Encyclopedia on Early Childhood Development

Stress and pregnancy (prenatal and perinatal)

Updated: April 2019

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Synthesis

How important is it?

Stress is a complex term that encompasses a large number of states such as mild stress, distress, anxiety and depression that can be experienced as a result of a range of phenomena including daily hassles, dysfunctional relationships, and adversity.

There is a consistent belief across cultures that maternal stress can have a negative effect on the development of the fetus, baby, and child. This is particularly important given the high levels of daily stress reported by women of childbearing age. For instance, of Canadian women between the ages of 20 and 34 in 2010, 25.4% sustain intense daily stress, compared with 20.5% for their male counterparts.[1] It is no surprise that programs focused on stress and coping programs have been at the major front of international efforts to promote mental health across countries.[2]

Working during pregnancy may have an impact on the level of stress (self-perceived or objectively assessed). The risk or premature birth labour is 70% higher among pregnant women who work in a stressful or noisy environment than other women.[3] In 2008, the international rate of maternal employment for women between the ages of 25 and 49 was approximately 61%, with the highest rates observed in Scandinavian and North-American countries, and once children reach school age.[4]

What do we know?

Maternal stress in humans

The core of the research on the connection between maternal stress and child development focuses on the lasting effect of prenatal exposure to stress. Although the placenta serves as a barrier to protect the baby against harmful substances, some hormones such as cortisol released in times of stress, can cross the placenta and alter the intrauterine environment. A few studies have detected small associations between prenatal stress and low birthweight and prematurity.

Generally, prenatal stress has been associated with a number of detrimental outcomes, including cognitive, language, behavioural, emotional, and neurodevelopmental problems. For instance, children whose mothers experienced high levels of anxiety during pregnancy are twice as likely as other children to experience difficulties of a behavioural or emotional nature persisting in early adolescence. However, the connection between the presence of elevated cortisol in the amniotic fluid and poorer cognitive development disappear when children experience sensitive and optimal parental care after birth.

The impact of stress also varies as a function of gestational period. Whereas the risk of developing schizophrenia later on in life is associated with acute stress during the first trimester, Attention deficit hyperactivity disorder (ADHD) is more common among children of expecting mothers who are exposed to

stress during late pregnancy. The amount of stress experienced by the mother is also important because mild stress may be related to positive outcomes on children's motor and cognitive development.

Babies of mothers from poor economic background are particularly at risk for the harmful effects of stress due to the frequency and uncontrollability of the stressors this population experiences. However, because stress is also associated with unhealthy behaviours such as smoking and alcohol consumption, it is often difficult to isolate the effects of stress itself and other negative events.

Given the potential risk that prenatal stress poses for child development, there is a pressing need to find ways of establishing the causal connections in humans so that successful and well-targeted interventions can follow. For instance, research should compare siblings exposed and not exposed to prenatal stress to tease apart the role of genes and parenting on the association between stress and postnatal development. The role of coping strategies in successfully reducing prenatal stress and later developmental problems is another encouraging avenue of research. Research designs should also include clinical trials (for both medications and behaviour therapies), biological and psychological measures of prenatal stress, and objective assessments of child development while ensuring adequate control of maternal stress after birth.

Animal research on maternal stress

The most conclusive evidence for establishing a causal link between prenatal stress and child development has been generated by studies on animals, primarily rodents (rats and mice) and non-human primates (monkeys and apes), in which prenatal stress can be experimentally manipulated.

Research with primates found that stress during pregnancy was related to slightly lower birth weight, as well as attentional, behavioural, and motor problems in the offspring. The negative effects of prenatal stress on birth weight and behaviour were strongest when paired with prenatal alcohol consumption. In addition, attentional and learning problems observed in the postnatal period tended to persist during adolescence. Although chronic stress in the second half of gestation was related to some of these deficits, stress overall was more detrimental in the early stages of pregnancy.

What can be done?

