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Review Article

Fetal programming of the metabolic syndrome

Aleksandra Marciniak, Jolanta Patro-Małysza, Żaneta Kimber-Trojnar*, Beata Marciniak, Jan Oleszczuk, Bożena Leszczyńska-Gorzelak

Department of Obstetrics and Perinatology, Medical University of Lublin, Jaczewskiego 8, 20-954 Lublin, Poland

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ABSTRACT

Prenatal development is currently recognized as a critical period in the etiology of human diseases. This is particularly so when an unfavorable environment interacts with a genetic predisposition. The fetal programming concept suggests that maternal nutritional imbalance and metabolic disturbances may have a persistent and intergenerational effect on the health of offspring and on the risk of diseases such as obesity, diabetes, and cardiovascular diseases.

Introduction

The aim of the paper is to analyze the influence of nourishment during pregnancy on the long-term health consequences for the child. It is commonly known that the welfare of an individual depends on genetic information along with environment and lifestyle. Current knowledge unambiguously emphasizes the fact that the intrauterine environment to which a fetus is exposed can have a long-term impact on health after birth [1]. During intrauterine development the fetus is vulnerable to various factors, mainly affected via maternal tissues. Maternal mental and physical status, environment to which she is exposed, physical activity, and nourishment habits can permanently affect the health and physical status of the growing child. Therefore, the most important factors involved in fetal programming include: endocrinological disorders of the pregnant woman, toxins, infectious agents, and nutrient availability, which is dependent on maternal nourishment status and placental functionality.

Fetal programming

Fetal programming was mentioned for the first time over 20 years ago. The term was introduced by British epidemiologist David Barker, who investigated the association between low birthweight and increased risk of coronary disease in adult life [2]. Later studies suggest that epigenetic alterations of certain genes comprise an adaptive reaction to a hostile intrauterine environment [3].

Fetal programming takes place when the optimal environment in which fetus grows is disrupted by hostile factors, especially during critical periods of development of essential organs. It seems to be an important mechanism that allows the new organism to maintain homeostasis in inadequate conditions. Once changes occur, the phenotype becomes permanent and may determine the outset of future health problems [4]. Although the exact mechanisms of fetal programming have not yet been examined, the correlation between intrauterine stress and adverse effects in offspring have been confirmed for diseases such as atopic syndromes including dermatitis, asthma, and eczema, increased vulnerability to infections, metabolic dysfunction, cardiovascular disease, and cancer (especially lymphoma, hepatic cancer, and testicular cancer) [5].

Epigenetic researches investigate the hypothesis of developmental provenance of diseases, which presumes an association between intrauterine environment factors emerging from availability of nutrients and the development of obesity and chronic diseases later in life [6]. Metabolic disorders and deviations from appropriate nourishment during pregnancy can trigger fetal gene expression modifications, which lead to vulnerability to chronic diseases in the future.

There are various factors that could trigger fetal programming, such as unhealthy habits including smoking, physical inactivity, psychosocial stress, mother's neurological disorders, depression, anxiety, infections, endocrine diseases including diabetes, complications such as preeclampsia, fetal hypoxia, nitrosative and

* Corresponding author. Department of Obstetrics and Perinatology, Medical University of Lublin, Jaczewskiego 8, 20-954 Lublin, Poland.
E-mail address: zkimber@poczta.onet.pl (Ż. Kimber-Trojnar).

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oxidative stress, or any deviations from the normal gestational environment [4,7]. The majority of the above-mentioned conditions are determined by inadequate placental function, which allows us to ascertain that the placenta plays an immense role in fetal programming. Mother–fetal transport provided by adequate activity of placental transporters, enzymes, vasculogenesis, and hormone secretion is disrupted when any pregnancy complications occur, which leads to a decrease of substrate delivered to fetus, and eventually changes in its development and initiation of epigenetic alterations (Figure 1).

