Maternal depression, anxiety and stress during pregnancy and child outcome; what needs to be done

Vivette Glover, PhD, Professor*

Institute of Reproductive and Developmental Biology, Imperial College London, Hammersmith Campus, Du Cane Road, London W12 0NN, UK

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Care for the emotional state of pregnant women remains a neglected aspect of obstetric medicine. Many prospective studies have shown that, if a mother is depressed, anxious, or stressed while pregnant, this increases the risk for her child having a wide range of adverse outcomes, including emotional problems, symptoms of attention deficit hyperactivity disorder, or impaired cognitive development. Although genetics and postnatal care clearly affect these outcomes, evidence for an additional prenatal causal component is substantial. Prenatal anxiety or depression may contribute 10–15% of the attributable load for emotional and behavioural outcomes. The Nurse Family Partnership remains the only intervention that starts in pregnancy and has been shown to have long-term benefits for the behaviour of the child. Several other interventions, however, are likely to be helpful. Depression, anxiety, and stress during pregnancy are frequently undetected by health professionals, and untreated. Programmes to help with this should eventually improve child outcome.

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Introduction

The physical care of pregnant women in the developed world has hugely improved over the past 100 years; however, the same has not been true of their emotional care. This is arguably the most
neglected aspect of obstetric medicine. It is important for the wellbeing of the pregnant woman herself, and also for that of her future child. This aspect will be discussed here.

Considerable evidence from many prospective studies show that if the mother is depressed, anxious, or stressed while she is pregnant her child is more likely to experience a range of adverse neurodevelopmental outcomes than do the children of other mothers [1–3]. These include an increased risk of emotional, behavioural and cognitive problems. It is also well-established that prenatal stress can cause lower birthweight for gestational age, earlier delivery and pregnancy, induced hypertension [4], and altered physical outcomes, such as an increased risk of asthma [5].

With physical outcomes, the phenomenon of fetal programming is well established. This is when the environment in utero during specific critical periods for different outcomes, can affect the development of the fetus and the child in the long-term. Fetal programming has been especially studied in relation to fetal growth and later vulnerability to cardiovascular and related diseases [6,7]. Fetal programming, however, seems to be equally important for the development of psychopathology.

Here, I shall discuss the evidence for the association between maternal prenatal stress and child outcomes (with a special focus on neurodevelopmental outcomes), and evidence that a component of this association is causal. I will then briefly discuss what should be done but will not cover antidepressant and anti-anxiety medication or drug studies.

**Types of stress associated with altered child outcome**

It is clear that it is not just a diagnosable mental illness or extreme 'toxic stress' that is linked with altered outcome. Stress is a generic term that includes a wide range of different types of exposure, and can be acute and chronic. It is defined in different ways, including biologically. The types of prenatal stress found to be associated with altered child outcome, however, have not been found to be associated with any specific biological parameter, such as increased production of cortisol. The types of stress are objective stressors and subjective stress, but this has not been studied in this context. It has also been suggested that mild stress may have different effects from more severe stress, and may be beneficial for some outcomes [8].

Exposures that have been shown to be associated with altered child outcome vary from the very severe, such as the death of an older child, to quite mild stresses, such as daily hassles. They include symptoms of maternal anxiety [9–13] and depression [9], as well as a diagnosis of depression [14], pregnancy-specific anxiety and daily hassles [15], bereavement [16], and stress caused by a bad relationship with the partner [17]. They also include exposure to acute external disasters [18], the September 11 attacks [19], Chernobyl [20], a Louisiana hurricane [21], or war [22,23]. Domestic abuse during pregnancy has not been studied as such for its effects on the fetus and the child, but is also likely to be important.

One issue of interest is whether some forms of stress have a greater effect than others, but little is yet known about this. A few studies have examined both prenatal anxiety and depression, and have found associations between both of them and child outcome [9,10]. Of course, anxiety and depression are quite strongly co-morbid, and it is hard to disentangle the effects of the two. It is possible that they can affect outcome but in somewhat different ways. Barker et al. [24] found that, in the prenatal and postnatal periods, maternal depression had a wider effect on different types of child maladjustment than maternal anxiety, which appeared more specific to internalising difficulties in the child.

