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Review

The Role of Malnutrition during Pregnancy and Its Effects on Brain and Skeletal Muscle Postnatal Development

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Abstract: "Foetal programming" refers to nutritional and hormonal variations during pregnancy. A maternal proper diet has a fundamental role in decreasing pregnancy complications and to prevent possible diseases in postnatal life. In our narrative review, we analyze and discuss the role of malnutrition during pregnancy and its effects on pre- and postnatal development of embryos. Our review proposes a comprehensive and careful analysis of the studies in this field regarding malnutrition and foetal programming. Evidence shows that nutrient imbalance before implantation may result in somatic hypoevolutism at birth, and endocrine and metabolic dysfunctions in postnatal life. In addition, the maternal malnutrition could exert a suppressive effect on the maternal and foetal immune response. It could also affect both the proliferation of myogenic precursors reducing the number of muscle fibres and the future reproductive maturation with possible consequent impaired fertility and quality of gametes. In conclusion, it is necessary to develop dietary strategies to optimize nutrition, not only during pregnancy but already when it is programmed, in order to improve the outcomes of pregnancy, promote growth, healthy child development, reduce the risk of chronic diseases, and slow down the metabolic decline associated with aging.

Keywords: malnutrition; pregnancy; foetal programming; postnatal life; maternal diet

1. Introduction

The nutritional status of the mother at conception is a key factor for development and foetal growth, so a healthy, balanced diet is essential both before and during pregnancy. During pregnancy, the mother's diet provides energy and nutrients to both herself and the foetus' growth and for future lactation. From the data in the literature, the linking between nutrition during foetal life and the potential risk of disease in adulthood emerged. The so-called "Barker Hypothesis" suggests that chronic diseases in adulthood are in relation with the "foetal programming", through which any stimulus or insult during embryonic development would have a permanent effect on the structure and physiology of the human body. Scientific data clearly indicates that the pre-implantation phase is the period of the greatest vulnerability for the future embryo in relation to several endogenous and/or exogenous factors, including nutritional ones [1]. Nutrient reduction, deprivation or imbalance before implantation, could result in somatic hypoevolutism at birth [2], alterations in endocrine and metabolic functions during postnatal life [3] and, often, impaired maturation of the reproductive system [4]. From clinical, epidemiological, and experimental studies, several nutrients seem to influence the regular course of pregnancy and the embryo-foetal development in different animal species, including humans. Experimental results in mice have shown that undernutrition in pregnancy significantly reduces the number of puppies, increases the resorption of foetuses and increases neonatal mortality [5]; in sheep, it retards intrauterine development of the foetus [6]; in rats, it reduces the

weight of pups at birth [4]. In relation to humans, to evaluate the specific influence of different nutrients on prenatal development is difficult, since a severe maternal undernutrition, with a reduction in caloric intake, will trigger a proportional increase in catabolic activity of the maternal tissues that cause the release in blood, and then in maternal-foetal circulation, of many amino acids, vitamins and minerals that will balance the deficit "diet" of the foetus. Some malformation syndromes, such as congenital defects of the neural tube, are the result of selective deficiency of essential micronutrients during the embryo-foetal development (Table 1) [7]. The intrauterine environment seems to "program" the developing foetus to be able to deal with a postnatal environment similar to the intrauterine one ("predictive adaptive response"). If the postnatal environment is discordant with the intrauterine one, diseases could establish.

The mother is the source of all molecules that allow a regular development and growth of the embryo until birth, therefore nutrition plays a key role, both before and during pregnancy. In the present narrative review, we will analyse some aspects of the influence of maternal nutrition on "foetal programming" and any consequent alterations of a maternal malnutrition.

Table 1. Beneficial effects of micronutrients intake during pregnancy.

