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Review

Prenatal stress, development, health and disease risk: A psychobiological perspective—2015 Curt Richter Award Paper

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ABSTRACT

The long-term consequences of exposure to excess stress, particularly during sensitive developmental windows, on the initiation and progression of many complex, common physical and mental disorders that confer a major global burden of disease are well established. The period of intrauterine life represents among the most sensitive of these windows, at which time the effects of stress may be transmitted inter-generationally from a mother to her as-yet-unborn child. As explicated by the concept of fetal or developmental programming of health and disease susceptibility, a growing body of evidence supports the notion that health and disease susceptibility is determined by the dynamic interplay between genetic makeup and environment, particularly during intrauterine and early postnatal life. Except in extreme cases, an adverse intrauterine exposure may not, *per se*, 'cause' disease, but, instead, may determine propensity for disease(s) in later life (by shaping phenotypic responsivity to endogenous and exogenous disease-related risk conditions). Accumulating evidence suggests that maternal psychological and social stress during pregnancy represents one such condition that may adversely affect the developing child, with important implications for a diverse range of physical and mental health outcomes.

In this paper we review primarily our own contributions to the field of maternal stress during pregnancy and child mental and physical health-related outcomes. We present findings on stress-related maternal-placental-fetal endocrine and immune/inflammatory processes that may mediate the effects of various adverse conditions during pregnancy on the developing human embryo and fetus. We enunciate conceptual and methodological issues related to the assessment of stress during pregnancy and discuss potential mechanisms of intergenerational transmission of the effects of stress. Lastly, we describe on-going research and some future directions of our program.

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1. Introduction

1.1. The concept of fetal programming of health and disease

The origins of health and disease susceptibility for many complex, common disorders that confer a major burden of disease in not only developed but also other societies in rapid transition can be traced back to the intrauterine period of life. Development is a plastic process, wherein a range of different phenotypes can be expressed from a given genotype. The unfolding of developmental processes from genotype to phenotype is context-dependent, wherein the developing embryo/fetus responds to, or is acted upon by, conditions in the internal or external environment during sensitive periods of cellular proliferation, differentiation and maturation, resulting in structural and functional changes in cells, tissues and organ systems. These changes may, in turn, either independently or through interactions with subsequent developmental processes and environments, have short- and/or long-term consequences for health and disease susceptibility. These concepts have variously been referred to as the fetal or developmental origins of health and disease (Gluckman and Hanson, 2004; Wadhwa et al., 2009).

1.2. Rationale for considering a role for stress in fetal programming

The rationale for considering a role for stress and stress biology in fetal programming of health and disease risk derives, in part, from concepts in evolutionary biology and developmental plasticity (Entringer, 2013; Entringer et al., 2012a, 2010b). From conception onwards the mother and her developing fetus both play an obligatory, active role in all aspects of development. Based on the consideration that the two fundamental processes that are believed to shape evolutionary selection and developmental plasticity are variation in energy substrate availability (nutrition) and challenges that have the potential to impact the structural or functional integrity and survival of the organism (stress), it is likely and plausible that prenatal stress represents an important aspect of the intrauterine environment that would be expected to influence many, if not all, developmental outcomes (Wadhwa et al., 2011).

To date, the majority of human studies on fetal programming have focused on energy substrate and nutrition (e.g., effects on central and peripheral organ systems of under- or over-nutrition and of specific macro- or micronutrients such as excess fat or protein intake). We suggest that studies of stress and stress biology in gestation and early postnatal life may be relevant even in the context of nutrition and its programming effects. Growing evidence supports the concept of a bi-directional interaction between nutrition and stress, such that the effects of nutrition on health may vary as a function of stress, or that the effects of stress on health may vary as a function of nutritional status. For example, several experimental studies in animals have demonstrated that nutritional manipulations, particularly in the preconception or early pregnancy period, may produce their effects on maternal and fetal outcomes via alterations in stress biology (cortisol, inflammatory cytokines (Bispham et al., 2003; Lingas and Matthews, 2001). Conversely, studies in animals and humans of stress induction (by exposure to laboratory-based stressors or endocrine stress analogues) have demonstrated effects on feeding behavior, food choice (high calorie dense food preference) and the metabolic fate of food in target tissues (Epel et al., 2001; Hitze et al., 2010).

Thus, we submit the application of a prenatal stress and stress biology framework offers an excellent model system for the study of intrauterine development and associated developmental, birth and subsequent health-related phenotypes because it is increasingly apparent that the developing fetus acquires and incorporates information about the nature of its environment in part via the same biological systems that in an already-developed individual mediate adaptation and central and peripheral responses to endogenous and exogenous stress (i.e., the maternal-placental-fetal neuroendocrine and immune systems (Wadhwa, 2005)). In this context, stress-related endocrine and immune/inflammatory mediators may serve as important signals or cues of a wide range of maternal, placental and/or fetal conditions including but not limited to nutrient availability, oxygen availability, presence of obstetric complications such as preeclampsia and infection, and other important conditions that can sculpt fetal development (Fowden and Forhead, 2009).

The following sections summarize findings on the association of prenatal stress and stress biology with neurodevelopmental and physical health outcomes. We note that the majority of the published studies reviewed here on prenatal stress and child neurodevelopmental outcomes were conducted by a research group led by Curt Sandman and Elysia Davis, in which one of us (Buss) was a collaborator, whereas the studies on physical health outcomes were conducted by our own research program.

2. Prenatal stress exposure and brain development

The fetal brain is highly plastic and is not only receptive to but in fact requires signals or cues from its environment in order to develop. Brain development is a product of the dynamic, bi-directional interplay between the individual's genotype, acquired at conception, and the nature of the early environment. The ontogeny of brain development is considerably longer than that of other organ systems. It extends from the fetal period of life into