**Types of outcome altered**

A wide range of different outcomes have been shown to be associated with prenatal stress in studies examining the children from birth until adulthood. At birth, an increase in congenital malformations has been found to be associated with severe stress in the first trimester, such as the death of an older child [25]. Many studies have shown that less severe stress is associated with somewhat lower birthweight and reduced gestational age [26,27]. Another finding at birth is an altered sex ratio, with fewer males to females being born than in an unstressed population [28,29]. Mothers scoring in the
upper quartile of the General Health Questionnaire had 47% boys compared with 52% in the undistressed groups [28].

Most studies have looked at neurodevelopmental and psychopathological outcomes. Some investigators have looked at the newborns of mothers who report stress during pregnancy and found a poorer performance on the Neonatal Behavioural Assessment Scale relative to newborns of mothers who do not report stress during pregnancy [30], showing that adverse behavioural outcomes are observable from the very beginning. Studies of infants and toddlers have shown them to have a more difficult temperament [10,31], sleep problems [32], and lower cognitive performance and increased fearfulness [17] associated with higher maternal stress during pregnancy.

Many studies have examined the association between prenatal stress and neurodevelopmental outcomes in children ages 3–16 years, rather than babies, infants or adults. Many independent groups have shown that prenatal stress increases the risk for child emotional problems, especially anxiety and depression, and symptoms of attention deficit hyperactivity disorder (ADHD) and conduct disorder [9,23,26,33–36]. Other studies have shown a reduction in cognitive performance [12,18] associated with prenatal stress.

Some studies have found an association between prenatal stress and increased risk of autism [21,37], with exposure in mid- to late-gestation, although a large population study has failed to confirm the increased autism [38]. Two studies have found an increased risk of schizophrenia in adults born to mothers who experienced stress during pregnancy. Both showed effects with severe stress, the death of a relative [16] or exposure to the invasion of the Netherlands in 1940 [22], and both showed that the sensitive period of exposure was during the first trimester.

A further set of studies have shown associations between prenatal stress and a range of altered physical and physiological outcomes. These include an altered fingerprint pattern [39], more mixed handedness [40,41], and specific regional reductions in brain grey-matter density [42]. Such altered grey matter may be associated with neurodevelopmental and psychiatric disorders, and cognitive and intellectual impairment.

Several studies have shown that prenatal stress is associated with an altered diurnal pattern or altered function of the hypothalamic–pituitary-adrenal (HPA) axis although the pattern of alteration is quite complex [43]. Finally, recent studies have shown that prenatal anxiety is associated with reduced telomere length [44,45]. This is an intriguing finding, as well as of concern, as reduced telomere length is associated with a reduced life span.

Research on the most sensitive time in gestation for the influence of prenatal stress is inconsistent. It is likely that sensitivity can occur at different times depending on the outcome studied and the stage of development of the relevant brain or other structures. Two studies of schizophrenia found that the most sensitive period was in the first trimester. This is when neuronal cells are migrating to their eventual site in brain, a process previously suggested to be disrupted in schizophrenia. In contrast, two studies of conduct disorder, or antisocial behaviour, found the greatest associations with stress later in pregnancy [26,33]. It is clear that these effects are not all over by the first trimester, but this is an area where much more research is needed.

Is maternal stress and altered outcome causal?

Many human studies, as discussed above, have shown an association between maternal stress during pregnancy and a risk for altered outcome for the child. The evidence for this is strong, and has been shown in many independent prospective studies from around the world. What is harder to establish is that the association is causal. If a mother is stressed while she is pregnant she may well be stressed postnatally and this could affect her parenting. Other associated confounding factors include smoking or alcohol consumption, which may affect behaviour and birthweight. Genetic continuity could also occur. The mother may have certain genes that make her more likely to become anxious or depressed, and she may pass these genes on to her child, which in turn makes them more prone to emotional or behavioural problems.

