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Prenatal maternal stress, fetal programming, and mechanisms underlying later psychopathology—A global perspective

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Abstract

There is clear evidence that the mother's stress, anxiety, or depression during pregnancy can alter the development of her fetus and her child, with an increased risk for later psychopathology. We are starting to understand some of the underlying mechanisms including the role of the placenta, gene–environment interactions, epigenetics, and specific systems including the hypothalamic–pituitary–adrenal axis and cytokines. In this review we also consider how these effects may be different, and potentially exacerbated, in different parts of the world. There can be many reasons for elevated prenatal stress, as in communities at war. There may be raised pregnancy-specific anxiety with high levels of maternal and infant death. There can be raised interpersonal violence (in Afghanistan 90.2% of women thought that "wife beating" was justified compared with 2.0% in Argentina). There may be interactions with nutritional deficiencies or with extremes of temperature. Prenatal stress alters the microbiome, and this can differ in different countries. Genetic differences in different ethnic groups may make some more vulnerable or more resilient to the effects of prenatal stress on child neurodevelopment. Most research on these questions has been in predominantly Caucasian samples from high-income countries. It is now time to understand more about prenatal stress and psychopathology, and the role of both social and biological differences, in the rest of the world.

Mental health problems affect 10%–20% of children and adolescents worldwide (Kieling et al., 2011), and are a leading cause of disability with long-lasting effects throughout life. However, the mental health needs of children and adolescents are neglected, especially in low-income and middle-income countries (LAMIC; Kieling et al., 2011). One cause of later mental health problems is the environment in utero. There is now considerable evidence that the mother's mood or stress during pregnancy can increase the risk of psychopathology in her child. Prospective, longitudinal analyses suggest these effects can persist through adolescence into early adulthood and are of a magnitude to be of clinical and public health relevance (Betts, Williams, Najman, & Alati, 2014; O'Donnell, Glover, Barker, & O'Connor, 2014; Pearson et al., 2013). However, children are affected in different ways, and most are not affected at all (Glover, 2015; van den Bergh et al., 2017).

The fetal brain develops at an astonishing rate (Vohr, Poggi Davis, Wanke, & Krebs, 2017). Neurogenesis can occur at 100,000 cells per minute; both it and cell migration are largely complete by midgestation. By gestational week 20, axons and synapses start to form in the cortical plate, and during the third trimester 40,000 synapses form per minute. The fetal brain is under construction, and how it is constructed can be affected by the biological signals it receives from the mother, including those caused by alterations in her own mood. The nature of the effects on the fetal brain depend on gestational age and the brain system being formed.

Such programming of the fetal brain, in response to signals caused by the mother's experience of stress, is likely to have been of evolutionary benefit to our human and animal ancestors. Many of the changes that we see as psychopathology today, such as increased anxiety or attention-deficit/hyperactivity disorder (ADHD), may have been protective in an environment that the pregnant mother found stressful because of real external physical danger. Extra vigilance or readily distracted attention may have enabled the offspring to detect and react more rapidly to real external danger such as the presence of predators (Glover, 2011). We are starting to understand some of the biological mechanisms that may underlie this fetal programming, including biological changes in the mother, the role of the placenta, changes in the fetal brain, and the role of specific systems such as the hypothalamic–pituitary–adrenal (HPA) axis, cytokines, and serotonin, as well as the importance of both genetics and epigenetics.

Most of the research has been in high-income countries, but the effects may be different and often even greater in LAMIC, because of greater stress due to wars, high levels of interpersonal violence, natural disasters, poverty, and potential interactions with infections (Goldstein, Norris, & Aronoff, 2017), food insufficiency, dietary deficiencies, crowded housing, and extremes of temperature (Herba, Glover, Ramchandani, & Rondon, 2016). In addition, the vast majority of research on the social determinants of mental

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health has been conducted in high-income country populations, and these may not apply or be different in LAMIC.

In this review we will discuss recent evidence concerning the effects of prenatal stress, anxiety, and depression on child psychopathology, the underlying biological mechanisms, and implications for LAMIC.

