EDITOR'S PERSPECTIVE

We have now the scientific rationale for advocating early detection and intervention during pregnancy

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Freud (1926) knew that "Intrauterine life and infancy are much more in continuity than the sharp break of delivery make us think". Still, we need scientific studies to prove the importance of human fetal experience in determining developmental patterns, and for the proposal that many illnesses begin in fetal life.

The concept of programming is defined as a process by which a stimulus or an insult during a critical developmental period has a long lasting or permanent influence. Different organs are sensitive to environmental influences at different times, depending on their rate of cell division. Critical periods are defined by epochs of rapid cell division within an organ.

Among fetal experiences, maternal stress turns out to have a special impact. Indeed, glucocorticoids, and especially cortisol, seem to be the main factor in programming the fetal brain and behavior: they are necessary for normal maturation of most regions of the CNS (Matthews, 2002). Cortisol in abnormal levels, may impede formation of neural connections, and reduce neural plasticity. Among the brain structures, the hippocampus has the highest levels of corticosteroid receptors and is thus highly vulnerable to excess levels of glucocorticoids. Sustained elevations of glucocorticoids, such as cortisol in stressful situations, can have deleterious consequences for brain structure and function. Nature has produced a physiological system where fetal exposure to circulating maternal cortisol is moderated by oxidation of the cortisol to its inactive form by placental 11beta-hydrosteroid dehydrogenase type 2. Still, 10-20% of active maternal cortisol passes through the placenta, and fetal cortisol levels are significantly correlated with maternal levels.

Consequently, in parallel to the increasing knowledge about the influences of various factors on the developing fetal brain, the issue of the impact of maternal stress on the fetus has become very relevant for adult as well as for child mental health clinicians.

The definition of a stressful event during pregnancy is obviously much more complicated in humans than in experimental animal studies. First, one needs to take into account pregnancy-related anxiety, i.e. the anxiety inherent to the state of pregnancy (mainly health issues, usually focused on her fetus, but also around herself, and around the fear of delivery itself), to which each woman relates in various ways, depending on her defense mechanisms, own maternal representations, self-image and marital relationship. Huizink et al (2000) have developed a pregnancy-related anxiety questionnaire, for studying the link between stress during pregnancy and developmental outcome in infancy (2003).

In addition, life hassles and extraordinary events may superimpose upon the pregnancy-related anxiety level. Again, the definition of what is a stressor for an individual pregnant woman may be quite difficult, because of the pre-pregnancy different levels of resilience and vulnerability. To address this issue of individual variability, Mohler et al (2006) have developed a Prenatal Emotional Stress Index.

Another issue is the timing and the chronicity of the stressor. Davis et al (2007) studied 247 women with singleton full term pregnancies. These were evaluated on their psychological state (anxiety, depression, and perceived stress) and saliva cortisol at three points, the 18th , 24th and 30th weeks of gestation. At 8 weeks post partum, the infant's temperament was assessed. Endogenous maternal stress hormones during the third trimester of pregnancy (30-32 wks) only, predicted impaired cortisol regulation, behavioral inhibition and fearfulness in response to novelty in their 8 weeks-old infants (very similar to findings in animal studies, Weinstock, 2001). It is of note that the effect of prenatal maternal cortisol and depression on infant temperament remained significant after controlling for postpartum maternal depression. In contrast, Lederman (2004) found that women who were in the first trimester of pregnancy at the time of the Word Trade Center bombing in New York delivered infants significantly earlier than women at later stages of pregnancy. According to the authors, the impact of the stressful event on the fetus depends on whether it occurs before or after the placenta produces the enzyme 11 beta-hydroxy-steroid dehydrogenase, which converts noxious cortisone to benign cortisone. This is probably not the only mediating factor, since in a sample of pregnant women exposed to earthquake, the same result of earlier delivery, but when the exposure occurred during the second trimester, was found by Glynn (2001). It seems that the time of onset of the production of the enzyme is only one factor among others, such as the intensity of its expression, as Diaz (1998) has found that the expression of the enzyme is dramatically reduced in the last period of pregnancy which allows glucocorticoids to interact with their receptor systems and to influence brain development.

Furthermore, the impact of a stressful event may impact on different developmental functions, at different periods of the pregnancy. Laplante et al (2004) studied 58 pregnant women exposed to an ice storm in 1998 and

followed their offspring up for 2 years: the more severe the level of prenatal stress exposure, the poorer was the toddler's language ability, regardless of the timing of the event. The cognitive functioning was worse when the stressor occurred in the first two trimesters, especially in the earliest period.