Several studies have tried to address these issues. These include animal studies, human studies showing changes at birth, human studies that have allowed for many possible confounders, and human studies that are starting to uncover possible underlying mechanisms.
With animal studies, it is much easier to establish that prenatal stress has a direct effect on the outcome for the offspring. Newborn rat pups of prenatally stressed mothers can be cross fostered to non-stressed mothers on the first day after birth, with control pups of unstressed mothers cross-fostered also. This can establish that any differences in outcome are caused by stress in the prenatal period. Many such studies have shown definite programming effects of prenatal stress on behaviour, cognitive development, the HPA axis, and brain structure and function of the offspring [46–49]. The nature of the effects can be affected by the timing of the exposure in gestation, the type of the stress, the strain of the animal, the age at which the offspring was tested, and the sex of the offspring [48]. Some altered outcomes are not observed in the youngest offspring, but become apparent as they mature. In general, although not always, prenatal stress increases anxiety and depressive behaviour to a greater extent in female offspring, and impairs learning and cognition more in the males [50]. The effects of prenatal stress on the offspring can often be mimicked by giving the stress hormone corticosterone or a synthetic glucocorticoid to the pregnant animal [49]. Some of the effects of prenatal stress can also be moderated by the quality of the postnatal maternal care [51].

In humans, an association between the mother’s emotional state and the behaviour or heart rate of her fetus is supported by good evidence. Monk et al. [52], for example, have conducted experiments in which a pregnant mother is asked to carry out a stressful computer task, while the fetal heart rate is monitored [52]. They showed that the fetal heart rate went up during the task, but only in the mother’s, who rated themselves as anxious. Thus, even before birth, the fetus can be affected by the maternal emotional state, although we do not know what the mechanism is. The effects are too fast to be caused by cortisol, which takes 10–20 mins to rise, and catecholamines do not cross the placenta. Evidence shows continuity from fetal behaviour and neurological maturation in the first weeks after birth. For example, fetal parameters, such as heart-rate variability and fetal movement, predicted neonatal motor behaviour and reflexes [53].

Several studies have shown that maternal stress during pregnancy is associated with altered outcomes at birth, including reduced birthweight [26], reduced scores on the Brazelton assessment [54], and a more difficult temperament [55] soon afterwards. Recently, an alteration in telomere length in cord blood leukocytes has been shown to be associated with pregnancy-specific anxiety [45]. These studies all provide some evidence for prenatal, independent of postnatal, effects.

Another approach is to carry out prospective human studies allowing for as many potential confounders as possible, such as prenatal smoking and alcohol consumption, and for postnatal maternal mood. Several studies have found a strong signal remaining for prenatal anxiety or depression on child emotional and behavioural problems [9,34,17] after controlling for many confounders, including postnatal depression and anxiety. In our study (unpublished data), we found that these effects are also apparent when allowing for paternal pre- and postnatal mood. If the observed associations are primarily due to an anxious mother passing on predisposing genes to her child, it would not be expected to be specifically associated with prenatal compared with postnatal mood, or maternal compared with paternal mood. One recent study, which just looked at the outcome of ADHD, found that the effect of prenatal maternal mood remained after controlling for paternal mood in one cohort, the Avon Longitudinal Study of Parents and Children, but not in another, Generation R [56]. Differences in design and the measuring instruments used may help to explain this discrepancy. Postnatal maternal mood and parenting both have clear effects. For example, the association between prenatal anxiety and child fearfulness was found to be greater in those children with an insecure attachment [57]. Most of the prospective cohort studies, allowing for confounders, also suggest a prenatal causal component.