Evidence for the Effects of Prenatal Maternal Mood on Child Psychopathology

Many studies have shown an association between prenatal maternal mood and child outcome, and some of this association is due to associated factors. The pregnant woman may drink alcohol or smoke, and she may pass on vulnerability genes to her offspring. If the mother is stressed, anxious, or depressed while pregnant, there is a likelihood that she will be similarly affected postnatally (Heron, O'Connor, Evans, Golding, & Glover, 2004), and this may affect her interaction with her baby, attachment, and her later parenting. There is much evidence that if the mother is depressed postnatally, this can increase the risk of later psychopathology in her child. There is also evidence that the quality of infant attachment may moderate some of the effects of what happens in the womb (Bergman, Sarkar, Glover, & O'Connor, 2010). However, several large community studies have found that even after allowing for all of these factors, there remains an association between prenatal mood and later child outcome, suggesting a direct causal pathway. These large community studies include the Generation R study in the Netherlands (Kooijman et al., 2016), the Finnish FinnBrain study (Nolvi, Karlsson, Bridgett, Korja, et al., 2016), the Finnish Prediction and Prevention of Preeclampsia and Intrauterine Growth Restriction study (Lahti et al., 2017), and the Western Australian Pregnancy Cohort (RAINE study) in Australia (Robinson et al., 2008), as well as Avon Longitudinal Study of Parents and Children (ALSPAC) in the United Kingdom (O'Donnell, Glover, Barker, et al., 2014). Some studies have found that associations with later child psychopathology are much stronger with prenatal maternal mood, than with paternal mood (Capron et al., 2015; Pearson et al., 2013). O'Donnell, Glover, Barker, et al. (2014) have shown in the large UK community sample, ALSPAC, that if the mother was in the top 15% for symptoms of anxiety or depression while pregnant, her child at age 13 years had a 13% risk of a probable mental disorder, compared to a 7% risk for the children of the other 85%. This was after allowing for a wide range of possible confounders, including postnatal maternal mood, parenting, paternal mood, maternal alcohol consumption, maternal education, and socioeconomic status. The effects of prenatal maternal mood were greater than those of paternal mood. The effects of prenatal and postnatal maternal symptoms were similar and additive. Thus, in this study (O'Donnell, Glover, Barker, et al., 2014) the risk from prenatal maternal symptoms of anxiety or depression, of a mental disorder in the child, was approximately doubled, and clinically significant, although nearly 90% of the children were not affected.

Different Types of Psychopathology Affected

Prenatal stress can increase the risk for a range of different psychopathologies, or emotional and behavioral problems in the infant, child, or adolescent (Glover, 2014; van den Bergh et al., 2017). Several studies have shown an increased probability for a difficult temperament in the infant, with more dysregulated sleeping and feeding and more crying and being harder to soothe (e.g., Laplante, Brunet, & King, 2016; Nolvi, Karlsson, Bridgett, Pajulo, et al., 2016). A study of the outcomes for infants of pregnant mothers exposed to the Queensland flood in Australia has shown a greater chance of a more difficult temperament, moderated by infant sex (Simcock et al., 2017). Other research has found increased risk for both internalizing and externalizing symptoms (Lahti et al., 2017; Robinson et al., 2008). Many studies have shown an increased probability for symptoms of anxiety and depression among children (e.g., Maxwell, Fineberg, Drabick, Murphy, & Ellman, 2017; O'Connor, Heron, Golding, Beveridge, & Glover, 2002; van den Bergh, van Calster, Smits, van Huffel, & Lagae, 2008), symptoms of ADHD (e.g., O'Connor, Heron, Golding, et al., 2002; van Den Bergh & Marcoen, 2004), and symptoms of conduct disorder (O'Connor, Heron, Golding, et al., 2002; O'Connor, Heron, Golding, Glover, & ALSPAC Study Team, 2003). Other studies have shown an increased chance of autism (Kinney, Munir, Crowley, & Miller, 2008) or severity of symptoms on the autistic spectrum (Varcin, Alvares, Uljarevic, & Whitehouse, 2017). The increased risk for both depression (Pearson et al., 2013) and anxiety (Capron et al., 2015) have been shown to persist into early adulthood. Several studies have shown an increased likelihood of lower cognitive performance (Bergman, Sarkar, O'Connor, Modi, & Glover, 2007; Laplante et al., 2004; Maxwell et al., 2017) and worse later school achievement (Pearson et al., 2016). Research with infants has found that effects can be different with males and females (Braithwaite et al., 2017; Glover & Hill, 2012; Tibu et al., 2014).

Very severe stress in the first trimester, such as the death of an older child, increases risk of later schizophrenia (Khashan et al., 2008; van Os & Selten, 1998). The first half of gestation is when many neurons are migrating to their final position, and it is known that this pattern of migration is disturbed in schizophrenia. Most of the studies referred to above, with other outcomes, have found associations with stress later in pregnancy, in both the second and third trimesters. Lahti et al. (2017), who assessed women biweekly, from week 12 to 38 during pregnancy, found an increase in child internalizing and externalizing symptoms associated with maternal depressive symptoms at all these times. Research is needed to understand more about the most sensitive gestational ages for different outcomes.

There has been very little research on child outcomes associated with pre- or perinatal mental health in LAIMC. However, Maselko et al. (2016) have shown in Pakistan, that children, especially boys, of mothers with both pre- and postnatal

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depressive symptoms had more emotional and behavioral problems than others.