More research is clearly needed in this area. We need to know more about the relative contributions of prenatal stress, postnatal care and genetic vulnerabilities, and the underlying mechanisms. However there is enough evidence now that prenatal stress increases the risk for an adverse child outcome to make some recommendations. Programs targeting the reduction of anxiety, depression and stress in expectant mothers should be a cost-efficient method to improve problems such as low birth weight, prematurity and particularly neurodevelopmental problems. These programs might include policies regarding maternal employment and parental leave, but should not equally direct the activities and actions of all pregnant women because stress is a subjective experience that is not rigidly dictated by environmental events. All new intervention programs should be evaluated as to child outcome.

One of the first steps toward the elaboration of appropriate intervention and prevention programs is to identify groups of women who are particularly at risk for experiencing different forms of stressors at different periods

during their pregnancy, and assess how these different groups differ in terms of child outcomes.Because parents themselves should have the opportunity to improve their understanding of their child's development, they should be informed by service providers of the mechanisms by which maternal stress can affect the intrauterine environment and subsequent development. Health care providers and psychosocial workers should be trained to communicate this information to parents because it can also help reduce mothers' worries about their own levels of stress. At the individual level, every expecting mother should have access to professional help tailored to her needs and circumstances.

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Prenatal Stress and Offspring Development in Nonhuman Primates

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January 2011, Rev. ed.

Introduction

Psychosocial stress during pregnancy has been linked to adverse developmental outcomes in children, including low birthweight and shorter gestation duration, reduced neonatal attention and habituation to stimuli, and increased risk for Attention Deficit Hyperactivity Disorder, schizophrenia, speech impairments and social abnormalities.[1-6] Primate studies conducted under controlled laboratory conditions have provided an inferential link between rodent studies and human epidemiological studies.

Subject

Increased stress and violence in everyday life has resulted in a growing concern about the effects of maternal stress on child outcomes. This is particularly true in the economically underprivileged sector of our society, where individuals are more likely to be subjected to uncontrollable daily pressures and more serious stressors such as relocation and unemployment. Because women under stress are more likely to smoke cigarettes, consume alcohol, and engage in other stress-related behaviours, there is often a clustering of negative events, which can compound the adverse effects on the developmental outcome of their children.

Problems

It is difficult to establish causal links between prenatal stress and developmental outcomes in human studies due to selection bias and possible confounding variables. Even with statistical corrections, it is impossible to ascertain whether major confounders have been eliminated or whether the method of adjustment has effectively removed confounders. In primate studies, one can use randomized experiments, inferring causal connections between prenatal stress on one hand, and offspring behaviour and development on the other. Nonhuman primate studies make an excellent model for studying prenatal stress because of the similarity in brain structure and biological processes of stress reactions to humans between nonhuman primates and humans. Other factors include the richness of nonhuman primate social organization and their complex cognitive capabilities, the opportunity to isolate prenatal stress from other factors and to employ a standard stress treatment, and the ability to investigate possible biological underpinnings.[7-9] The disadvantages of nonhuman primate studies are that it is necessary to use small sample sizes, cost is high compared to rodent studies, and one must still generalize from animals to humans, albeit this inferential leap is smaller with nonhuman primates than it is with rodents.

Research Context

Stressful events stimulate the release of stress hormones, which can cross the primate placenta (at least in small amounts), and can influence fetal development. Studies with rodents and with nonhuman primates have demonstrated that when dams were injected with a stress hormone (corticotrophin-releasing hormone) (CRH), or when pregnant rhesus monkeys were injected with adrenocorticotrophic hormone (ACTH), their offspring showed effects similar to those observed in prenatally stressed offspring.[10,11]

Key Research Questions

Our research used daily exposure to three short bursts of noise (115 dB sound at 1 m, 1300 Hz) as a prenatal stressor to answer the following questions:

- Does unpredictable daily psychological stress during pregnancy have an adverse effect on birthweight, gestation duration, neonatal neurobehaviour and/or stress reactivity?
- Is there a sensitive period or time of enhanced vulnerability for prenatal stress effects?
- Are maternal stress hormones an important part of the mechanism for the prenatal stress effects on the offspring?
- Does prenatal stress interact with other potential negative events, such as fetal alcohol exposure?
- Is there continuity between effects observed during infancy and later cognitive functions?
- Does prenatal stress have long-term effects on dopamine system function as assessed with *positron emission tomography (PET)* imaging?