In a study by Rice et al. [26] in children born after in-vitro fertilisation [26], prenatal stress and child outcome in babies who were genetically related to the mother was compared with those who were not [26]. They showed an association between maternal stress in pregnancy and child symptoms of ADHD and conduct disorder, and that the association with conduct disorder was apparent in the unrelated mothers. This gives strong support to the idea that the association between prenatal stress and child conduct disorder is independent of genetic factors. The fact that the increase in symptoms of ADHD was apparent only in those with related mothers does not conclusively rule out a prenatal environmental component. A gene environment interaction may also be involved. Prenatal stress may only
have the effect of increasing symptoms of ADHD in the genetically vulnerable mother and child pairs. More research is needed to disentangle the role of genetic factors for all outcomes.

Another indication that the effects of prenatal stress are not just caused by genetic continuity are the group of studies that have studied children of mothers exposed to acute disasters. These have included a Canadian ice storm [18], the September 2011 attacks [19] and Chernobyl [20]. With these ‘natural or man-made experiments’, as for example in the ice storm study, the level of stress was objectively assessed, and the exposure was of a specific duration. This reduces the confounding effects of pre-existing emotional problems and genetic continuity.

**Underlying biological mechanisms**

Little is understood about the mechanisms that may underlie fetal programming by prenatal stress in humans. One early suggestion was a decrease in blood flow to the fetus [58]. It is not clear, however, if the decrease observed in that study would be clinically significant, and others have failed to replicate the original finding [59].

Another possible mediating factor is increased exposure of the fetus to cortisol. Glucocorticoids (e.g. cortisol in humans and primates, corticosterone in rodents) are known to have a range of effects on the developing fetus, including on the brain [60]. Although they are essential for fetal development and tissue maturation, overexposure can have effects that predispose to ill health in later life. [61] 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 mechanism. The human HPA axis functions differently in pregnancy from most animal models, because of the placental production of corticotropin-releasing hormone, which in turn causes an increase in maternal cortisol. The maternal HPA axis becomes gradually less responsive to stress as pregnancy progresses [62], and there is only a weak, if any, association between maternal mood and the woman’s cortisol level, especially later in pregnancy [63]. It thus seems unlikely that an increase in maternal cortisol is the mediating mechanism between prenatal maternal stress, anxiety or depression in later pregnancy and altered fetal outcome.

It is possible that fetal programming may be partially mediated by cortisol without increases in maternal levels. Depression, stress, or anxiety may cause increased transplacental transfer of maternal cortisol to the fetal compartment. 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 [63]. Thus, another mechanism by which the fetus could become overexposed to glucocorticoids is through changes in placental function, especially the enzyme 11\(\beta\)-hydroxysteroid dehydrogenase type II (11\(\beta\)-HSD2), the barrier enzyme which converts cortisol to the inactive cortisone. If there is less of this barrier enzyme then the fetus will be exposed to more maternal cortisol, independently of any change in the maternal level. Some evidence in rat models shows that prenatal stress can down-regulate placental 11\(\beta\)-HSD2. Restraining pregnant rats in the last week of pregnancy, a procedure they find stressful, has been shown to result in decreased placental 11\(\beta\)-HSD2 expression and activity [64]. Our laboratory has found direct evidence that maternal prenatal anxiety and depression are also associated with a down-regulation of 11\(\beta\)-HSD2 in humans [65].

It is unclear which changes in maternal chemistry associated with maternal mood in pregnancy have this influence on placental function. One possibility is the cytokines. Psychosocial stress during pregnancy has been shown to be associated with raised levels of inflammatory cytokines such as interleukin-6 [66]. How, if at all, these affect placental function remains to be determined.

Serotonin is another possible mediator of programming effects induced by prenatal stress on the offspring’s neurocognitive and behavioural development. During gestation, serotonin acts as a trophic factor regulating cell division, differentiation and synaptogenesis [67]. Animal studies have shown that increased serotonin exposure during gestation is associated with alterations in many neuronal processes and subsequent changes in offspring behaviour. Recent work has identified an endogenous serotonin biosynthetic pathway in the human placenta [68], suggesting a possible role for alterations in placental serotonin in human fetal programming.

