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Review Article

Fetal programming of the metabolic syndrome

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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

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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

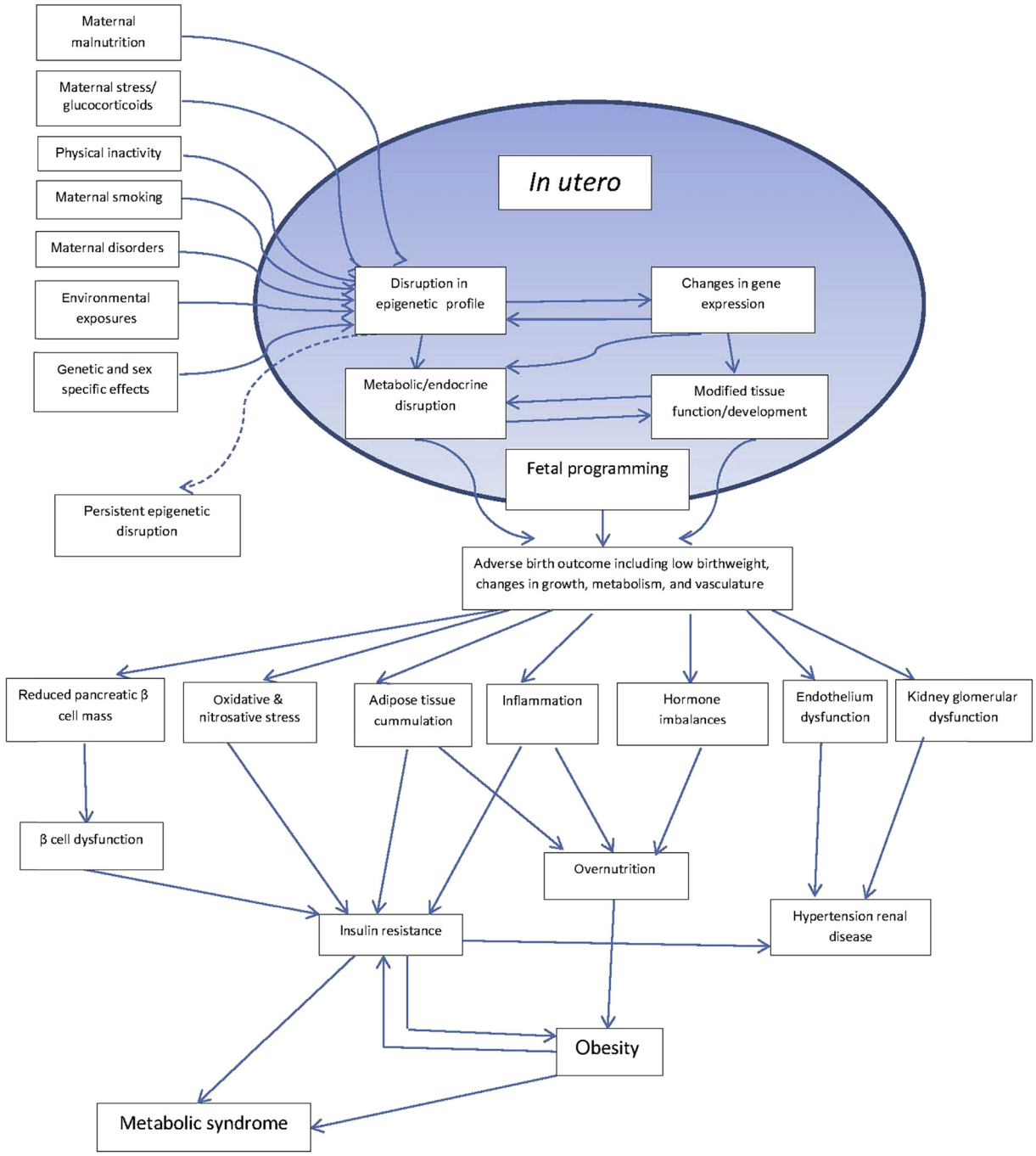

Figure 1. Programming effects of an inadequate *in utero* environment on early growth and consecutive development of the metabolic syndrome.

environmental and/or genetic conditions. Also, constraining evidence connecting epigenetic variation to the origin of health disorders is compelling. Eventually, the functional importance of particular epigenetic changes must be established [8,9].

The fetus differentiates rapidly during the early period of pregnancy. Multiple cell divisions that occur throughout this time (known as critical developmental periods) appear to contribute to immense cell sensibility to the impact of environmental factors. A multitude of agents to which pregnant woman can be exposed lie beyond our influence, i.e., environment pollution, place of residence, and health status. However, we are capable of modifying a few of the factors that determine a child's intrauterine development, of which the greatest is the nourishment of the pregnant mother.

