REVIEW ARTICLE

Effects of prenatal stress on pregnancy and human development: mechanisms and pathways

Mary E Coussons-Read PhD

The University of Colorado, Colarado Springs and The Colorado School of Public Health, 1420 Austin Bluffs Parkway, Colorado Springs, CO 80918, USA

Summary: A growing body of research shows that prenatal stress can have significant effects on pregnancy, maternal health and human development across the lifespan. These effects may occur directly through the influence of prenatal stress-related physiological changes on the developing fetus, or indirectly through the effects of prenatal stress on maternal health and pregnancy outcome which, in turn, affect infant health and development. Animal and human studies suggest that activation of the maternal stress response and resulting changes in endocrine and inflammatory activity play a role in the aetiology of these effects. Ongoing research is focusing on clarifying these mechanisms, understanding the role of racial and cultural factors in these effects, and examining the epigenetic and transgenerational influences of prenatal stress.

Keywords: pregnancy, stress, inflammation, development

INTRODUCTION

It is clear that that psychosocial, cultural and environmental stressors experienced during gestation can be detrimental to pregnancy and maternal and fetal health, and recent studies suggest that prenatal stress can have consequences that span generations. Prenatal stress can range from severe (e.g. trauma) to moderate (e.g. life event changes) to mild (e.g. experience of daily hassles), and although some early studies showed minimal stress effects on pregnancy,[1] the majority of human studies show that mild, moderate and severe stress can have negative influences on pregnancy outcome and the behavioural and physiological development of offspring.[2] Several conceptualizations of 'prenatal stress' are evident in the human literature, reflecting the diversity of stressors that may be experienced during gestation. The concept of a psychosocial stressor encompasses changes in, for example, personal life, job status, housing, domestic violence and family makeup which require adaptive coping behaviour on the part of the affected individual.[3] Whereas 'psychosocial stress' refers to stressful things that happen whether a person is pregnant or not (daily hassles, financial or marital strain, social stress), 'pregnancy-specific' distress and anxiety refer to worries about things that are directly connected to the pregnancy itself, such as concerns about the outcome of prenatal screenings, fears about infant health and development, and uncertainly about the life changes that will come with motherhood.[4] Studies show that both psychosocial stress and pregnancy-specific stresses can have marked effects on pregnancy and human development.

There is accumulating evidence from human and animal studies that exposure to prenatal stress can affect the health, development and long-term functioning of offspring via both direct and indirect pathways (Figure 1). Prenatal stress can indirectly affect infant health and development by increasing the risk of the occurrence of adverse birth outcomes which are, in turn, associated with substantial developmental and health consequences.[5] In addition, stress may exert an indirect effect on infant development by, for example, predisposing mothers to perinatal depression, which can have a negative effect on the interaction of the mother with her infant and/or affect the quality of postnatal care. Prenatal stress can also have direct effects on infant health by altering the course of fetal neurobiological development. Studies suggest, for example, that exposure to glucocorticoids *in utero* either through maternal stress or exogenous administration, can affect the development of the stress response in the fetus, which can have long lasting effects on behaviour and physiology.[6] Both the direct and indirect effects of prenatal stress can have lasting consequences for both development, and functioning of offspring across the lifespan. This review focuses on psychoneuroimmunology-oriented studies of the effects of prenatal stress on human pregnancy, infant development and the development of offspring across the lifespan. Starting with an introduction to the effects of prenatal stress on maternal physiology and health, evidence for both direct and indirect effects of gestational on pregnancy and development is presented in the context of animal and human studies seeking to characterize the mechanisms of these effects.

Correspondence to: Mary E Coussons-Read
Email: mcousson@uccs.edu

MATERNAL RESPONSES TO PRENATAL STRESS

During pregnancy the maternal endocrine, nervous and immune systems adjust to support pregnancy success (Figure 2), and it has been suggested that prenatal stress affects pregnancy by