Folic Acid-Zinc	Reduction in Incidence of NTDs (Neural Tube Defects) and Neonatal Malformations; Reduction in Preterm Birth Incidence; Reduction in Low Birth Weight Incidence
Calcium	Reduction in incidence of PMS (premenstrual syndrome); Improved bone mineral composition in the newborn; Reduction in gestosis incidence
Vitamin C-Vitamin E	Reduction in gestosis incidence
Vitamin A-β-Carotene	Reduction in maternal mortality
Polyvitamins	Reduction in foetal mortality; Higher levels of immune cells in HIV (human immunodeficiency virus)-positive pregnant women; Reduction in incidence of NTDs and neonatal malformations; Reduction in preterm birth incidence; Reduction in low birth weight incidence

2. Developmental Origins of Health and Disease (DOHaD)

In the last years, epidemiological studies have demonstrated a relationship between the early growth of the individual and the risk of diseases such as type 2 diabetes, cardiovascular disease, and metabolic syndrome. Several studies on humans and animal models have highlighted that the uterine environment plays an important role in mediating this relationship. The hypothesis "Developmental Origins of Health and Disease" (DOHaD) suggests that environmental conditions during foetal and early postnatal development influence health and ability of an individual for the lifetime, with permanent effects on growth, structure and metabolism. Nowadays, this hypothesis is widely accepted and is called "programming". Nevertheless, the mechanisms by which events of the prenatal life may affect cell function and then the metabolism of an organism after several years, are just beginning to emerge. Alterations of these mechanisms may induce: permanent structural alterations of organs resulting from sub-optimal concentrations of an important factor during a critical period of development; persistent structural and/or metabolic alterations due to epigenetic changes leading to alterations in gene expression; permanent effects on cellular aging regulation. The phenomenon known as "foetal programming" implies that nutritional and/or hormonal changes in the embryo-foetal microenvironment may affect the foetal genomic expression and exert permanent effects on a wide range of physiological processes [8].

The hypothesis of the thrifty phenotype, proposed by Hales and Barker [9], suggests that non-optimal conditions of nutrition in uterus permanently alter the structure of organs of the foetus which also adapts its metabolism to ensure its own survival. This is possible through the "saving" of some organs, in particular the brain, to the detriment of others, such as heart, pancreas, kidney, and skeletal muscle. Barker et al. [10] and Hales et al. [11], in their epidemiological studies, showed

how individuals with a lower weight at birth and at one year of age, had a higher mortality rate by Ischemic Heart Disease (IHD) [10], a higher incidence of diabetes type 2 and abnormal glucose tolerance [11]; effects amplified by an inadequate postnatal nutrition. The DOHaD hypothesis includes several critical time windows, including preconception, foetal, and early postnatal periods, during which it is possible to establish the "foetal programming". Actually, the first time window should be considered puberty, since sexual reproduction begins long before fertilization. Indeed, the prerequisite for fertilization is the existence of the germline and the subsequent gametogenesis, which will be completed at puberty onset. In the male and female sex, germ cells have a different path differentiation: males are probably more susceptible to foetal life because in the male germ cells DNA methylation is reacquired during spermatogenesis proliferation (foetal life). In contrast, the female gametes may be more sensitive to perturbations during folliculogenesis, since the methylation of the DNA takes place during the growth and maturation of oocytes (adult life) [12]. So, for a good outcome of the foetal programming, optimal nutrition is crucial not only during pregnancy, but also in adult life from puberty. Structural changes in organs and the onset of postnatal endocrine-metabolic disorders, such as insulin resistance, type 2 diabetes, obesity, and for puberty disorders, should be consequences of alterations in nutrient intake during prenatal life [3]. Moreover, results of recent studies confirm that maternal-foetal malnutrition exerts a suppressive effect on the immune response of both mother and foetus, with inevitable repercussions on the development of the immune system [13]. Under-nutrition induces a significant hypertrophy of lymphoid organs, and over-nutrition, especially if characterized by the abundance of fat, may have a suppressive effect on the immune response [13]. Maternal malnutrition is a serious risk even during postnatal life and childhood, when the child no longer enjoys the, albeit precarious, maternal protection [14]. Malnutrition during weaning and in early childhood can affect important aspects of the whole postnatal life, such as somatic growth and protection against infectious diseases [13]. In addition, the gastrointestinal immune system mainly develops through the relationship with bacteria [15]. The development of bacterial flora begins at birth and continues with a precise temporal series of bacterial strains that change depending on the nutritional steps of the baby, from breastfeeding to weaning [16]. Furthermore, the bacterial flora intervenes directly on the digestive function, and for this reason acts as an indirect supplier of nutrients to the gastrointestinal tract [15], with subsequent effects on the development of the gut immune system of the child [14] (Table 2).