Recent Research Results

- Prenatal stress significantly reduced birthweight, but did not shorten gestation durations, although all birthweights were within the range of what is considered normal for rhesus monkeys.[12] Prenatal stress was also associated with a neurobehavioural profile that included reduced neonatal attention, motor maturity and motor activity.[13-15,10] When exposed to stressful events, prenatally stressed monkeys showed more disturbance behaviour and higher levels of stress hormones, compared to controls.[16-18,12]
- The effects of prenatal stress on birthweight and early neurobehaviour appear to peak during early gestation and taper off during mid-to-late gestation.[14]
- Maternal endocrine activation was shown to be one of the underlying mechanisms for the effect, since administering ACTH to pregnant females resulted in effects similar to those observed in prenatally stressed monkeys.[10]
- When prenatal stress was combined with fetal alcohol exposure, the most adverse effects on birthweight and behaviour were observed, compared to controls.[19-21]
- There was a significant association between reduced neonatal attention and learning deficits during adolescence in nonmatch-to-sample, showing some continuity between early deficits and later outcomes.[20]
- Prenatally-stressed and prenatal stress + prenatal alcohol-exposed monkeys showed two differences in

dopamine function compared to monkeys that were not exposed to prenatal stress: 1) higher ratio of *dopamine D2 receptor* binding to dopamine (DA) synthesis in the striatum.[22] Less dopamine is synthesized and the receptors increase or up-regulate to compensate, and 2) higher dopamine transporter binding which regulates extracellular levels of dopamine in the *striatum*.

Conclusions

Nonhuman primate studies, conducted under carefully-controlled laboratory conditions, are an important link between rodent research and human studies. Primate studies indicate that prenatal stress induced lower birthweights, reduced early attention and motor maturity, slower learning, impaired emotion regulation and induced long-term changes in dopaminergic function in the striatum. It is interesting to note that adolescents and adults with ADHD show a 40-50% increase in dopamine transporter binding in the striatum, however not all studies have found this effect. Early gestation appears to be a period of enhanced vulnerability for some of these effects, although effects are also observed from chronic stress during mid-to-late gestation. More research is needed to study the severity of stress, chronicity versus single episodes of stress, timing of stressful events, and the effects of clustering of negative events. In people, coping strategies are very important in ameliorating the impact of stress, and such strategies cannot be studied in animals. Research to date supports a tentative conclusion that there is a causal connection between prenatal stress and developmental outcomes in humans and nonhuman primates.

Implications

Because development is shaped by a highly complex process involving the interplay of biological and environmental factors,[23] it is reasonable to add prenatal stress to the list of risk factors that may adversely affect development, especially when combined with other risk factors. Relevant public policy issues in this area of research include the identification and reduction of existing risk factors and the enhancement of available protective factors in pregnant women. The public needs to be educated about risk factors during pregnancy, including prenatal stress, and the clustering of negative events. Professional training for service providers should include information relevant to risk factors, including stress, and the possible effects on offspring.

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Prenatal Stress and Child Development: Translating Animal Studies to Human Health

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January 2011

Introduction

Prenatal stress is a leading paradigm used in experimental animal studies to demonstrate that early stress exposure can have lasting impact on the behaviour and biology of the offspring.[1] If the strength, persistence, and diversity of effects of prenatal stress from these studies extend to humans, then the implications for public health and prevention are enormous. Accordingly, research on stress in human pregnancies has burgeoned in recent years, and this now constitutes a major research area on several continents.

Subject

A model underlying research on prenatal stress in humans has been discussed by several groups.[2-3] The starting point is that the fetal period is one of particular *ontogenetic* vulnerability. That is, exposures – good or bad – during this time would be expected to have lasting effects. Even casual observers of science and medicine would be familiar with how certain molecules, such as folic acid, could have a dramatic influence on the long-term health outcomes of the developing fetus. The prenatal stress model makes a parallel hypothesis focusing on stress hormone exposure, and *cortisol* in particular – although there may be a number of mechanisms involved. Cortisol is a downstream product of the *Hypothalamic-Pituitary-Adrenal (HPA) axis*, one of the most-studied mind-body systems. Research has focused on the HPA axis for several reasons. One is that there are human data showing that cortisol crosses the placenta.[4] Although the placenta screens out many substances, and there is an enzyme (11BHSD2) that prevents the crossing of cortisol, but it does so imperfectly. That implies that stressed or anxious mothers who have elevated cortisol may have fetuses who are exposed to elevated levels of cortisol in utero. If prenatal maternal anxiety or stress did alter fetal HPA axis via early cortisol exposure, then the implications for development would be substantial. That is because of the wide reaching impact of the HPA axis on many areas of functioning, including stress physiology, cognition and memory, immunology and cardiovascular health.[5]