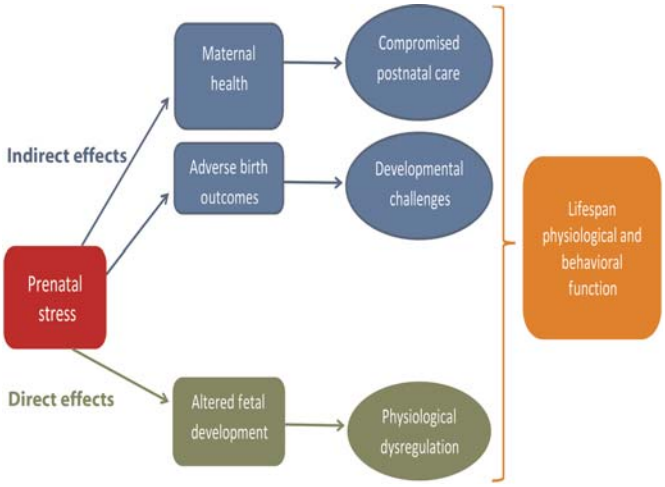

Figure 1 **Schematic of the direct and indirect pathways through which prenatal stress may affect the health and development of human offspring**

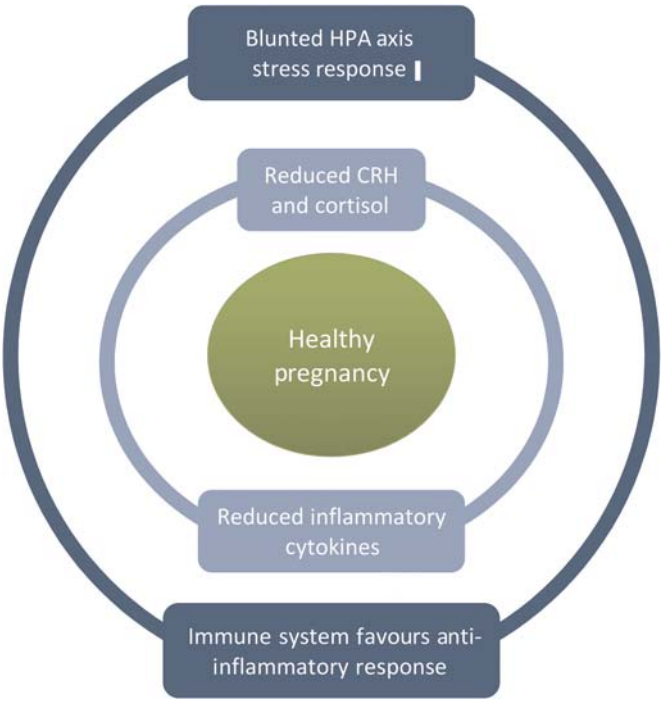

Figure 2 **Schematic of how maternal immune and endocrine adjustments can support healthy pregnancy. HPA, hypothalamo-pituitary-adrenal; CRH, corticotropin-releasing hormone**

disrupting these processes. Among the physiological changes that occur in pregnant women are a tendency toward reduced stress responsiveness of the hypothalamo-pituitary-adrenal (HPA) axis and a shift in the immune system to favour an anti-inflammatory profile.[7] Notably, however, studies show that maternal stress and inflammatory responses, although down-regulated in pregnancy, are intact; both stress and infection can strongly activate the HPA stress response and increase production of corticotropin-releasing hormone (CRH) and stimulate the production of inflammatory cytokines during gestation.[7,8] This is an important piece of information, as it confirms that although maternal stress and inflammatory responses are altered during pregnancy,[9] they are stimulated by stress and may be of sufficient magnitude that they could have the potential to modulate other aspects of maternal health and fetal development. As described below, increased maternal HPA axis and/or inflammatory activity may affect fetal HPA development and aspects of maternal physiology involved in pregnancy and birth, and may set the stage for the lasting effects of stress across the developmental trajectory. Activation of HPA and inflammatory responses during pregnancy can affect maternal health during and beyond pregnancy. Stressed mothers are more susceptible to infection and illness during pregnancy as a result of the suppressive effects of stress on the ability of the immune system to respond to challenge.[10] Maternal illness during pregnancy may not only affect pregnancy through increased inflammatory activity, but also through behavioural changes such as poorer nutrition, reduced physical activity and disordered sleep which may accompany a period of illness.