Figure 1 is a graphic illustration of the programming effects of an inadequate *in utero* environment on early growth and consecutive development of the metabolic syndrome. It has been suggested that fetal vulnerability to an adverse intrauterine environment can manifest as invariable alterations of the developing fetus, conceivably involving modified tissue physiology, hormone secretion, and glucose and lipid metabolism. The molecular mechanisms responsible for this process are mostly hypothetical but are unlikely to be conditioned by the DNA sequence. Permanent epigenetic alteration has appeared as a key candidate for the environmentally provoked molecular changes responsible for fetal programming. Conditions which constitute a causative correlation include exposure of interindividual epigenetic alteration in early life, as a reaction to particular

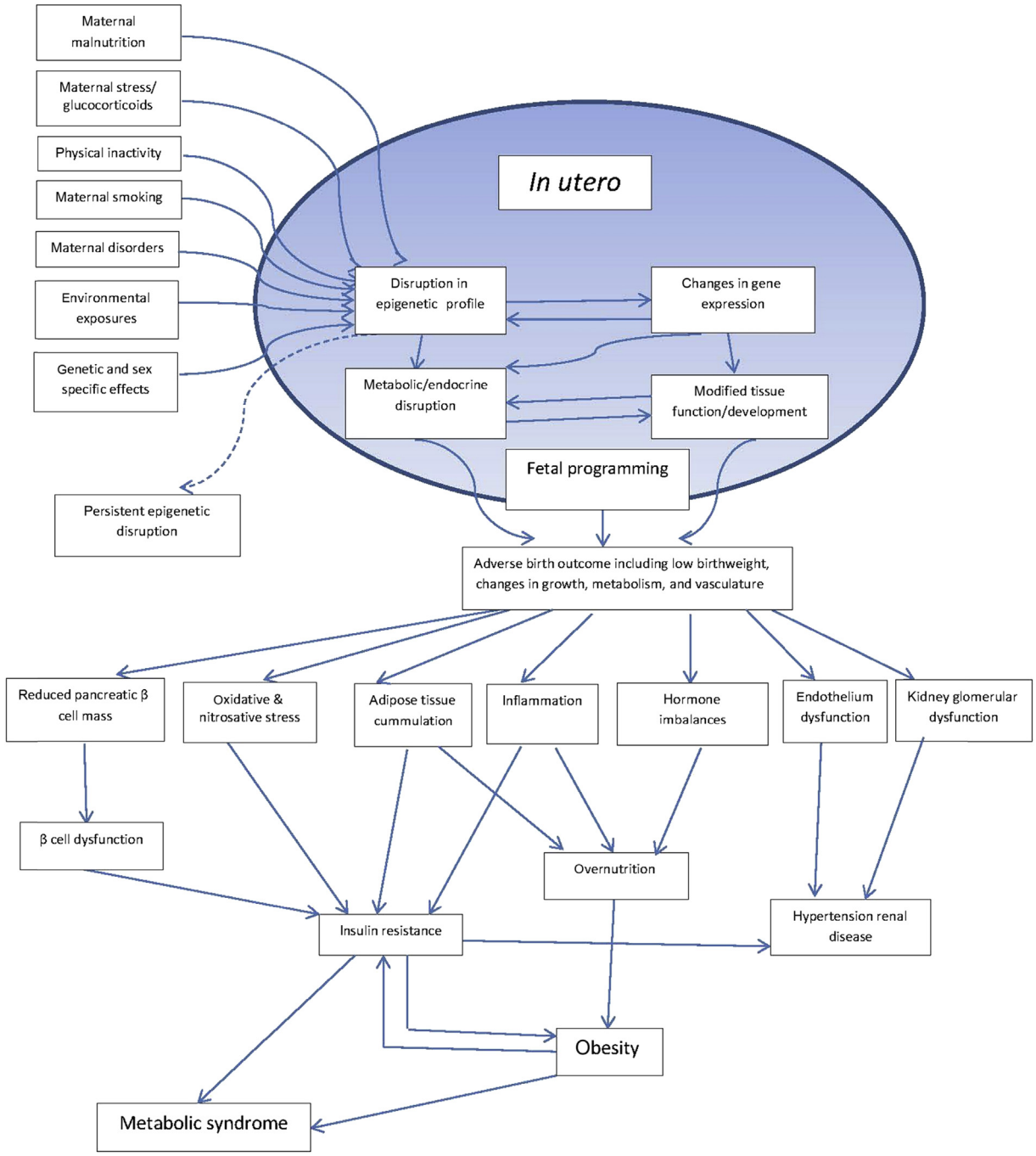

Figure 1. Programming effects of an inadequate *in utero* environment on early growth and consecutive development of the metabolic syndrome.