These findings altogether suggest significant complexity. A precise definition of the nature of the measured stress is therefore crucial to the interpretation of the findings. For instance, is there a different impact of endogenous individual stress compared with exogenous, collective stress (such as war, natural disaster)? Not a less important issue, is the chronicity of the stressor. To our best knowledge, there is no comparative study of the impact of chronic stress and acute stress during pregnancy on the fetus and the child's later development.

The definition of endogenous stress is also complex. Field et al (2003) studied 166 pregnant women with high and low anxiety during the second trimester, and showed that the high anxiety group had high scores on depression and anger, and raised prenatal norepinephrine and low dopamine levels. High scores on depression and anger were found both pre- and postnatally. The authors concluded that maternal stress, anxiety and depression may be confounded, and that postnatal anxiety and depression must be controlled in follow-up studies on the impact of stress from pregnancy to childhood.

The Avon Longitudinal study (O'Connor et al, 2002, 2003, 2005) from pregnancy to 10 years (N= 6,493) showed that children whose mothers experienced high levels of anxiety (though mostly not clinical) in late pregnancy exhibited higher rates of mothers' report of emotional/ behavioral problems (though mostly not in the clinical range) at 4 years and at 6 years, and predicted individual differences in cortisol at age 10 years. Leech et al (2006) followed 636 mother-child pairs from month 4 of pregnancy to age of 10 years, and found that prenatal exposure to maternal anxiety and depression, together with poor support in pregnancy, predicted clinical childhood anxiety and depression at age 10 , independently of an effect of postnatal maternal depression.

The findings described above have strengthened the notion that prenatal stress has a significant, but not linear, nor necessarily clinical, effect on the development of the fetus, the newborn, and the child. Still, the underlying mechanisms of the association between prenatal stress and infant development are unknown. There are a number of plausible hypotheses:

• Prenatal stress may reduce uterine placental blood flow since cortisol and catecholamines are known to affect vessel tone (Teixei et al, 1999). Reduced supply of oxygen and nutrients to the fetus mobilizes a response of the fetal Hypothalamus Pituitary Adrenal (HPA) axis, that is operative from mid-pregnancy on.

• Maternal stress may lead to increased production of placental CRH that further activates the fetal HPA axis.

• Maternal cortisol is directly transported across the placenta and 10-20 of it enters the fetal circulation, in spite of the protection of the enzyme.

One of the hypothesized pathways of prenatal maternal stress, from pregnancy to adulthood, based on the above data, is the following: Maternal stress during pregnancy may cause, in the fetus, to an alteration in programming and development of the HPA axis and the limbic system. This, in turn, would in the child and adult, lead to dysregulation of the HPA and/or alteration in limbic functions, with possible long term outcomes of anxiety, depression, memory impairment, and sensitization to post-traumatic stress disorder. Still, the issue whether prenatal stress has specific psychopathological effects or it induces a general susceptibility, is still in debate (Huizink et al, 2004).

The risk factor of poor support during pregnancy is very important to remember, since its association with childhood problems in the clinical range has been shown (above).

To our best knowledge, protective factors have not been systematically studied; for instance, is there a link between the level of pregnancy-related anxiety and stress in pregnancy in the mother and her general attitude towards her pregnancy?

The main clinical implication of knowing that prenatal maternal stress may have a long-term impact on the child's mental health is the need to detect clinical levels of stress, anxiety, depression early in pregnancy. Obviously, universal prevention is unrealistic, therefore the preventive effort should be selective, targeted to women at-risk for significantly stressful pregnancies. Exogenous as well as endogenous sources of stress should be identified. Raphael-Leff (1993) suggests the following categorization of stressful pregnancies:

1. Conflicted pregnancies (unplanned, untimely, acute ambivalence, possibly such as hyperemesis gravidarum (El Mallakh, 1990).
2. Emotionally-overloaded pregnancies (post-infertility pregnancy, family history of perinatal complications, maternal borderline disorders/ psychiatric history).
3. Complicated pregnancies (physical illness of mother, lack of emotional support, socioeconomic factors, adverse life events).

The decision to give pregnancies a priority in preventive medicine is a social one. The more scientific data we can gather on the impact of external factors on fetal brain development, the stronger will be the advocacy for early detection and intervention.

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