Antenatal mood disorders are common and are associated with adverse pregnancy outcomes, although the relationship between stress and prenatal maternal mood is still under investigation. Between 8% and 13% of women are diagnosed with anxiety or depressive disorders during pregnancy and many more already have such a diagnosis when they become pregnant.[11] Even women with subclinical symptoms of depression and anxiety during pregnancy that do not result in a diagnosis have an increased occurrence of adverse outcomes such as restricted fetal growth and preterm birth (PTB).[12–14] Although the majority of research on perinatal mood disorders has focused on postnatal depression, 50% of cases of 'postnatal depression' begin prenatally and over 30% of cases of antenatal depression extend into the postpartum period.[15] Maternal depression and anxiety in pregnancy have been connected to emotional and dysregulation and neurological alterations in human offspring.[16,17] Exposure to stress and inflammatory mediators have also been implicated in the aetiology of depression; studies suggest that perinatal mood disorders are more common in women who report high levels of life events stress during pregnancy.[18,19] This is a critical finding as maternal mood disorders have been reliably linked to poorer postnatal care including reduced duration of breastfeeding, impaired mother–infant interactions, and delays in infant behavioural development.[20,21] Interestingly, depression during pregnancy is associated with elevated HPA activity, although the relationship between inflammatory markers and antenatal mood disorders is still under study.[22] Ongoing work is focused on examining the relationships and possible synergies between stress, inflammatory markers, the HPA axis, and maternal mood disorders in pregnancy and how these relationships affect birth and infant development.

STRESS EFFECTS ON PREGNANCY AND BIRTH

Prenatal stress can indirectly affect infant development and health by increasing the occurrence of adverse pregnancy outcomes which are themselves predictive of substantial and ongoing challenges for affected offspring (Figure 3). Severe stress appears to have its greatest impact on birth outcome when it occurs early in pregnancy. For example, Carmichael and Shaw[23] noted that major stress around conception (e.g. death of a loved one, divorce) resulted in increased risk of a woman delivering an infant with conotruncal heart defects,

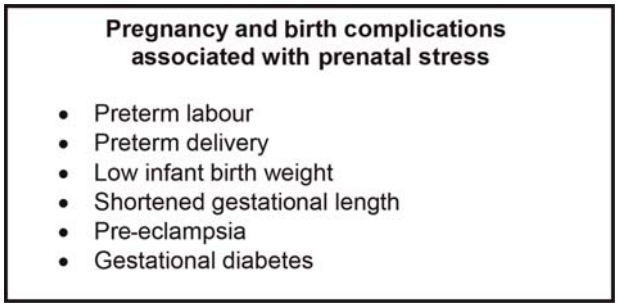

Figure 3 **Summary of pregnancy and birth complications associated with prenatal stress**

neural tube defects or isolated cleft lip, and Glynn *et al.*[24] found that earthquake trauma had a greater negative effect on shortening gestational length if experienced early in pregnancy. Similarly, death of a loved one or a terrorist attack increased the incidence of adverse outcomes including pregnancy loss when experienced early in pregnancy.[25,26]

Less severe types of stress (perceived stress, pregnancy-specific distress and anxiety) appear to have a more pronounced effect in increasing the risk of delivering a low birth weight (LBW) infant as well as PTB,[27–29] and several studies have implicated even moderate gestational stress in the aetiology of PTB and LBW.[30,31] The occurrence of PTB and LBW, regardless of root cause, can result in lasting deficiencies in infant behavioural and physiological development and function. PTB and LBW offspring are more likely to experience asthma and allergies, and may also experience more severe health conditions which require ongoing medical treatment through childhood and sometimes into adulthood, including increased susceptibility to affective disorders.[32,33] While some studies show that psychosocial stress as described above is associated with increased occurrence of PTB and LBW, increasingly studies are showing that pregnancy outcome is affected by stressors that are specifically tied to the experience of being pregnant. For example, pregnancy-specific distress and anxiety increase the risk for PTB and shortened gestational age at birth.[4,34] Both overall stress and pregnancy-specific distress are associated with higher rates of PTB, LBW and unplanned caesarean sections.[4,35] The implications of these studies are important: 70% of infant perinatal deaths in the USA are related to LBW, PTB and restricted fetal growth. Those infants who survive the perinatal period are at greater risk for physical and developmental delays in later years.[5]

Studies suggest that prenatal stress increases the risk of adverse pregnancy outcomes by disrupting adaptations in the maternal immune, endocrine and nervous systems that support healthy pregnancy.[30,36] Prenatal stress appears to stimulate activity of the maternal endocrine and immune systems, which, in turn, increase the likelihood of PTB, LBW and shortened gestational age at birth (birth between 37 and 40 weeks' gestation).[30,37] Consistent with this suggestion is the finding that women experiencing preterm labour have elevated levels of inflammatory cytokines compared with women who deliver normally, and the lymphocytes of women delivering preterm produce more inflammatory cytokines in culture.[38,39] In addition, psychosocial stress and pregnancy-specific distress are associated with elevated serum levels of inflammatory cytokines (interleukin-6 and tumour necrosis factor-α) in pregnancy[40,41] and stimulated lymphocytes cells from women reporting moderate or high levels of stress late in pregnancy produce more inflammatory cytokines (interleukin-6 and interleukin-1) than cells from low stress women.[41] In addition, recent work from our laboratory shows that the effects of stress experienced early in pregnancy in reducing gestational age at birth are mediated by elevations in serum levels of tumour necrosis factor-α, and similarly, that the effects of pregnancy-specific distress on shortening gestational age at birth are mediated by levels of interleukin-6 across pregnancy.[42]