Many physical outcomes have been found to be altered by exposure to prenatal stress, including an increased risk of early delivery, preterm birth, and lower birthweight for gestational age (Glover, 2014). Rahman, Bunn, Lovel, and Creed, (2007) showed in a Pakistani cohort that those with prenatal depression were at double the risk for giving birth to a low birthweight infant. However, these effects are somewhat inconsistent and generally quite small. For example, Blackmore, Gustafsson, Gilchrist, Wyman, and O'Connor (2016) found an effect size (Cohen's *D*) of 0.26 for either prenatal anxiety or depression on birthweight, whereas O'Donnell, Glover, Barker, et al. (2014) found an effect size of 0.04 for the association between maternal prenatal anxiety and birthweight. This contrasts with an effect size of 0.47 for the effect of prenatal anxiety on child Total Strengths and Difficulties score at 13 years in the same cohort (O'Donnell, Glover, Barker, et al., 2014). Further, it does not seem that in general the effects on later psychopathology are mediated by effects of fetal growth (O'Donnell & Meaney, 2017). There is also an increased risk of asthma (Cookson, Granell, Joinson, Ben-Shlomo, & Henderson, 2009; Khashan et al., 2012), allergic diseases (Suh, Chang, Lee, Yang, & Hong, 2017), and reduced telomere length (Entringer et al., 2011), which may be associated with reduced longevity. An altered fingerprint pattern (King et al., 2009), and increased mixed handedness (Glover, O'Connor, Heron, Golding, & ALSPAC Study Team, 2004; Rodriguez & Waldenstrom, 2008) have also been observed. Both these are thought to be modified in utero, mixed handedness being a downstream measure of brain development reflecting atypical lateralization.

Some studies have found that antenatal stress, anxiety, or depression can be associated with an altered stress reactivity in the child. One study in rural India has shown an association between prenatal depression and an altered cortisol response to immunization in the infant (Fernandes, Stein, Srinivasan, Menezes, & Ramchandani, 2015). However, this literature is complex, and it does not seem that, in general, any alteration in stress reactivity is a major mediator of later psychopathology (Glover, O'Connor, & O'Donnell, 2010).

Types of Stress Associated With Later Psychopathology

A wide range of different types of prenatal stress have been associated with an increase in offspring psychopathology. Many studies have looked at symptoms of prenatal anxiety and depression (O'Connor, Heron, Glover, & ALSPAC Study Team, 2002; O'Connor, Heron, Golding, et al., 2002). Others have looked at life event stress (Bergman et al., 2007), daily hassles (Huizink, Robles de Medina, Mulder, Visser, & Buitelaar, 2003), exposure to a natural disaster such as an ice storm in Canada (King, Laplante, & Joober, 2005), or human made disaster such as Chernobyl (Huizink et al., 2007). It is not clear yet whether different types of stress have differential effects on outcome (whether, for example, symptoms of prenatal anxiety have a different effect from symptoms of prenatal depression). There is some suggestion that prenatal anxiety may have a somewhat stronger effect than prenatal depression, although they are often comorbid. One study found that symptoms of prenatal anxiety, but not depression, had a significant effect on child academic achievement at 16 years (Pearson et al., 2016).

Rates of prenatal depression and stress can be higher in minority ethnic groups living in high-income countries than in the rest of the population (Liu, Giallo, Doan, Seidman, & Tronick, 2016). Bécares and Atatoa-Carr (2016) in the Growing Up in New Zealand study found that experiences of racial discrimination among Māori, Pacific, and Asian women had severe direct consequences for the mother's mental health. Many studies have found that symptoms of prenatal depression and anxiety are much higher, often about double, in LAMIC than in higher income countries (Fisher et al., 2012). Gelaye, Rondon, Araya, and Williams (2016) report that whereas prenatal depression estimates range from 7% to 15% in high-income countries, the pooled prevalence rate across 51 studies from LAMIC was 25.3%, although with a wide range. In a study in rural South Africa, for example, the prevalence rate was 47% (Rochat, Tomlinson, Barnighausen, Newell, & Stein, 2011). There can be problems with using questionnaires, developed in high-income countries in LAIMC, where the questions may not be appropriate and cutoff scores may be different. This has been explored with the Edinburgh Postnatal Depression Scale (e.g., Hanlon et al., 2008). Therefore, estimates of prevalence rates for anxiety and depression in LAMIC have to be treated with some caution, with possible over- or underestimates due to altered sensitivity and specificity.

There is evidence that exposure to war and conflict increases levels of stress, anxiety, and depression in pregnant women. In the Swat valley, Pakistan, an area with much armed conflict, over a third of women were found to show significant psychological distress (Khan et al., 2015). Many remained affected 1 year after the conflict ended, showing the long-term effects on maternal mental health.

Several studies have found that anxiety specifically related to the pregnancy outcome, pregnancy-specific anxiety, is especially associated with altered child outcome (e.g., in telomere length; Entringer et al., 2013) and in the epigenetic pattern in the glucocorticoid receptor (Hompes et al., 2013) in the newborn. In low-income countries there can be very valid reasons for pregnancy-related anxiety, given the very high rates of maternal and child mortality (Hussein, 2017). For example, in a recent study in rural Nigeria it was found that among 262 women giving birth, 5 died and 52 women had a severe obstetric complication in which the mother narrowly escaped death (Mbachu et al., 2017).

