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Gender health and early days of life: when does the influence of psychosocial factors start?

Daria Minucci

Senior studious, Department t of Women and Children Health, University of Padua, Italy

The first 1000 days – from conception to two years – are crucial for the health and well-being of all life. Rapid growth and plasticity, with particularly sensitive windows in relation to periods with greater rapidity of foetal development in the first 280 days, call for autonomous development planning; about the contemporary and integrated development of the body with its functions and therefore also of cognitive, emotional, relational and social capacities. The deep psychological core of each of us is formed during pregnancy.

Sexual differentiation

The presence of the Y chromosome conditions, the development of the male gonad from the undifferentiated gonad, and the testosterone produced by the male gonad are essential for male fetal development. Sexual differences affect the entire fetus: different growth trajectories; different reactions to environmental stimuli. The placenta also shows differences related to sex.

Mother and fetus: genetically diverse, each with its own autonomy, but in close relationship with each other; both play an obligatory active role in all aspects of development with the placenta as an interface and mediation.

Placenta of embryonic origin

Obligate passage of oxygen and nutrients to the fetus. Major endocrine functions for – orchestrating maternal adaptation to pregnancy, – mobilizing resources for the fetus. Selective barrier to minimize exposure of the fetus to maternal hormones such as glucocorticoids, xenobiotics, pathogenic microorganisms, parasites, etc.

Mother-placenta-fetus

The placenta originates from the embryo cells and has the same genetic sex. In females, an X chromosome is inactive. In the placenta the inactive X chromosomes are repressed less stringently than those of the somatic cells, with the possibility of reactivations in response to intrauterine conditions. This plasticity of the X chromosome may be a more powerful protective mechanism in females that can express multiple X-linked genes. The placenta XY may be more efficient in extracting nutrients, while the XXs have more capacity to store energy (Tamimi, 2003, Erickson, 2010). The placenta XX produces larger quantities of HCG. The placenta XX tends to have a higher expression of genes involved in immunological regulation, in endocrine functions, and placental growth, while the XY has more in the inflammatory profiles.

How do psychosocial factors work in the mother-placenta-fetus "system"? When? Are there any gender differences? Popular experience and "wisdom", empirical evidence of retrospective epidemiological studies, indicate excessive stress as a possible source of damage to the fetus and the mother.

Effects of prenatal stress related to elevated maternal anxiety. In the births by mothers with high anxiety during pregnancy the following were found: at birth: low weight, reduced cranial circumference, increased risk of preterm birth, etc.; in childhood: increased risk of emotional problems such as hyperactivity, problems of attention, higher levels of impulsivity and reaction to novelties, etc.; cognitive problems such as learning delay, academic delay; laterality or other neurodevelopmental disorders. Some studies have shown a distribution of sex-specific psychopathological outcomes (Talge NM, 2007).

Fetal programming and developmental plasticity

Embryo-foetal development is a plastic process where a single genotype can express many different phenotypes. Developmental processes from genotype to phenotype are context-dependent. The embryo and the fetus during sensitive periods of proliferation, cell differentiation and maturation, respond to the conditions of the internal and external environment with structural and functional changes at the cellular, tissue and organ system levels.

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Origin in the foetal development of health and disease

If the changes are such that they do not correspond to post-natal reality then they can have short and / or long-term consequences for health and predisposition to diseases, sometimes also permanent and transmissible to future generations (Gluckman, 2004, Wadhwa, 2009).

Stress during intrauterine development

Excessive stress, especially during the sensitive windows of intrauterine life development, helps to initiate and advance complex physical and mental disorders that can give rise to many short and / or long-term illnesses (programming foetal). For each individual the likelihood of a stress-related effect is a joint function not only of the amount and duration of stress exposure, but also of the biological ability to respond to stress (Entringer, 2015).

Possible effects of psychosocial stress during intrauterine life on some key physiological parameters: increase of BMI and % of body fat; primary resistance to insulin; lipid profile compatible with metabolic syndrome; impaired immune function with shift of Th2 to Th1 / Th2 (increased risk of autoimmune disorders); impaired endocrine function with increased ACTH and reduced cortisol levels during pharmacological and psychological stimulation; weakening of performance related to the prefrontal cortex (Entringer, 2008,2009,2015).