Hypothalamic-Pituitary Adrenocortical Axis or Stress Hormone Axis.

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Figure 1. Hypothalamic-Pituitary Adrenocortical Axis or Stress Hormone Axis.

Problems

The number of studies linking stress or anxiety to child outcomes is impressive and mostly consistent, but uncertainties remain about the mechanisms involved. Additionally, most of the studies included largely middle-class samples; whether or not the effects of prenatal stress extend to high-risk samples, including samples from developing countries, is unknown and represents a notable gap in the literature.

Research Context

Research on prenatal stress in humans follows an established paradigm in experimental animal work dating back many decades. The research context of the animal work is especially compelling, but the translation to human development is incomplete. That is partly because the precisely-timed, well-controlled nature of stress exposure used in most animal studies does not easily apply to the kinds of chronic stress-exposed families of most interest to clinicians and social policy-makers.

Key Research Questions

Findings emerging from studies in the U.S., Canada, Europe and Australia all suggest that there is an association between prenatal anxiety or stress and a range of child development outcomes. The questions for research are now:

- What are the mechanisms by which prenatal stress or anxiety causes (if it is causal) a range of

biobehavioural outcomes in the child?

- Are the effects of prenatal stress or anxiety modifiable by intervention in pregnancy or the postnatal period, or by the early caregiving environment?
- Is it practical to identify which children may be at risk based on a prenatal screening of the mother?

Recent Research Results

Research groups in several countries link prenatal stress or anxiety to a range of child outcomes. The more reliable links are with lower cognitive and language ability;[6] more difficult, inhibited, or emotionally reactive temperament;[7] behavioural problems;[8] and poorer neurodevelopmental outcomes.[9] Studies linking prenatal stress or anxiety to child outcomes have extended the longitudinal follow-up to adolescence.[10]

Significantly, the push to examine the prenatal stress/anxiety hypothesis often missed another key element, the role of postnatal rearing. Experimental animal studies demonstrated that the effects of prenatal stress could be eliminated by positive postnatal rearing.[11] Unfortunately, with few exceptions, human research on prenatal anxiety or stress has ignored the early caregiving environment. One exception is a recent study[12] that found that elevated levels of cortisol in amniotic fluid, taken at an average age of 17 weeks gestation, predicted lower cognitive ability in the infant. More impressive was that this association was entirely dependent on the quality of the child-parent relationship: for children who experienced less than optimal care, amniotic fluid cortisol strongly negatively predicted infant cognitive ability; however, for children who experienced a sensitive-response caregiving environment, there was no association between amniotic fluid cortisol and infant cognitive ability.

Research Gaps

Two main gaps remain in the human research on prenatal stress and anxiety and child outcome. The first is confirmation of a mechanism or mechanisms. Cortisol, as noted, is the leading candidate mechanism, but research has yet to show that it clearly mediates the effects of prenatal maternal stress on child outcomes; indeed, evidence of non-mediation has been reported.[12] In addition, it is essential not to see cortisol as an inevitably adverse exposure. Cortisol, and *glucocorticoids* more generally, have numerous biological functions, including a functional role in childbirth, for example. That is, it is important to understand cortisol as both serving essential, functional and potential adverse roles in human development – a tricky balance that is not yet firmly rooted in how research is conducted.

A second major gap concerns intervention. One might speculate that reducing anxiety or stress during pregnancy through an array of psychological treatments might prevent the adverse effects in the child. Unfortunately, no clear evidence yet exists. Randomized controlled trials that capitalize of the leverage of a treatment study would provide the most powerful demonstration of a causal effect and offer concrete clinical guidance for those caring for stressed and anxious pregnant mothers. It is unfortunate that so much of the attention on treatment focuses on psychiatric medications. Psychological treatments such as cognitive behaviour therapies are effective and do not carry *iatrogenic* risk.