Epigenetic changes, which involve reversible changes to the structure of DNA, such as the addition of a methyl group, control the amount of mRNA and protein produced. Such
epigenetic changes can be induced by the environment, and may underlie many of the processes of fetal programming. Prenatal stress has been shown to cause epigenetic changes in the rodent brain, in the DNA, which codes for the receptor that binds the stress hormone cortisol [69]. In humans, stress during pregnancy caused by violence from the partner, has been shown to cause epigenetic changes in the DNA for this same receptor, in the blood of their adolescent children [70].

Clinical magnitude of the effects of prenatal stress

The magnitude of many of the effects described above are not just statistically significant but also clinically significant. In the large Avon Longitudinal Study of Parents and Children population study, it was found that, if the mother was in the top 15% for anxiety, her child was at double the risk for emotional and behavioural problems at ages 4 and 7 years [9,33] after controlling for a wide range of possible confounders, including postnatal maternal mood. The risk was raised from about 5% in the general population to about 10% in the children of the high anxiety group. Most children were not affected, and those that were, were affected in different ways. It is possible to calculate from this that the attributable risk of childhood behavioural problems caused by prenatal stress is about 10–15% [2]. Similar results have been reported at age 13 years (unpublished data). The effects of prenatal stress on cognitive development also seem to be clinically significant. In a study correlating prenatal life events with child cognitive development at 17 months, Bergman et al. [17] found that prenatal stress accounted for 17% of the variance in cognitive ability, after allowing for a range of confounders, including postnatal maternal mood. Prenatal partner relationship strain accounted for most (73%) of the variance in cognitive ability related to life-event stress. If the woman said she had suffered from three or more partner-related life events (e.g. your partner was emotionally cruel to you), her infant had a mean Bayley Mental Developmental index of 89, compared with 98 for the rest of the group. King and Laplante [71] found even greater effects on cognitive ability. They examined 2-year old children of mothers who had been exposed to a Canadian Ice storm during pregnancy, and compared the outcome for those who had been exposed to high or low stress. For children of mothers exposed to high stress in the first or second trimesters, the Bayleys’ scores were 14 and 19 points respectively, lower than the children of the low stress mothers.

What should be done?

These findings have important clinical implications. If maternal depression, anxiety, or stress during pregnancy can increase the risk for an adverse outcome for the child, then interventions to reduce such stress should improve the outcome. It is clear that not all the adverse effects described above are caused in the first trimester. Many also seem to be caused by changes in the second and third trimesters. Therefore, although it is best to start interventions as early as possible, later interventions are likely to be beneficial too.

No study has yet been conducted on interventions specifically designed to reduce maternal depression, anxiety, or stress during pregnancy with a long-term follow-up study of outcomes for the child. The only intervention that starts during pregnancy and that has included long-term follow up studies is the Nurse Family Partnership. This is targeted at deprived, especially teenage, and poor single mothers, and includes multiple home visits by specially trained nurses during pregnancy and for the first 2 years. It was not designed to target stress but to help the mothers with diet, health care, their own education, reduction in smoking, and with parenting. These special nurses, however, do provide much support for these mothers from early pregnancy onwards. The results of this intervention have been impressive, with many long-term improvements in self care and parenting behaviour, as well as child outcome [72–74]. A notable finding was a reduction of criminal behaviour, especially in girls [75]. Compared with the comparison group, by 19 years of age, girls in the pregnancy and infancy nurse-visited group were less likely to have been arrested (10% v 30%) and convicted (4% v 20%). No comparable benefit was observed for boys. As prenatal stress causes an increased risk for conduct disorder, ADHD, and cognitive problems, and all these are major risk
factor for later criminal behaviour, one would expect a reduction in prenatal stress to reduce crime as well as improving other outcomes. It may be that, for boys, a ‘top up’ intervention in the teenage years is needed. Olds et al. [76] have shown that this programme is of great benefit and is cost effective. After assessment when the children were 12 years old, the government spent less on various types of aid to the families than the cost of the programme, with a net saving of about $800 per family.