In low-income countries there can also be a high level of interpersonal violence (Tran, Nguyen, & Fisher, 2016). A maternal history of domestic violence is a significant risk factor for prenatal depression (Howard, Oram, Galley, Trevillion, & Feder, 2013). It is known that a good relationship

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with the partner can be an important source of support, and is protective of women's mental health; conversely, an unsupportive or abusive relationship can be a major source of stress, and this can affect the development of the fetus and the child. Bergman et al. (2007), for example, showed, in a prosperous London sample, that if the mother reported that her partner was emotionally cruel to her, this was associated with increased fear reactivity and impaired cognitive development in her 18-month-old child, after allowing for a range of possible confounders including education, postnatal life events, and postnatal symptoms of anxiety and depression. Fisher et al. (2013) have shown that levels of interpersonal violence are high in rural Vietnam and associated with high levels of symptoms of perinatal depression. Tran, Nguyen, et al. (2016) have reviewed attitudes to interpersonal violence in different countries. They found that the proportions of women who held attitudes that "wife beating" was justified varied widely among countries from 2.0% in Argentina to 90.2% in Afghanistan. The belief that wife beating is acceptable was most common in Africa and South Asia, and least common in Central and Eastern Europe and Latin America and the Caribbean. They found that in general this belief was more common among people in disadvantaged circumstances, including being a member of a family in the lowest household wealth quintile, living in a rural area, and having limited formal education.

There is currently interest in the early life causes of maternal prenatal symptoms of anxiety and depression, and also how these may be related to her physiology during pregnancy and the development of her fetus. Early life exposure to trauma of the mother, as in adverse childhood experiences, predicts later anxiety and depression as well as other mental and physical health outcomes, and this does not seem to be modified by race/ethnicity (Lee & Chen, 2017). Lifetime trauma is often much higher in LAMIC that in higher income countries. For example, Koen et al. (2016) found in a study of South African pregnant women that lifetime trauma was reported in approximately two-thirds of mothers, with about a third exposed to past-year intimate partner violence. Gelaye et al. (2016) report that in a survey of seven LAMIC, 25% of girls described experiencing childhood sexual violence.

Plant, Jones, Pariante, and Pawlby (2017) have shown, using the large UK ALSPAC cohort, that a maternal history of child maltreatment was significantly associated with internalizing and externalizing difficulties in the child. Maternal antenatal depression, postnatal depression and child maltreatment all independently significantly mediated this association. Moog et al. (2017) have shown that maternal early trauma was linked with altered neuroanatomy in her newborn child, independently of prenatal anxiety and depression. Moog et al. (2016) have also shown that childhood trauma in the mother was associated with raised corticotrophin-releasing hormone (CRH) during pregnancy, thus linking her early experience with placental–fetal stress physiology. Blackmore et al. (2011) found that a history of trauma, although not current symptoms of prenatal anxiety or depression, was associated with significantly elevated levels of the pro-inflammatory cytokine, TNF-α, after controlling for psychosocial and obstetric covariates.

Many women with symptoms of anxiety and depression during pregnancy may have complex posttraumatic stress disorder (PTSD). Complex PTSD is composed of the six standard PTSD symptoms plus an additional set of symptoms that reflect "disturbances in self-organization." These symptoms are intended to capture the pervasive psychological disturbances that can occur following exposure to trauma, particularly those of an interpersonal nature that occur in early development, are of a repeated and prolonged nature, and from which escape is difficult or impossible (Hyland et al., 2017). Pregnant women are not usually screened for a history of early trauma, or for PTSD, even in high-income countries, but it is increasingly recognized that they should be (Geller & Stasko, 2017).

Genetics

Although there is a clinically significant increased risk from various forms of prenatal stress on later child psychopathology, most children are not affected, and those that are, are affected in different ways. This is due, at least in part, to the genetic makeup of the child and gene–environments interactions. Qiu et al. (2017) have shown that the effects of both prenatal maternal depressive symptoms socioeconomic status on neonatal brain development are modulated by genetic risk. They conclude that their findings suggest gene–environment interdependence in the fetal development of brain regions implicated in cognitive–emotional function, and that candidate biological mechanisms involve a range of brain region-specific signalling pathways (e.g., glutamate receptor signaling that influences both the right amygdala and the right hippocampus).

Others have examined gene–environment interactions looking at specific genes. Chen et al. (2015) have shown that a genetic variant in brain-derived neurotrophic factor (*BDNF*; a growth factor involved in neural development, cell differentiation, and synaptic plasticity) affects the degree of association between maternal prenatal anxiety and neonatal DNA methylation, as well as neonatal brain structure. O'Donnell, Glover, Holbrook, and O'Connor (2014), using the ALSPAC cohort, showed an interaction between prenatal anxiety and different genetic variants of *BDNF* and later child internalizing symptoms from age 4 to 15 years. O'Donnell et al. (2017) showed that there was also a significant interaction between maternal prenatal anxiety and child catechol-O-methyltransferase (*COMT*) genotype that predicted symptoms of both ADHD and working memory in the child. There was no interaction between maternal prenatal anxiety and variants in *BDNF* to predict working memory or ADHD, or between maternal prenatal anxiety and *COMT* in the prediction of internalizing symptoms. The interactions in both O'Donnell studies only explained a small part of the variance, and there are probably very many genes involved in the predisposition to the many types of psychopathology outcomes affected by prenatal stress.