Conclusions

Prenatal maternal stress or anxiety has been shown in a variety of studies to be a risk for poor or compromised

development in the child, indexed by such measures as cognitive and language ability, temperament, neurodevelopment, and behavioural and social adjustment. The weight of the evidence suggests that this is rightly seen as a potential clinical and public health concern that warrants particular attention. No causal link can yet be drawn due to the limited leverage of existing human studies. Much of the speculation about mechanisms focuses on the HPA axis and its downstream product cortisol. One important benefit for research is that cortisol can be measured from saliva, making it an accessible – if not fully understood – biological marker of stress in the mother and risk to the child. One of the more notable findings from recent studies is that early parent-child relationship quality may eliminate or otherwise modify the effects of prenatal stress on the child. That raises implications for intervention that are only now being investigated.

Implications for Parents, Services and Policy

The identification of causal mechanism is important for scientists for advancing theories and biological models and for clinicians whose construction of intervention relies on a clear and sound understanding of how an intervention works. Policy-makers are equally dependent on understanding mechanisms so that money is not wasted on mis-targeted programs. The case for parental understanding of mechanisms – to understand better their children's development – is no less subtle. Thus, curiosity about why prenatal stress may pose a risk is not merely an academic concern.

A more obvious implication is prevention. If it were possible to prevent the adverse effects of maternal prenatal stress or anxiety on the child – and this has not yet been soundly demonstrated – then policies could be put in place to cost-effectively promote the well-being of women and children. Several outcomes linked to prenatal stress or anxiety, namely, low birthweight, prematurity and neurodevelopmental problems in children carry sizable costs and prevention efforts have not been very successful. It is not certain that reduction to maternal prenatal stress or anxiety would reduce the likelihood of these outcomes, but even the possibility should instigate systematic efforts and clinical trials. Work of this kind would have a positive side-effect of directly identifying which of the many programs promoted for pregnant women (mostly without an evidence base) actually benefit the mother or the child.

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The Effects of Prenatal Stress on Child Behavioural and Cognitive Outcomes Start at the Beginning

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April 2019, Rev. ed.

Introduction

The importance of development during the fetal period is well established with regards to the association between the baby's growth in the womb, and later vulnerability to physical disorders such as cardiovascular disease and other aspects of *metabolic syndrome*.[1] It is now clear that environmental effects on fetal development are important with respect to emotional, behavioural and cognitive outcomes too. Animal studies have shown that stress during pregnancy can have long lasting effects on the neurodevelopment of the offspring.[2]

Subject and Research Context

Many groups around the world are studying how the emotional state of the mother during pregnancy can have long-lasting effects on the psychological development of her child.[3-4] Some are using large population cohorts, which have the advantage of being able to statistically allow for many confounding factors including postnatal maternal mood.[5] Others are smaller observational studies which can examine the child in more detail.[6] Stress is a generic term which includes anxiety and depression, but also includes distress due to poor relationships or the response to an acute disaster. All these have been shown to be associated with altered outcome for the child.

Key Research Questions

What type and degree of prenatal stress have an effect on the fetus and the child? What are the gestational ages of vulnerability for different outcomes? What are the range of effects on the child and how long do they last? How does prenatal stress interact with genetic vulnerabilities? How are the effects of prenatal stress moderated by the nature of the postnatal care. How do outcomes vary with different ethnic groups and in different parts of the world?[7]

Recent Research Results

Many independent prospective studies have now shown that if a mother is stressed, anxious or depressed while pregnant, her child is at increased risk for having a range of problems, including emotional problems,

ADHD, conduct disorder and impaired cognitive development. Both altered brain structure[8] and function[9] have been shown to be associated with prenatal stress, and also the mother's experience of early childhood trauma.[10] While genetic transmission and the quality of postnatal care are likely to contribute to some of these findings of association, there is good evidence that there is a causal influence of the mother's emotional state while pregnant also. Some studies have found stronger associations with prenatal maternal mood than paternal.[11] Several large cohort studies have found associations independent of possible confounding factors, such as birthweight, gestational age, maternal education, smoking, alcohol consumption, and most importantly, postnatal anxiety and depression.[5] Thus, although the mother's postnatal emotional state and the quality of early postnatal care are clearly important for many of these outcomes, the evidence suggests that there are substantial prenatal effects also.

