

## STRESS AND PREGNANCY (PRENATAL AND PERINATAL)

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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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### 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,<sup>1</sup> Glover<sup>2</sup> and O'Connor<sup>3</sup> focus on the observed association in humans, while the article by Schneider<sup>4</sup> 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,<sup>5</sup> this was only very recently the case in humans.<sup>6</sup> We briefly describe the research field and implications for policy as seen by each author and give some critical reflections.

## Research and Conclusion

DiPietro<sup>1</sup> 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<sup>1</sup> view on public policy is motivated by her findings showing that moderate (but not overwhelming) stress can in a way facilitate development.

Glover<sup>2</sup> 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<sup>3</sup> 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<sup>4</sup> 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*<sup>[4]</sup>. 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 fetoplacental structures and function? It is known that *glucocorticoids*<sup>[5]</sup> exert many actions that impact both negatively and positively on key aspects of early pregnancy and fetal development throughout pregnancy.<sup>7</sup> Placental 11 $\beta$ -hydroxysteroid dehydrogenase type 2 (11 $\beta$ -HSD2), represents one key enzyme that selectively regulates the transplacental passage of glucocorticoids as it converts cortisol into inactive cortisone.<sup>8</sup> Decrease in the placental glucocorticoid barrier, for instance by prenatal maternal stress early in pregnancy leading to elevated maternal and/or fetal *catecholamine*<sup>[6]</sup> levels,<sup>9</sup> 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.<sup>10,11</sup>

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?<sup>12</sup> In what way can the interplay between genetic and acquired vulnerability be studied?<sup>13</sup>

Is it necessary or advisable to take preventive actions? Concerning international, national or more regional policies on health and well-being, DiPietro<sup>1</sup> and O'Connor<sup>3</sup> see public policy promoting of the well-being of pregnant women as “conditional;” (i.e., prevention is needed only when prenatal stress is overwhelming<sup>1</sup> 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<sup>3</sup>). Glover<sup>2</sup> and Schneider<sup>3</sup> explicitly subscribe to what Joffe already stated in 1969<sup>14</sup>: “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.<sup>14</sup> 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.”<sup>15</sup>

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.<sup>16-18</sup> 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<sup>1</sup> 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., cardiovascular 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.