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With schizophrenia, for example, there is evidence that multiple genetic factors confer increased risk, with each variant showing a relatively small effect size (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014).

Ethnicity is, in part, a reflection of genetic variation across different groups, and this raises the interesting possibility of differential susceptibility to prenatal stress. The importance of the pattern of genetic frequencies in different ethnic groups in influencing birth outcome is shown by the study by Wadhwa et al. (2012). They have shown that the different frequency of different alleles for the gene for the CRH binding protein in African Americans, Hispanics, and Whites in the United States helps explain variations in birthweight in these populations. The idea that there are both shared and unique genetic predictors of birthweight is also supported by more recent large-scale genome-wide association studies (Horikoshi et al., 2016).

Genetic variation can affect epigenetic changes too. Teh et al. (2014) have shown both that different ethnic groups in Singapore can be separated by their genetic profile and that genotype influences epigenetic variation. Twenty-five percent of the variability in specific methylated regions in the neonate could be explained by genetic differences. They further showed substantial interaction between genotype, different in utero environmental exposures, including maternal prenatal depression, and variably methylated regions.

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 (Cao-Lei et al., 2017; Nemoda & Szyf, 2017). Epigenetics, stemming from the Greek *epi-* meaning "upon" and *genetics*, refers to a series of chemical modifications to chromatin, such as the addition of methyl groups that regulate genomic transcription. Increased DNA methylation, in certain parts of the gene, results in reduced transcription. Epigenetics has become largely synonymous with the study of transcriptional regulation, that is, the degree to which a gene is expressed or repressed, turned on or off. Epigenetic changes can last throughout the lifetime, but in some cases, can also be reversed.

Epigenetic changes in the fetus and the child after prenatal stress have been found both in animal models (Jensen Pena, Monk, & Champagne, 2012) and in humans. Several studies have looked at alterations in the methylation of specific genes, and especially in the promoter region of the glucocorticoid receptor (*NR3C1*), the receptor for cortisol. Hompes et al. (2013) have shown epigenetic changes in this region using the cord blood from mothers who suffered from pregnancy-related anxiety. Oberlander et al. (2008) have shown altered *NR3C1* promoter methylation in cord blood from neonates born to mothers with prenatal depression. Mulligan, D'Errico, Stees, and Hughes (2012) found methylation changes in this site in newborns of mothers exposed to prenatal stress in the Democratic Republic of Congo. In a study of mothers and children exposed to the Tutsi genocide in Rwanda compared with controls, Perroud et al. (2014) found that mothers exposed to the genocide, as well as their children, had lower cortisol and glucocorticoid receptor levels, and that exposed mothers and their children had higher methylation of the promoter region of *NR3C1* than nonexposed groups. They suggest that transmission of parental PTSD to offspring might be explained by transmission of epigenetic processes such as the methylation status of the glucocorticoid receptor (Perroud et al., 2014). Kertes et al. (2017) have shown altered gene methylation for *BDNF* in both mothers and newborns associated with maternal exposure to war trauma, in the Democratic Republic of Congo.

Epigenetic changes have also 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 increased methylation of the *NR3C1* promoter in the blood of their adolescent children (Radtke et al., 2011). While this finding is interesting and suggestive of intergenerational effects of domestic violence, these findings, like most of the epigenetic studies in this field, should be treated with some caution. The majority of adolescents examined in this study had undetectable levels of methylation within the *NR3C1* promoter ($n = 22$) with low levels of methylation (<10% methylated) detected in a small subgroup ($n = 7$). Eight women reported exposure to domestic violence during pregnancy, and of these cases, three adolescent offspring had undetectable levels of methylation in the *NR3C1* promoter while five adolescents had low levels of DNA methylation <6%, which presumably drive the observed association between maternal domestic violence exposure and adolescent DNA methylation.

An important consideration for all of these studies is that the changes in DNA methylation were small, the functional association with gene expression was not usually determined, nor were proportion of different cell types in the original biosample considered, which can be an important confound. Thus, though epigenetics remains a promising mechanism for the mediation of prenatal stress on the development of the brain of the fetus and the child, evidence for its importance in this is still quite limited.

Potential Interactions With Diet and Other Mediating Factors

There can be other environmental factors that can cause mothers to feel stressed during pregnancy. Lin et al. (2017), in a study in Shanghai, found that both acute and chronic exposure to either extremely high or low external temperatures caused many mothers to report feeling stressed.