Work in other laboratories demonstrates a role of maternal HPA axis activity in the effects of stress on PTB and LBW. Stress and anxiety-related elevations in CRH and cortisol early in pregnancy are associated with increased risk of PTB.[35,43] Within this context, several studies have connected stress-related changes in maternal and fetal HPA axis activity and stress responsiveness with shorter gestational length, higher probability of preterm labour and delivery, and LBW. Women who encounter psychosocial stress during pregnancy have higher levels of CRH and cortisol than non-stressed pregnant women[36] and women who deliver preterm have significantly higher levels of plasma cortisol and CRH prior to onset of labour than women who deliver normally.[37] Others have shown that women who experience stress and have higher levels of stress-related hormones are more likely to deliver LBW infants.[44] Stress and HPA axis activation have also been implicated in the development of other complications during pregnancy such as pre-eclampsia and gestational diabetes.[45,46]

LIFESPAN EFFECTS OF PRENATAL STRESS

A growing body of work shows that prenatal stress can have persistent effects on behavioural, physiological and immunological functioning throughout the lifespan and may even be evident across generations (Figure 4). Animal studies show that the adult offspring of stressed rat dams exhibit impaired reproductive and grooming behaviour, demonstrating lasting neurobehavioural effects of maternal prenatal stress.[47,48] Human studies also show persistent effects of gestational stress on development and behaviour. For example, cognitive performance at 5 1/2 years was impaired in children whose mothers experienced the stress of a catastrophic ice storm in pregnancy.[49] This group of investigators also found that risk factors for schizophrenia were more frequent in the offspring of mothers who endured the storm during their pregnancies.[50] Prenatal stress has also been shown to increase the stress reactivity of infants,[51] which is of particular importance given other studies showing that early stress reactivity is connected to emotional temperament later in life.[52] Many of these effects can be characterized as direct effects of stress on behavioural and cognitive development as they can occur independently of the occurrence of PTB and/or LBW. For example, infants from otherwise uncomplicated stressed pregnancies are harder to soothe and have been characterized as being more temperamental than infants from pregnancies in which the mothers did not report significant stress.[53] Stress during pregnancy is related to slower cognitive development even in the absence of PTB or LBW, and has been correlated with slower infant growth and development in animals and humans.[54,55] Exposure of the developing fetus to stress hormones and resulting alterations in neurobiological development are responsible,

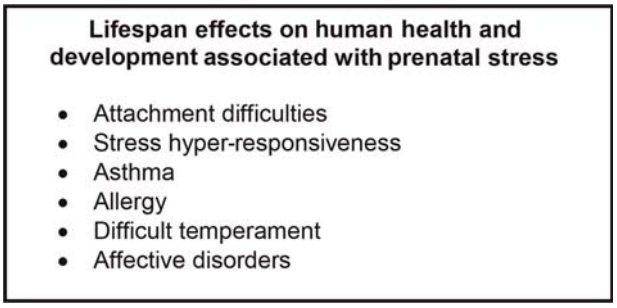

Figure 4 **Summary of lifespan effects on human health and development associated with prenatal stress**

in part, for these effects.[56] Prenatal stress induces the release of glucocorticoids in the mother which enter the fetal circulation and gain access to the developing nervous system.[47] Neurons in the developing hippocampus express high numbers of glucocorticoid receptors, and appear to be especially sensitive to the effects of stress in both infant and adult animals.[57] The cognitive and memory impairments observed in the offspring of stressed pregnancies may be tied to stress-related perturbations in development of the hippocampal system.[57] It is hypothesized that increases in stress hormones in the fetus induced by maternal stress alter hippocampal development by binding to these receptors and either have a neurotoxic effect or disrupt development in other ways such as reducing dendritic arborization.[57,58] Animal-based studies indicate that brain development, specifically that of the hippocampal system which is heavily involved in learning and memory, is adversely affected by prenatal stress and stress hormones during gestation, creating lasting effects on learning and memory.[59] Other animal studies show that prenatal stress affects not only brain development but also the emergence of anxiety behaviour and acoustic startle responses, creating effects that last through adulthood.[60] Similarly, human studies show that stress-related exposure to maternal cortisol creates lasting changes in the morphology of the amygdala and hippocampus in infants and is associated with subsequent affective symptoms in children and young adults.[61]