We have shown that, within a normal population, the children of the most anxious mothers during pregnancy (top 15%), had double the risk of emotional or behavioural problems, compared with the children of the less anxious mothers.[5] Most children were not affected, and those that were, were affected in different ways. However a doubling of risk is of considerable clinical significance. Several studies are finding that boys and girls can be affected in different ways.3 There are gene environment interactions too, in that a child with a specific genetic vulnerability is more likely to be affected in a particular way.[12]

It is clear that it is not just toxic or extreme prenatal stress that are important, as several studies have shown that problems such as daily hassles, pregnancy specific anxiety or relationship strain[6] can have an adverse effect on the developing fetus. Effects of acute disasters such as 9/11[13] have also been demonstrated. Different studies have shown different gestational ages of vulnerability. This may vary for different outcomes. Increased vulnerability to schizophrenia has been found to be associated with extreme stress in the first trimester.[14] The risk for other outcomes, such as ADHD, has been found to be associated with stress later in pregnancy.5

The mechanisms underlying all this are just starting to be understood; altered function of the placenta, allowing more of the stress hormone cortisol to pass through to the fetus, may well be important,[15] as may the function of the maternal immune system.[16]

Research Gaps

It has been suggested that a small degree of stress is actually beneficial for child outcome, as DiPietro has shown for motor and cognitive development.[17] It may be that different outcomes are affected in different ways; for example prenatal stress may cause both a more rapid physical development and more anxiety in the child.[4] Much remains to be understood about what types of stress, and at what level, stress has effects on the developing fetus. We know little about the effects of different types of work stress during pregnancy. We need to know more about gestational ages of vulnerability for different outcomes. There are research gaps in our understanding of the contribution and interactions between prenatal stress and the genetic vulnerabilities of both mother and child. We also need to know more about to what extent, and at what times, it is possible for sensitive postnatal care to counteract the effects of prenatal stress.

Conclusions

Maternal stress during pregnancy increases the risk of the child having a range of altered neurodevelopmental

outcomes. The stress can be of different types, and at least for some outcomes, there seems to be a linear dose response effect. Not all children are affected, and those that are, are affected in different ways. The gestational age of vulnerability probably differs for different outcomes. It is of interest to view all this in terms of our evolutionary history. In a stressful environment it may have been adaptive for our ancestors to have children who were more vigilant (anxious) or with readily distracted attention (ADHD), and possibly with more rapid motor development. But in our modern world several of these changes can be maladaptive, and cause problems for the child and their family.

Implications for Parents, Services and Policy

The implications of this research are that if we want the best outcomes for our children we need to provide the best possible emotional care for pregnant women. There needs to be more public health education about this issue, and pregnant women encouraged both to look after themselves emotionally, and to seek help if needed. At present most anxiety and depression in pregnant women is undetected and untreated. We need to make sure that pregnant women are sensitively questioned when they first come into contact with health professionals about their emotional history and current state. It is important to note that it is not just diagnosable disorders that can affect fetal development, but a range of symptoms of stress, anxiety and depression, including a poor relationship with the partner. Appropriate personalized help should be instituted for each woman. This has the potential to prevent a range of neurodevelopmental problems arising in a clinically-significant proportion of children.

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Pre/Perinatal Stress and its Impact on Typical and Atypical Offspring Development: Commenting on DiPietro, Schneider, O'Connor and Glover

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March 2011

Introduction

It has been hypothesized that by the interplay of prenatal/early postnatal environmental stress and genetic susceptibility, the offspring acquires neurobiological vulnerability for later atypical development and health problems. The articles by DiPietro,[1] Glover[2] and O'Connor[3] focus on the observed association in humans, while the article by Schneider[4] focuses on offspring development in nonhuman primates. The interpretation each author gives of the results of the research in this field seems to be legitimated within the chosen framework. Apparently this does not mean that there are no conflicting interpretations. In humans, the past 25 years have in general shown empirical evidence for an association between maternal stress, anxiety and depression during pregnancy and offspring behavioural, brain behaviour and physiological outcome measures. While direct evidence for an interplay with genetic factors has been shown for a little while in animals,[5] this was only very recently the case in humans.[6] We briefly describe the research field and implications for policy as seen by each author and give some critical reflections.