Diet

Messer, Boone-Heinonen, Mponwane, Wallack, and Thornburg (2015) discuss how racial and/or ethnic minorities carry the highest burden of many adverse health outcomes intergenerationally, and how there can be interactions between

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stress, diet, and air pollution. Prenatal stress and prenatal nutrition each have demonstrable impacts on fetal development, with implications for child neurodevelopment and behavior (Vohr et al., 2017). However, few studies have examined their joint influences despite the likelihood of potential interactive effects, based on some evidence from animal studies and nonpregnant humans (Lindsay, Buss, Wadhwa, & Entringer, 2017). Maternal undernutrition is very common in some parts of the world, such as South Asia, where greater than 10% of women have a body mass index of less than 18 (Vohr et al., 2017). The quality of the diet is also important. Several micronutrient deficiencies, of folate, choline, vitamin B12, zinc, iodine, and iron, are common globally and have been shown to cause various forms of impaired neurodevelopment (Vohr et al., 2017). Hanieh et al. (2013) found that twice-weekly iron/folate supplementation to pregnant women in rural Vietnam improved infant cognitive outcome at 6 months. Tran, Hetzel, and Fisher (2016) report that 28.5% of the world's population have insufficient dietary iodine intake, and that this, during pregnancy, can result in mental and physical growth deficits among children.

Brunst et al. (2014) showed a high frequency of vitamin E (52%), magnesium (38%), iron (57%), and vitamin D (77%) inadequacies in an urban US population as well as suboptimal intakes of choline (95%) and potassium (99%). They also found that maternal exposure to prenatal negative life events was associated with higher child negative affectivity at 30 months in the presence of lower intakes of zinc and selenium, and that modification effects approached significance for vitamins A and C. They suggest that increased antioxidant intakes during pregnancy may protect against influences of prenatal stress on child temperament (Lipton et al., 2017).

Microbiome

There is increasing interest in the influence of the microbiome on mental health, and alterations in its composition as one pathway for the effects of prenatal stress on later psychopathology of the child (O'Mahony, Clarke, Dinan, & Cryan, 2017; Rakers et al., 2017). Gut bacteria strongly influence our metabolic, endocrine, immune, and both peripheral and central nervous systems (Rieder, Wisniewski, Alderman, & Campbell, 2017). Microbiota do this directly and indirectly through their components, including serotonin and dopamine (Leclercq, Forsythe, & Bienenstock, 2016). Thus, disruption of the microbiome in early life has the potential to influence neurodevelopment and mental health outcomes in the long term, particularly through its interaction with the immune system and the gut–brain axis. There is good evidence that prenatal stress alters the composition of the microbiome in the offspring in rodent models (Golubeva et al., 2015; Jasarevic, Howard, Misic, Beiting, & Bale, 2017). Zijlmans, Riksen-Walraven, de Vos, and de Weerth (2015) have shown that maternal prenatal stress was strongly and persistently associated with the infants' microbiota composition for the first 110 days. Clear links were found between maternal prenatal stress and the infant intestinal microbiota and health, and the authors suggest a potential for bacterial interventions to enhance offspring health and development in pregnant women with stress. This is another area where there may well be different effects of prenatal stress in different parts of the world and among different ethnic groups. Variations have been found in different ethnic groups in both the vaginal microbiome and in cytokine concentrations during pregnancy (Dutt, Raker, & Anderson, 2015).

Mediating Biological Mechanisms—The Role of the HPA Axis, Cortisol, Cytokines, and the Placenta

Cortisol

The role of the HPA axis and cortisol has been the most studied as a potential mediator of the effects of prenatal stress on the fetus and the child. There is good evidence for its role in animal models of fetal programming by prenatal stress (Weinstock, 2005). Maternal exposure to synthetic glucocorticoids during pregnancy has been shown to be associated with worse mental health in childhood and adolescence (Khalife et al., 2013). Davis, Sandman, Buss, Wing, and Head (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. In addition, the children of mothers who had consumed high levels of licorice during pregnancy, which contains a natural inhibitor of 11-β-hydroxysteroid dehydrogenase type II (11β-HSD2), the enzyme that converts cortisol to its inactive form cortisone in the placenta, and were thus exposed to higher levels of cortisol in utero, were over three times more likely to have ADHD symptoms, as well as lower IQ and earlier puberty (Raikkonen et al., 2017).

However, it is not likely that prenatal stress is altering fetal neurodevelopment primarily via raised maternal cortisol levels. The human maternal HPA axis functions differently in pregnancy from most animal models, because of the human placental production of CRH, which in turn causes an increase in maternal cortisol. The maternal HPA axis becomes gradually less responsive to stressors as pregnancy progresses, and there is only a weak, if any, association between maternal mood and cortisol level, especially later in pregnancy (O'Donnell, O'Connor, & Glover, 2009; Sarkar, Bergman, Fisk, & Glover, 2006). Bleker, Roseboom, Vrijkotte, Reynolds, and de Rooij (2017), with a large cohort of pregnant Dutch women at median 91 days gestation, have shown that the variables that were associated with higher cortisol levels were lower maternal age, being nulliparous, lower prepregnancy body mass index, higher C-reactive protein, carrying a female fetus, nonsmoking, and being unemployed. A total of 32% of all variance in cortisol was explained by these variables. None of the psychosocial stressors they examined, including depression, anxiety, pregnancy-related anxiety, work stress, parenting stress, and fatigue, was significantly associated with maternal serum cortisol levels.