Epigenetic patterns, arising under the influence of the intrauterine environment and passed during divisions to umpteen cells of the developing organism, consolidate and limit the possibilities of further modifications. Early-life programming causes permanent structural alterations of developing organs and their reactions to various stimuli. Animal model observations validate the assumption—progeny of mothers exposed to a high-fat diet during pregnancy despite proper nourishment after birth still present an adverse metabolic profile [10]. This indicates the vital role of the intrauterine environment in determining the welfare of an organism in the future.

Despite diverse mechanisms, intrauterine programming occurring under the conditions of undernutrition or an excessive supply of nutrients to the embryo leads to the development of individual tendency for metabolic syndrome, type 2 diabetes, obesity, and cardiovascular diseases [11]. Current studies suggest that birthweight impact on blood pressure rate throughout life is profoundly complex. Most likely, hypertension can not only be induced by low birthweight, but also weights exceeding the adequate limits for the pregnancy stage [12].

Epigenetics

Mechanisms responsible for fetal programming have not yet been fully understood. Conrad Hal Waddington, a British developmental biologist, was the first to introduce the term "epigenetics". In 1942 he used this term to define the result of interactions between genes and environment in the establishment of phenotype [13]. Currently, epigenetics pertains to mechanisms relying on the development of features that are inherited by progeny cells, although they are not associated with nucleotide sequence mutations [14].

Epigenetic modifications capable of altering the organization and functionality of chromatin include: core histone modifications, DNA molecule posttranslational methylation, and regulatory impact of noncoding RNA molecules (microRNA, long noncoding RNA) [15].

DNA methylation is a postreplicational alteration of the DNA molecule and is mainly responsible for inactivating genes, and also controlling the processes engaged in gene expression in cells. DNA molecule methylation pattern is determined during early phases of embryonic development and is maintained throughout life by DNA methyltransferases. Particular methylation patterns are tissue specific, consistent, reversible, and hereditary.

The aim of this paper is to define the correlation between hostile environmental factors occurring during fetal development and the effects on the health status of offspring; therefore it is important to present some of the causative mechanisms that lead to increased risk of diseases constituting metabolic syndrome.

Hyperglycemia during early periods of pregnancy is responsible for upregulation of glucose transporters in the placenta, which causes excessive fetal growth until birth and during the early stages of life. This important hostile factor also leads to functional changes of placental cells, which trigger a proinflammatory reaction resulting in reduced blood flow and constriction of blood vessels [7]; a similar effect may be obtained by excess glucocorticoid supplementation in response to any other intrauterine stress. Moreover, an overabundance of glucocorticoids during the critical period of organogenesis induces a decrease in nephron quantity, vascular dysfunction, permanent changes in hormone secretion, and angiotensin response inefficiency. These alterations are responsible for an increased risk of hypertension, as well as a predisposition to cardiovascular disease and hyperglycemia later in the development of the offspring [4].

Undernutrition

The influence of a low-calorie diet on fetal development was first acknowledged in The Netherlands in a cohort of 200 participants born between November 1943 and February 1947 in Amsterdam. The observation period lasted until 1996. The examined participants were born from pregnancies that developed during famine; daily calorie intake ranged between 400 kcal and 700 kcal and 18,000 deaths were reported. The participants were prone to hypertension, coronary disease, type 2 diabetes, obesity, adverse lipid profile, and even schizophrenia [16,17]. The likelihood of a particular syndrome occurring in adulthood depended on the moment of pregnancy in which the harmful factor appeared—the earlier the pregnancy stage, the greater the risk of severe complications [18].

Nutrient shortage during pregnancy leads to intrauterine growth restriction. Insufficient supply of elements essential for development may be a result of either placental insufficiency as a consequence of preeclampsia or hypertension, or inadequate diet during pregnancy. Intrauterine undernutrition activates adaptation processes which enable preferable nutrient management through a sparing and selective contribution to paramount organs (brain, heart). Consequently, these life-saving alterations result in growth restriction and have adverse consequences on the development and efficiency of other organs [3]. A disparate hypothesis suggests the suppression of cell division, which results in the reduced cell size and mass of specific organs, is the primary adaptive mechanism. Reduced pancreatic β cells, muscle tissue, and hepatic cell mass induces the development of insulin resistance and diabetes. Restricted access to nutrients results in fetal programming, ultimately leading to storage of energetic supplies such as fat. Regulatory mechanisms are biased in favor of ceaseless energy storage after birth, despite adequate or excessive availability of nutrients, resulting in obesity, diabetes, and various metabolic disorders [6].