Research and Conclusion

DiPietro[1] accentuates the roots that pre/perinatal research has in cultural tradition (i.e., the belief that negative maternal emotions may harm the fetus) and sees studies on associations between maternal stress and anxiety in humans as a scientific inquiry of this belief. Defining stress and distinguishing it from other psychological and personality characteristics is seen as a major problem. She therefore suggests that focusing on neuroendocrine and physiological parameters, instead of maternal self report, would be a promising line of research in this field. She argues that implications of maternal stress on the postnatal environment are likely to be of greater consequence than biological effects of prenatal exposure and that because of the fact that experience of stress is a matter of subjective appraisal; public policy should not govern the behaviour or activities of pregnant women in order to improve child developmental outcomes. DiPietro's[1] view on public policy is motivated by her findings showing that moderate (but not overwhelming) stress can in a way facilitate development.

Glover[2] starts from the *Barker hypothesis[1]* and the Developmental Origins of Health and Disease (DOHaD)

hypothesis and she sees studies of the effects of prenatal stress on behaviour, cognitive and emotional development as an extension of these hypotheses. Maternal stress during pregnancy leads to altered neurodevelopmental outcomes and these alterations may be maladaptive and confer problems for the child and his family. She therefore argues that pregnant women should be offered the best possible emotional care, with more public health education and institutionalization of appropriate personalized care.

O'Connor[3] argues that, when the results of animal research showing a lasting impact on the behaviour and biology of the offspring can be translated to humans, potential implications for public health and prevention will be enormous. However, up until now the leverage of human studies is limited and no causal link can yet be drawn, he writes. Therefore, more research should focus on identifying underlying causal mechanisms (e.g., starting from the concept of *ontogenetic[2]* vulnerability, further exploring the role of *cortisol[3]* and starting to look for the role of other factors). Even if it is not certain that a reduction in maternal stress or anxiety improves child outcome, the possibility should instigate clinical trials not only with psychiatric medication drugs but with different forms of behaviour therapies as well.

Schneider[4] sees primate studies as providing an inferential links between rodent studies and epidemiological studies. Long-term changes in dopaminergic function are an important target for future research in humans, as well as the study of coping mechanisms. Public policy issues should find ways to identify and reduce risk factors and enhance protecting factors in pregnant woman and implement professional training for service providers that include health education in the (pre)-pregnancy period.

Implications for Development and Policy

I agree with the view of all four authors that the identification of causal mechanisms is an issue of high priority on the science policy agenda. Critical questions that remained unanswered so far, or for which much more research is needed, are situated at the level of (1) the mother, (2) the mother-fetus-placental interaction and (3) the child after birth:

1. Are some women more vulnerable than others to the negative influences of stress? Stress sensitivity depends on the activity of both the autonomous nervous system (ANS) and the *hypothalamo pituitary adrenal (HPA) axis[4]*. More studies are needed that focus on both the HPA axis and the ANS system. Moreover the interaction between the (genetic and acquired) vulnerability of the pregnant woman and the current living conditions of the pregnant woman (e.g., relationship with the partner, pregnancy anxieties, work stress, family stress, type of social support or lack thereof) should be studied.
2. In what ways does maternal stress influence feto-placental structures and function? It is known that *glucocorticoids[5]* exert many actions that impact both negatively and positively on key aspects of early pregnancy and fetal development throughout pregnancy.[7] Placental 11?-hydroxysteroid dehydrogenase type 2 (11?-HSD2), represents one key enzyme that selectively regulates the transplacental passage of glucocorticoids as it converts cortisol into inactive cortisone.[8] Decrease in the placental glucocorticoid barrier, for instance by prenatal maternal stress early in pregnancy leading to elevated maternal and/or fetal *catecholamine[6]* levels,[9] may increase fetal exposure to maternal glucocorticoids. Fetal overexposure to glucocorticoid may alter programming of brain development, lead to changes in the developmental trajectory of the offspring and increase susceptibility to physical and mental disease.[10,11]