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However, increased fetal exposure to cortisol may still alter fetal neurodevelopment. Bergman et al. (2010) showed that higher levels of cortisol in amniotic fluid was negatively correlated with cognitive scores in the Bayley's Mental Developmental Index, when the infant was 18 months old. In this study the infant's attachment to the mother, assessed using the Strange Situation procedure, was also measured. The negative association between amniotic fluid cortisol level and later infant cognitive ability was strong in the insecurely attached infants, but absent in the securely attached. This suggests that at least some fetal programming may be reversible in the early postnatal period by caregiving practices that promote secure attachment.

Cytokines

We currently do not know what biological changes in the mother are involved in fetal programming induced by prenatal stress, anxiety, or depression. As discussed above, there must be other maternal factors in addition to cortisol. Pro-inflammatory cytokines are promising candidates. There is increasing evidence linking depression in general with altered function of the immune system including raised levels of pro-inflammatory cytokines. Exposure to early life stressful events can act through the modulation of inflammatory responses over the entire life span. A history of exposure to intimate partner violence has been associated with raised levels of the cytokine TNF-α during pregnancy (Blackmore et al., 2011). Several studies have now linked symptoms of depression or anxiety or a history of abuse to altered cytokine patterns during pregnancy (Chang et al., 2017; Karlsson et al., 2017; Walsh et al., 2016). However, we do not yet know how, if at all, this affects the function of the placenta or the development of the fetus.

Placental functioning

The placenta is crucial in controlling fetal exposure to maternal cortisol, and several studies have examined aspects of prenatal maternal mood and the expression of HPA-related genes in the placenta. The placenta has high levels of 11β-HSD2 during the second and third trimesters of human pregnancy, and this controls the passage of cortisol from the maternal to the fetal circulation. It is possible that fetal programming, caused by prenatal stress, may be mediated by raised fetal exposure to cortisol without increases in maternal levels (Glover, Bergman, Sarkar, & O'Connor 2009). Maternal prenatal anxiety and depression and maternal prenatal cortisol have been found to be independent predictors of infant temperament (Karlsson et al., 2017). 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 as part of a predictive adaptive response (Glover, 2011). Thus, another mechanism by which the fetus could become overexposed to glucocorticoids is through changes in placental function, especially in a down regulation of 11β-HSD2, the barrier enzyme that converts cortisol to the inactive cortisone. 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 (Glover, 2011). Glover et al. (2009) showed that the correlation between maternal plasma and amniotic fluid cortisol was significantly increased with greater symptoms of maternal anxiety, suggesting that with more anxiety the placenta becomes more permeable to cortisol, with potentially increased fetal exposure. This effect was independent of gestational age (mean 17.7 weeks, range 15–37 weeks). Thus, raised maternal cortisol may affect fetal cortisol exposure even if it is not itself directly associated with maternal mood.

O'Donnell et al. (2012) have shown that both the expression and the activity of placental 11β-HSD2 are downregulated with higher levels of maternal anxiety. Seth, Lewis, Saffery, Lappas, and Galbally (2015) also found trend associations with increased symptoms of both anxiety and depression. Neither O'Donnell et al. (2012) nor Reynolds et al. (2015) found an association with maternal prenatal symptoms of depression, but Togher, Treacy, O'Keeffe, and Kenny (2017) have found a downregulation of 11β-HSD2 associated with a composite measure of prenatal stress. Monk et al. (2016), also using a composite measure of maternal prenatal distress, have found an association with increased methylation of 11β-HSD2 in the placenta, which also suggests a downregulation of its expression (Capron, Ramchandani, & Glover, 2018). This in turn was associated with reduced fetal movement and heart rate coupling, an index of fetal central nervous system development. Coupling reliably increases over gestation, reflecting the coordination of the autonomic and somatic systems, and is positively associated with more mature neural integration at birth.

Maternal prenatal depression has been associated with an increase in the expression of *NR3C1* in the placenta in several studies (Conradt, Lester, Appleton, Armstrong, & Marsit, 2013; Reynolds et al., 2015). Togher et al. (2017) found an upregulation associated with their composite prenatal stress measure. *NR3C1* is a nuclear receptor that functions both as a transcription factor and as a transcription factor regulator, and is highly expressed in the placenta. Although the function of *NR3C1* in the placenta is unclear, it has been suggested that it may be an upstream regulator of placental 11β-HSD2 gene expression, and an increase may be a mechanism through which the placenta increases its sensitivity to glucocorticoids and fetal glucocorticoid exposure (Seckl & Holmes, 2007).