Animal and human studies also demonstrate that infants of stressed pregnancies have poorer immune function and are more likely to contract childhood illnesses.[62,63] For example, studies of non-human primates show that monkeys whose mothers were chronically stressed during pregnancy had lower proliferation of immune cells in response to a challenge relative to non-stressed offspring, suggesting lasting reductions in the ability of the immune system to adequately respond when necessary.[64] Human studies, although not as numerous, suggest the same pattern, showing persistent and functionally-relevant changes in immune function in the offspring of stressed mothers. Specifically, gestational stress experiences are associated with increased occurrence of allergy and asthma in childhood as well as reduced response to infection and lowered immunity at birth.[63] These effects can persist into adulthood, as demonstrated in the work by Entringer *et al.*[65] showing that lymphocytes of adult women whose mothers experienced a major negative event during pregnancy exhibit altered production of cytokines when challenged *in vitro*. Exposure to stress hormones in the prenatal environment can also have lasting effects on the function of the immune system, illustrating the co-regulation of the endocrine and immune systems (Figure 2). Evidence for this is provided by studies showing that prenatal administration of dexamethasone reduces cell numbers in the thymus and spleen, altering early immune function. Such exposures also alter the developing HPA axis in a manner which predisposes rats to being stress hyper-responsive later in life.[63,66]

FUTURE DIRECTIONS

An ongoing challenge for researchers is understanding the role of racial and cultural stress in augmenting the effects of the types of prenatal stress described above in minority women. Increasing data suggest that racial stress is a contributor to the persistently higher rates of LBW, infant mortality and small for gestational age infants observed in African American women compared with white women.[25,67] Researchers have found that although many prenatal behaviours such as smoking and hypertension in pregnancy are risk factors for LBW for both Caucasian and African American women, exposure to stress is sometimes only predictive of LBW for African American women.[25] Non-white women experience more adverse birth outcomes associated with stress and low social support than white women overall, further suggesting that being a member of a minority group may exacerbate the effects of prenatal stress in pregnancy.[68] These findings emphasize that the concept of stress is multifaceted and an individual's experiences of stress during pregnancy are influenced by not only by the 'stressors' themselves as described above, but also by the cultural, social and environmental context in which the stressors occur. Clearly, additional work is needed to tease apart these complex relationships in a manner which can inform interventional research and clinical care.

Ongoing research is not only continuing to probe the mechanisms of how prenatal stress affects pregnancy outcome and offspring development, but also the extent and duration of its effects. Together, work in this area supports the concept of 'developmental programming', in which early stress experiences have lasting effects on development and function that are evident long past the end of the stress.[47] Although the adaptive advantage conferred by such programming is still unclear, numerous studies confirm that the effects of prenatal stress can extend across generations. For example, animal studies show that alterations in glucocorticoid receptor function and sensitivity can be observed not only in the immediate offspring of experimentally-stressed rats, but also in the subsequent generation, even in the absence of direct maternal stress.[56] Human studies are also suggestive of transgenerational effects of gestational stress. Increasingly, human studies are showing that stressful prenatal events such as intimate partner abuse, poverty, and food insecurity have enduring effects on the stress physiology of offspring, and that prenatal and early childhood stress can set the stage for lasting psychological and health challenges.[69,70] Of particular note are findings that these effects may persist across generations. Specifically, human studies indicate that second-generation offspring of women who experience stress during pregnancy may have alterations in glucocorticoid signalling and increased susceptibility to affective disorders.[56] The implications of these findings are important as they suggest that the effects of prenatal stress may not only affect several generations, but potentially, they can be magnified when additional stress is encountered by affected offspring. Additional longitudinal studies are required to fully characterize

the extent and significance of these epigenetic effects of prenatal stress, and at this time, few studies have concurrently and longitudinally assessed the necessary biological, psychological and lifespan variables necessary to accomplish this. Within this context, others are focusing on developing effective and efficient clinical interventions to reduce the effects of prenatal stress on maternal health and fetal development.

DECLARATION

Competing interests: None.
Funding: Not applicable.
Ethical approval: Not applicable.
Guarantor: Not applicable.
Contributorship: Not applicable.
Acknowledgements: None.

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(Accepted 11 December 2012)