3. What kind of behavioural, brain-behavioural and physiological measures in the newborn and child are sensitive enough to capture the effect of prenatal influences? Why do prenatal early life events enhance the risk for developing behavioural problems and stress-related disorders? What are the underlying mechanisms?[12] In what way can the interplay between genetic and acquired vulnerability be studied?[13]

Is it necessary or advisable to take preventive actions? Concerning international, national or more regional policies on health and well-being, DiPietro[1] and O'Connor[3] see public policy promoting of the well-being of pregnant women as "conditional;" (i.e., prevention is needed only when prenatal stress is overwhelming[1] and it should only be installed after it is shown that it is possible to prevent the adverse effects of maternal stress or anxiety on the child[3]). Glover[2] and Schneider[3] explicitly subscribe to what Joffe already stated in 1969[14]: "even if uncertainty about etiological relationships exists, human studies provide sufficient evidence to enable preventive action to be initiated with regard to a variety of childhood disorders, without waiting for the methodological issues to be unraveled, though the action may be more effective when they are." Van den Bergh and al. [14] earlier expressed agreement with Joffe, and his statement remains unchanged. "There is enough evidence to warrant active research into prevention, intervention, and support programs to reduce stress or anxiety during pregnancy and their effects on child outcome. Research on underlying mechanisms, on the effect of the timing, intensity and duration of anxiety/stress, and the effect of gender, can be carried out in parallel, and actually would be helped by successful intervention strategies."[15]

To update this agreement, the following two comments are in place:

First, it is realistic to expect that only in studies in which a substantial part of the pregnant mothers have high scores for anxiety, stress or depression will it be possible to find significant associations between negative maternal emotions and childhood disorders. However, even in these samples, associations may not be unveiled in a variable-oriented method, in which values are averaged over the whole sample used. It is therefore recommended to use person-oriented methods in which subgroups (or clusters) of women sharing a similar profile of emotions can be detected, such as cluster analysis or latent class analysis.[16-18] For instance, women scoring high on depression as well as on anxiety can be discerned from those scoring only high on anxiety or depression or scoring low on both anxiety and depression. Interestingly, the latter methods can also take differences between individual trajectories of emotions (changes over the course of pregnancy) into account (e.g., women scoring high during all pregnancy trimesters can be discerned from those scoring high during only one trimester and from those scoring low in all trimesters). Once these subgroups are detected, differences in outcome measures in offspring of the different groups can be statistically explored. It is clear that, especially for those groups of mothers for which unfavorable child offspring are shown, appropriate prevention and intervention measures should be installed.

Second, while we agree with DiPietro[1] that it may be interesting in future studies to focus on physiological measures, one should be aware of the fact that replacing psychological variables by physiological measures (or biomarkers) also runs the risks of not unveiling potentially existing significant associations. As long as we do not have sensitive biomarkers and/or when studies do not include enough pregnant mothers with high-stress reactivity and/or difficulties with stress regulation, associations will be difficult to find.

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Note:

[1]

The hypothesis is that what happens during prenatal development (e.g., mother's poor nutrition) has a direct impact on long-term health and disease (e.g., cardiovasuclar disease, diabetes, etc.) in postnatal life.

[2]

The origin and the development of an organism.

[3]

Often called the stress hormone, this glucocorticoid is secreted by a part of the adrenal glands. Produced when the body is under stress, cortisol modifies various parameters (blood sugar levels, blood pressure, etc.), which enables the body to react to the situation (fight or flight).

[4]

Axis made up of the three main structures in the body (hypothalamus, pituitary and adrenal glands) activated by stress. It regulates the body's response to this stress by having all three structures communicate with each other.

[5]

These hormones from the corticosteroid family influence protein and carbohydrate metabolism (physical and chemical transformations). In humans, the main glucocorticoid is cortisol.

[6]

Substances occurring naturally in the body that can act as neurotransmitters or hormones.