Several studies have shown an association between placental HPA axis genes and infant neurobehavior, providing some evidence that the alteration in the placental expression

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of these genes associated with prenatal maternal mood or stress may have a direct mediating role in increasing later vulnerability to psychopathology (Appleton, Lester, Armstrong, Lesseur, & Marsit, 2015; Paquette et al., 2015). Raikkonen et al. (2015) found that higher placental NR3C1 mRNA partly mediated the association between maternal depressive symptoms during pregnancy and infant regulatory behaviors.

Capron, Ramchandani, and Glover (2018) have found, in a small study, that the association between prenatal maternal stress and alterations in the expression of HPA-related genes in the placenta depended on the ethnicity of the mother. While in Caucasians there was a clear downregulation of 11β-HSD2 expression and upregulation of the glucocorticoid receptor *NR3C1*, confirming previous studies, this was absent in the non-Caucasians, with a significant interaction with ethnicity. The non-Caucasians were predominantly from the Indian subcontinent. This raises the interesting possibility that the effects of prenatal stress on later child psychopathology may be different in different groups, with some being more resilient and some more susceptible. The possibility of different genetic vulnerabilities in different ethnicities is an important area for future research.

Although HPA axis genes have been the most studied in the placenta, it is likely that other systems are involved also, including serotonin. Blakeley, Capron, Jensen, O'Donnell, and Glover (2013) found that prenatal symptoms of maternal depression were associated with a downregulation of monoamine oxidase A, the enzyme that metabolizes serotonin, thus regulating its transplacental passage from mother to fetus. Animal experiments have shown that increased exposure to serotonin can alter fetal neurodevelopment and later behavior (Ansorge, Morelli, & Gingrich, 2008; Bonnin et al., 2011).

Implications for Prevention, Early Intervention, and Treatment

Thus, there is considerable evidence that stress, anxiety, and depression in the mother during pregnancy increases the risk for psychopathology in her child. This suggests that better emotional care of pregnant women should reduce psychopathology in the next generation. Even though methods to reduce anxiety and depression during pregnancy are well known, there are no long-term studies of subsequent child outcome. Many types of talking therapies have been shown to be effective in reducing prenatal anxiety and depression (e.g., Spinelli & Endicott, 2003). There is good knowledge of the safety of appropriate drugs for the perinatal period (McAllister-Williams et al., 2017). However, it is important to determine whether, and which of these interventions do improve child outcome. The Nurse Family Partnership, in the United States, remains the only intervention that starts in pregnancy and has been shown to have long-term benefits for the behavior of the child (Olds et al., 1998). Although the Nurse Family Partnership intervention does give considerable social support to the mother during pregnancy and for the first 2 years, it was not designed to help with perinatal mental health.

There have been some short-term small studies of the effect of psychological interventions on child outcome that look promising (Glover, 2014). Millgrom et al. (2015) showed that eight prenatal sessions of cognitive behavioral therapy for depressed pregnant women reduced antenatal depression and anxiety. Nine-month-infant outcomes showed several medium to large effects favoring the intervention in domains including problem solving, self-regulation, and stress reactivity, which were independent of maternal postnatal mood. Netsi, Evans, Wulff, O'Mahen, and Ramchandani (2015) in a small pilot study of cognitive behavioral therapy for antenatal depression found that improvement in depression scores was associated with easier temperament in the infant.

There has been even less research about benefits to child outcome in improving prenatal or perinatal mental health in a low-income setting, although some are starting to be carried out (Turner et al., 2016). In many low-income countries, there are very few mental health services and little access to psychiatrists or psychologists. New approaches need to be developed. The value and appropriateness of different types of talking therapies need to be assessed, as is the peer-delivered Thinking Healthy Program currently being evaluated in Pakistan (Turner et al., 2016). Other interventions, such as yoga, need to be explored in different cultural settings. Remarkably, maternal stroking of the infant has been shown to reduce the effect of prenatal anxiety on internalizing and externalizing symptoms in the 3-year-old child in a large UK sample (Pickles, Sharp, Hellier, & Hill, 2017). The potential benefit of music, either singing or listening, is another promising area for future research. There is evidence that appropriate music can reduce anxiety and depression (Corbijn van Willenswaard et al., 2017). A recent pilot study in which pregnant women listened to specially composed songs for pregnancy showed promise in reducing prenatal symptoms of anxiety and depression (Nwebube, Glover, & Stewart, 2017).

Conclusion

Prenatal stress, anxiety, and depression can have long-lasting effects on child and adult psychopathology. Distressed maternal prenatal mood is also likely to persist into the postnatal period, and this can further affect child development via impaired parenting. Although there is considerable evidence that levels of prenatal stress, anxiety and depression can be very high in LAIMC, there is little research, as yet, linking this to child psychopathology. It is very probable that many children are affected, as they are in high-income countries. The effects of the stress may be exacerbated by interactions with other factors such as poor diet. We do not know whether different genetic patterns in different ethnic groups provide increased susceptibility or resilience. New, culturally appropriate and low cost, interventions need to be developed and evaluated for both mother and child.

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