Furthermore, undernutrition during pregnancy causes disturbed nitric oxide production and leads to an inadequate endothelium structure of the blood vessels, which results in a greater risk of hypertension for the child [19]. Experiments conducted on animals showed increased left ventricle wall thickness in the offspring of malnourished mothers compared to those whose mothers maintained proper nutrition status [20].

Amino acid availability during pregnancy determines insulin secretion by fetal pancreatic β cells. A low-protein diet is not adequate for proper pancreatic cell proliferation elements, and manifests in reduced cell size, restrained enzyme activity, disturbed ability to produce insulin, and insufficient islets vascularity. Alterations caused by intrauterine programming also affect receptor systems of insulin-dependent tissues which may develop into insulin resistance [21,22]. A low-protein diet can interfere with the natural fat balance and is conducive to cardiovascular diseases, including hypertension, in adult life [23]. This association is

assumed to be caused by epigenetic modifications of angiotensin II gene and endocrine disorders due to a suboptimal environment during pregnancy [24,25].

Particular importance is attached to catch-up growth, which is an accelerated body weight increase in infants whose intrauterine growth has been restricted [26]. Adipose tissue gain and insulin resistance development can be noticed as rapidly as during the first year of life. Fetal exposure to a low-protein diet during pregnancy triggers epigenetic alterations of the DNA molecule within the leptin gene [27], which leads to increased dietary intake in the future. Intrauterine undernutrition causes a decrease of insulin and insulin-like growth factor 1 concentrations, and consequently disrupts fetal growth. An abrupt increase of insulin and insulin-like growth factor 1 caused by adequate nutrition after birth eventually results in an increased risk of hypoglycemia and insulin resistance [28].

Vitamins and microelements intake disorders

An excess, as well as shortage, of vitamins, micro-, and macroelements can trigger intrauterine programming. Low vitamin B12 and zinc levels in the blood serum of pregnant women is conducive to the development of insulin resistance by the infant in adult life [29–31]. An excessive level of folic acid can induce a tendency for the offspring to cumulate adipose tissue and develop insulin resistance [31], whereas a low iron level in maternal blood serum predisposes the offspring to low birthweight and elevated blood pressure in later life [32].

Obesity

Overweight conditions and obesity during pregnancy are valid agents leading to chronic-disease development in progeny. Nowadays, the unlimited availability of highly processed food is a distinctively significant issue, as well as decreased physical activity. This interferes with the energetic balance in organisms and leads to the epidemic of obesity. Excessive body weight during pregnancy fosters the adverse effect of fetal macrosomia: newborns and infants of overweight mothers are characterized by increased adipose tissue content (i.e., via boosted intermuscular adipogenesis during fetal development) [33], and are predisposed to escalation of obesity in childhood, as well as type 2 diabetes and cardiovascular diseases in adult life [34]. Thus, the intrauterine environment (which is dependent on maternal nutrition) establishes not only the risk of disease, but also the moment of its onset and intensity of the pathological medical condition.

Specific mechanisms responsible for these relations have not yet been discovered. However, there are speculations about the role of systemic metabolism and immunological system changes in organisms exposed to adverse intrauterine environment factors. An investigation conducted by Heerwagen et al indicates that excessively developed adipose tissue produces and secretes vast amounts of proinflammatory cytokines, which activate immunological reactions leading to the development of insulin resistance [35].

One theory of intrauterine programming suggests that excessive dietary intake during pregnancy results in impaired functionality of the hypothalamus infundibular nucleus, responsible for controlling food intake, mainly via leptin (the hormone that regulates energy homeostasis by inhibiting hunger) resistance development [36].

Research performed by Guenard et al suggests a positive correlation between elevated body mass index, high glucose, total cholesterol, and low-density lipoprotein cholesterol levels in the mother's blood serum and metabolic syndrome and occurrence of cardiometabolic syndrome in the progeny [37]. This relation can be explained by the fact that a high-calorie diet during pregnancy, with accompanying metabolic disorders, results in hyperlipidemia, hyperglycemia, and hyperinsulinemia, which have an adverse effect on placental development and function [33,34]. Accordingly, as the placenta is responsible for providing nutrients for the fetus, it appears that there is an overlap of these adverse effects, causing an adverse synergistic effect on the progeny and resulting in the development of intensifying unfavorable epigenetic patterns.

The offspring of mothers who ingested a high-fat diet during pregnancy are prone to attaining a higher body weight. It is suspected that in this case a shortage of adiponectin (the hormone responsible for insulin sensitivity) is the factor initiating epigenetic modifications [38]. A high-fat diet during pregnancy transpires to play a role in the determination of invalid vasodilating reaction upon acetylcholine in the offspring. That leads to a significant disorder in the basic endothelium function and a predisposition to hypertension development and severe cardiovascular diseases [39] (Figure 1).