Brain development and programming

The foetal brain is highly plastic; to develop it is not only receptive but needs signals and stimuli from its environment. Brain development is the product of the dynamic and bidirectional interaction between the acquired genotype at conception and the nature of the environment. The ontogenesis of the brain is longer than that of any other organ or system, extending from the foetal period to adolescence. The foetal period is particularly important because it is the stage of development in which the growth and differentiation of the major brain structures take place.

Prenatal stress and brain development

Brain development is a cascade of bi-directional interactions with the environment. Even small and delicate changes in brain structure and function during foetal life can be progressively and substantially amplified over time producing permanent or semi-permanent deficits. In epidemiological studies there is substantial empirical evidence that exposure to excessive stress during foetal life may result in negative outcomes of both short-term and long-term neurodevelopment. Maternal-placentary-foetal biological processes related to stress play a triple role as sensors, transducers and effectors of maternal stress on foetal development. Endocrine and immunological mediators play a mandatory critical role in many important aspects of brain development, including: migration of neuronal and glial cells, differentiation, synaptic maturation; inappropriate levels of these biological mediators can produce harmful effects on the developing brain (Buss, 2012).

Prenatal stress and brain damage

The duration (even after 37 weeks) of pregnancy is positively correlated with the development of gray matter (Davis, 2011) and of the efficiency of the brain network in the average child (Kim, 2014). The children of mothers with high levels of anxiety in the 2nd trimester of pregnancy had a reduction of gray matter in the prefrontal cortex, premotrice, temporal lateral, post-central gyrus, (Buss, 2010) and a high incidence of reduced executive functions (Buss, 2011). The children of mothers with depression during pregnancy had, at 7-year old, a reduction in cortical thickness of the right frontal lobe and there was a significant association with deviant behaviour (Sandman, 2015).

Mediators of stress in pregnancy: cortisol

Cortisol is one of the main biomarkers of stress because its production, bioavailability and activity are altered in all conditions that have shown the ability to program brain development (Entringer, 2011). The direct exposure of the fetus to the maternal cortisol is regulated by the 11 beta-hydroxystero-dehydrogenase type 2 (11beta HSD2) which oxidizes the cortisol to the inactive form (cortisone), but is a partial barrier, moreover: – 11beta HSD2 activity is down regulated by high levels of maternal anxiety (O'Donnel 2012), serious infections (Johnstone, 2005), high levels of proinflammatory cytokines (Kossintseva, 2006), alcohol exposure (Liang 2011); – maternal cortisol can stimulate and increase the production of the placental Corticotrophin Releasing Hormone (CRH) that stimulates foetal adrenal steroid biosynthesis (Cheng, 2000, Rehman, 2007, Sandman, 2006); – high concentrations of maternal cortisol in the early part of pregnancy were associated with a greater volume of the right amygdale in females but not in males, no variation of the left amygdale and of the hippocampus, neither in females nor in males (Buss, 2012).

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Conclusion

The placenta responds to stimuli including those from stress with altered DNA methylation associated with childhood behavioural alterations: In a study (Appleton 2013) of pregnant women experiencing severe socioeconomic difficulties, a low methylation level of 11 beta HSD2 was found placental, especially in males. Low methylation levels of 11 beta HSD2 may be an adaptive mechanism to increase the expression of 11 beta placental HSD2 to protect the fetus from maternal cortisol. Childhood behavioural difficulties have been associated with increased methylation of Nr3c1 encoding for glucocorticoid receptors. Combinations of different degrees of methylation of 11 beta HSD2 and Nr3c1 are associated with different behavioural alterations (reflex asymmetry, reduced excitability, and difficulty in getting used to the stimulus).

In conclusion the epidemiological evidence and the results of the first studies on metabolic, endocrine, genetic, biomolecular mechanisms of the stressors action on the first 280 days of life are a potent stimulus for more research and studies. Obviously the gender point of view appears mandatory.

Correspondence to
Daria Minucci
Department t of Women and Children Health
Univerisity of Padua
via Giustiniani 2
35128 Padova, Italy
email daria.minucci@unipd.it