature associating pro-inflammatory cytokines with depression in humans (Hepgul, Mondelli, & Pariante, 2010). Increased cytokines have been associated with psychosocial stress during pregnancy (Coussons-Read, Okun, & Nettles, 2007). Elevated maternal stress was related to higher serum IL-6 both in early and late pregnancy. No relationships between stress and cytokines were apparent during the second trimester. However, elevated stress levels across pregnancy were predictive of elevated production of the pro-inflammatory cytokines interleukin-1B and IL-6 by stimulated lymphocytes in the third trimester, suggesting that stress during pregnancy affects the function of immune system cells. A recent study has confirmed that depressed pregnant women have higher levels of IL-6 in the first trimester (Haeri, Baker, & Ruano, 2013). However, another study has failed to find any association between maternal symptoms of anxiety and depression during pregnancy and levels of IL-6 (Blackmore et al., 2011), at 18 or 32 weeks gestation. This is clearly an area that needs further exploration.

Epigenetics

There is currently great interest in the potential role of epigenetics in underlying the long term effects of prenatal stress on the development of the fetus and the child (Monk, Spicer, & Champagne, 2012). Epigenetic changes have been shown to underlie some other developmental origins of vulnerability to disease, such as diabetes (Keating & El-Osta, 2011).

Epigenetics means literally "above" or "on top of" genetics. It is the process through which cells can achieve individuality despite having identical genes. It allows a stem cell to differentiate to form many cell types in embryonic development. The epigenetic modifications to a particular gene control whether it is expressed or silenced and if it is turned on, by how much. These epigenetic changes are heritable in some cases without changes to the genotype. There are many mechanisms by which epigenetic changes can be achieved, and many still remain unknown. Of those we know of, there are direct DNA methylation, chromatin structure modification, histone modification, noncoding RNAs and small RNAs (Gibney & Nolan, 2010). DNA methylation in vertebrates almost always occurs at CpG sites (methylation of the 5′-position of cytosine residues to produce 5-methyl-cytosine). The methyl groups occupy the major groove of DNA, and may disrupt normal recognition of transcription factors and thus suppress expression, or less frequently, enhance expression (Gibney & Nolan, 2010). DNA methylation has been the most studied form of epigenetics in relation to fetal programming.

Several studies have now shown epigenetic changes in the fetus or child after prenatal stress, in both animal models (Jensen Peña, Monk, & Champagne, 2012; Mueller & Bale, 2008; Van den Hove et al., 2013), and in humans (Provençal & Binder, 2014). In a study by Non et al. (2012) investigating genome wide methylation in the umbilical cord blood of neonates exposed to non-medicated maternal depression or anxiety or selective serotonin reuptake inhibitors during pregnancy, compared with unexposed neonates, significantly different DNA methylation levels were found at 42 CpG sites in the neonates exposed to maternal depression or anxiety relative to the controls. Methylation levels were not significantly different between SSRI exposed neonates and controls. Hompes et al. (2013) have shown epigenetic changes in the promoter region of the glucocorticoid (cortisol) receptor in the cord blood from mothers who suffered from pregnancy related anxiety. Oberlander et al. (2008) also have shown epigenetic changes in

this same gene in mothers with prenatal depression and Mulligan, Stees, and Hughes (2012) in newborns of Congolese mothers exposed to extreme psychosocial stress. Teh et al. (2014) have shown the complex relationship between biological inheritance, as represented by genotype and individual prenatal experience and suggest the importance of considering both fixed genetic variation and environmental factors in interpreting epigenetic variation. They found that the best explanation for the variance in the epigenetic pattern in cord blood was the interaction of genotype with different in utero environments, including maternal smoking, maternal BMI, infant birth weight, gestational age, and birth order, as well as maternal depression. All these changes were found at birth, supporting an in utero effect of maternal depression on the epigenome.

Epigenetic changes are likely to underlie some of the placental changes described above, which are associated with prenatal anxiety or depression. For example increased methylation of the placental 11β-HSD2 gene has been shown in the lowest birth weight, healthy, term infants (Wilhelm-Benartzi et al., 2012). Epigenetic changes also may underlie some of the long-lasting effects of maternal adversity, not necessarily mediated by anxiety or depression. Appleton et al. (2013) investigated the association between methylation of the promoter region of 11β-HSD2 in the placenta and markers of prenatal socioeconomic adversity, such as poverty, in 444 healthy newborns. It was found that there was less methylation of 11β-HSD2 in neonates whose mothers experienced the most socioeconomic adversity, and particularly in the male infants.

Epigenetic changes also have been found in older children whose mothers experienced stress during pregnancy. For example maternal prenatal stress, caused by violence by the partner, has been shown to be associated with epigenetic changes in the DNA for the glucocorticoid receptor, in the blood of their adolescent children (Radtke et al., 2012).

Gene/Environment Interactions

A notable finding of all the prenatal stress and child outcome studies is that most of the children are not affected (O'Donnell, Glover, Barker, et al., 2014), and those that are affected can be so in different ways (Bergman et al., 2007). The lack of effect may, in some cases, be due to sensitive postnatal care (Bergman, Sarkar, Glover, & O'Connor, 2008). But it also is probably due, at least in part, to different genetic vulnerabilities, and gene environment interactions (Caspi et al., 2003). Although no interactions have been found between prenatal anxiety, genetic variation in the 5-HT transporter and child outcome (Braithwaite et al., 2013), we are finding interactions between prenatal anxiety and variants of the COMT (unpublished observations) and BDNF genes (O'Donnell, Glover, Holbrook, et al., 2014). If the child has one form of the gene for BDNF, he or she is more sensitive to the effects of prenatal anxiety on internalizing symptoms, but with another form they are less affected. With one form of the gene for COMT cognitive development (working memory assessed by backward digit span recall) is quite sensitive to prenatal anxiety; with another form, there is no effect. A recent study has shown an interaction between prenatal stress and different forms of the D4 dopamine receptor and child outcome. Under conditions of higher prenatal maternal stress, carriers of the DRD4 seven-repeat allele displayed more aggression in adulthood and attenuated cortisol secretion (Buchmann et al., 2014), and also increased antisocial behavior (Zohsel et al., 2014). Homozygous carriers of the DRD4 four-repeat allele were insensitive to the effects of prenatal stress.

All these gene environment interaction effects are quite small and very many different genotypes are likely to be involved. This is certainly an area where further research is warranted, in order to understand more about which children are likely to be affected by prenatal stress, and in what way. Eventually, this research should help in knowing which mothers and children are most likely to benefit from targeted help.

Conclusion

There is good evidence that maternal stress, anxiety and depression during pregnancy can have a long term effect on a variety of outcomes for the child. These effects can be clinically significant and warrant much more effort to provide appropriate intervention and help during pregnancy than is currently the case (Glover, 2014). We have some clues as to potential underlying mechanisms, but much remains to be understood. We need to understand how an altered emotional state in the pregnant woman affects her biology in a way that in turn affects the development of her fetus. Cortisol may play some role but many other factors are also likely to be important. The role of the pro-inflammatory cytokines in pregnancy warrants more investigation. There is evidence that the function of the placenta is altered if the mother is anxious or depressed and that this may control the exposure of the fetal brain to hormones, neurotransmitters, and other factors such as BDNF that can affect brain development. Epigenetic changes are likely to underlie both changes in placental function and changes in brain structure. Finally, we know that most children are not affected by prenatal stress, and that those that are can be affected in different ways. There is evidence that this is, at least in part, because of differential genetic susceptibilities. We need to understand more about these specific vulnerabilities in order to develop the most appropriate interventions.

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