Gestational diabetes mellitus

Gestational diabetes mellitus (GDM) and accompanying hyperglycemia, even when isolated from maternal obesity, appear to be relevant factors determining intrauterine programming. Transcription factors in pancreatic insulin cells seem to be eminently sensitive to a suboptimal intrauterine environment. It has been observed that intrauterine hyperglycemia is the main agent in the establishment of epigenetic modifications and elevated risk of development of glucose intolerance in progeny [11]. Metabolic disorders attributable to GDM foster accumulation of reactive oxygen species, which arises from shortage of antioxidants in not only maternal, but also fetal organisms. This results in long-term effects including energy homeostatic disturbance, obesity development in childhood, and early onset of type 2 diabetes in offspring [40].

Deceased length of telomeres in the developing organism is a confirmed intrauterine programming mechanism triggered by GDM [41]. Correlation between alterations mentioned above and high vulnerability to cardiovascular diseases in adult life have been observed [42].

Intergenerational inheritance

Consistency and permanence of environmental conditions over previous years explain the incremental amount of metabolic disorders, obesity expansion, and correlated cardiovascular diseases [43]. Fetal exposure to excessive maternal dietary intake determines redundant food admission by the offspring after birth; this behavior leads to diabetes development in early life and obesity and metabolic syndrome, which are significant risk factors of GDM. Also, a high socioeconomic status in society is becoming more and more common, broadening the population trapped in this vicious cycle [36].

Epigenetic signals are essential for the correct development of mammals. Most of the epigenetic patterns are erased at the beginning of embryonic development (blastocyst stage) [44]. Pattern erasure is necessary for a new epigenetic record to develop and is responsible for normal cell differentiation. Most of the processes connected with cell differentiation are initiated and maintained via epigenetic alterations. Those modifications that occur during cell separation are usually deleted in the germ line.

It has been expressed that programming effects could also be observed in multiple generations following the specific epigenetic alteration, even with optimal availability of nutrients. This allows us to discern epigenetic mechanisms as a basic method of devolving phenotype by parents on their progeny, and following generations,

correspondingly. Maternal metabolic syndrome is viewed as an initiating factor for epigenetic modifications in fetal oocytes, which can be indicative of intergenerational inheritance of a predisposition to metabolic and cardiovascular diseases [45].

Prevention

Through proper diet modification pregnant women impact not only the body weight of the child but also, via epigenetic action, long-term effects on health, including exact nervous and skeletal system functionality throughout life, and minimizing cardiovascular disorders and metabolic syndromes related to obesity hazards.

Adequate nutrition during pregnancy may not only enhance the mother's health, but may also cause a significant decrease in the risk of developing diabetes and prevent child obesity. Research conducted on animal models suggests that intrauterine exposition to a low-protein diet can, in specific conditions, result in increased fetal sensitivity to insulin [46]. Therefore, a well-adjusted dietary intake during pregnancy may contribute towards new "healthier" epigenetic pattern creation and elimination of adverse modifications. Retrospective studies substantiate the validity of this theory [47]; modification of maternal dietary habits results in glucose intolerance and a decrease in the frequency of type 2 diabetes. It has been acknowledged that a balanced Mediterranean diet significantly diminishes the maternal and fetal blood serum levels of glucose, lipids, and lipoproteins and reduces the risk of GDM and low birthweight [48].

Studies conducted on animal models assume the possibility of constraining epigenetic mechanisms and avoiding adverse effects caused by intrauterine programming in response to suboptimal nutrient availability; beneficial and protective effects of using folic acid while undertaking a low-protein diet during pregnancy have been claimed [49], and similar results have been observed in the course of taurine supplementation [50].

Conclusions

On a final note, nutrient shortage and famine during pregnancy, as well as maternal obesity and excessive dietary intake, lead to elevated risk of obesity and metabolic and cardiovascular diseases. The intrauterine environment is dependent upon maternal nutrition status and determines not only the risk of disease occurrence but also the moment of disease onset and intensity of the pathological process (Figure 1).

Long-term nutritional programming results depend not only on disruption of optimal intrauterine conditions, but also on the moment this disruption occurs, owing to the fact that certain organs are characterized by diverse "critical periods" in development.

In order to prevent chronic disease manifestation it is essential to educate pregnant women within the area of adequate nutrition and lifestyle, and also inform future mothers about potential unfavorable outcomes of defective diet and negative health consequences for their offspring.

Conflict of Interest

The authors have no conflicts of interest relevant to this article.

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