Although no other long-term follow-up studies have been published, several studies of interventions that reduce aspects of depression, anxiety and stress during pregnancy have been conducted [77]. Interpersonal therapy has been shown to be effective at reducing depression during pregnancy [78]. A randomised-controlled trial of cognitive–behavioural therapy for anxious or depressed pregnant women is being conducted [79]. New models of perinatal care are being developed [80], and evidence shows that interventions delivered in the home setting may be especially helpful [81].

Listening to music has been found to decrease maternal plasma cortisol and self-reported state anxiety score in pregnant women awaiting amniocentesis [82]. Maternal relaxation has also been shown to improve indices of fetal neurobehaviour, such as heart rate variability [83]. One study compared active (directed by a therapist) and passive (sitting in a chair) relaxation [84]. Both active and passive relaxation significantly reduced state anxiety and maternal heart rate, but the effect was significantly greater with the active relaxation. In contrast, the passive relaxation significantly reduced noradrenaline levels, whereas active did not. Both methods significantly reduced cortisol. Overall, however, a striking lack of correlation existed between the psychometric and biological indices. To reduce specific biological effects of anxiety or depression during pregnancy, different methods may be needed from those which are most effective at reducing subjective psychological symptoms.

It is still true that most depression, anxiety, and emotional and physical abuse experienced by pregnant women is undetected by health professionals, and little help seems to be available [85]. Symptoms of anxiety and depression are at least as common during pregnancy as postnatally [86], and domestic abuse can increase. Midwives and obstetricians need to be trained to detect all this and offer appropriate support or help. If women are anxious or depressed they should be referred to their general practitioner, as recommended in the National Institute for Health and Clinical Excellence 2007 guidelines on antenatal and postnatal mental health. If suffering abuse, they should be referred to specific agencies focusing on domestic abuse. Up to 15% of pregnant women and their children would benefit from this type of support. For most depressed or anxious women, some sort of counselling or talking therapy, such as cognitive–behavioural therapy [87] will be most appropriate. For the more severely depressed, more specialised care may be necessary, and antidepressants may be the best option. Although the use of antidepressants has not been discussed here, some evidence shows that their use in anxious women may benefit at least some aspects of child outcome [88].

Conclusion

Good evidence shows that the emotional state of the mother during pregnancy, as well as in the postnatal period, can have long-term effects on her child, especially on neurodevelopmental outcomes. The mechanisms underlying such fetal programming are only just starting to be uncovered and, often, a limited correlation between psychometric indices and biological ones. Research is still needed to determine which interventions during pregnancy are most effective at improving child outcome. More needs to be done to detect and treat emotional problems and disorders during pregnancy. This will benefit the woman herself, and eventually will benefit the next generation also.

Conflict of interest

None declared.
Practice points

- Mental health is fundamental to health.
- A psychosocial assessment that includes enquiring about the woman’s overall wellbeing, including stressors, important relationships and strengths, should be part of her routine maternity care. This discussion can open the conversation about psychosocial issues, including intimate partner violence and people who may be able to support her.
- Routinely use a screening instrument, such as the Edinburgh Postnatal Depression scale (EPDS), which also assesses symptoms of anxiety, and is validated for use in pregnancy. This does not give a diagnosis but, if the woman’s score is of concern (13 or above), she should be receive additional evaluation for the presence of an episode of major depression or other mental disorder and intervention.
- Evidence suggests that fetal development can be affected in women in the top 15% for symptoms of anxiety, depression, or stress, even if they do not meet criteria for a disorder. An optimal service will provide an appropriate intervention or help for such women.
- A system of care, ideally including a perinatal mental health care team, should be in place so that health professionals know to whom they should refer a women in need of mental health assessment and treatment.

Research agenda

- The effects of domestic abuse on child outcome needs to be investigated.
- More research is needed on the underlying mechanisms by which maternal stress affects child outcome.
- Interventions that help the mother may not necessarily help the outcome for the child. Research is needed to follow up children of depressed, anxious, or stressed mothers after different specific interventions to determine their effects on different child outcomes.

References


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