Table 2. Micronutrients supplementation effects on immune system during pregnancy.

Vitamin C	Better Response to DTH (Delayed-Type Hypersensitivity) Skin-Test
Vitamin E	Proliferation of immune cells; Reduction in levels of IGF-2 (insulin-like growth factors); Improvement in immune response to hepatitis B Vaccination; Increase in IL-2 levels; Better response to DTH skin-test
β-Carotene	Better NK (natural killer) cells function; Stop to UV-induced immunosuppression
Polyvitamins	Antibody levels increase in influenza vaccination; Reduction in infectious disease morbidity; Better response to DTH skin-test; Control in T-helper cells number

It should be also considered that a general or selective deficiency in essential nutrients is not the sole cause of potential congenital deficits. Indeed, many important endocrine and paracrine factors are involved in the growth and differentiation of embryonic tissues. Among them, insulin and insulin-like growth factors (IGFs) play a crucial role, during both development and postnatal life. These molecules are considered the most potent regulators of cell proliferation, apoptosis, oogenesis, embryogenesis, and ovarian secretion [17]. During intrauterine life, IGFs play an important role in regulating the nutrient metabolism (the later stages of gestation), while in the immediately neonatal period, they promote and control the use of energy for growth and for the definitive differentiation of tissues, such as musculoskeletal and nervous ones, and the progressive adaptation to the extrauterine

environment [18]. IGFs perform essential functions, such as increasing protein synthesis and, at the same time, limiting their catabolism.

Epigenetics, defined as "heritable modifications in gene function which cannot be explained by changes in the DNA sequence" [19], is an area of research analysing if and how epigenetic alterations in utero may have the ability to program diseases in adulthood. Scientific research has begun to investigate if epigenetic changes through nutritional interventions can affect the health of an individual, for example, in old age.

In the following paragraphs only some aspects of "foetal programming" will be analysed, including the importance of mother's diet during pregnancy and its effects on the development of certain tissues and organs of particular importance and the possible consequences on postnatal life.

3. Prenatal Development and Nutrients

3.1. Neurulation

Complex processes of interaction between genetic and environmental factors influence the development of the brain. Nutrition, from conception to adulthood, is one of the environmental factors that is particularly important for the role of nutrients in specific metabolic pathways during the pre- and postnatal development and a diet lacking in essential nutrients may be responsible for permanent brain alterations [20]. Given the strong neuronal proliferation and myelination characterizing neuronal development, the brain is particularly vulnerable to adequate nutrition from the 24th week of pregnancy until the early stages of postnatal life [21]. In particular, tryptophan, folate, and B vitamins are nutrients of particular relevance. The B vitamins are fundamental for metabolic pathways of the brain, so that are crucial for a healthy brain development and maintenance throughout life [22]. Additionally, the B vitamins appear to have direct roles on neuronal development through their involvement in the C1 metabolism (group of reactions involved in amino acid and nucleotide metabolism, characterized by transfer of one-carbon groups) and particularly in the production of *S*-adenosylmethionine, necessary for the production of neurotransmitters; in addition folate and B vitamins are essential in the processes of nucleotide synthesis and methylation, because they are donors of methyl groups. B vitamins effects on cognitive health may be independent or mediated by nutrient-nutrient and/or gene-nutrient interactions. The importance of C1 metabolism in a wide range of processes is well known so that its possible perturbations could have strong effects on both brain development and brain aging. A recent clinical study, performed in patients with mild cognitive impairment, showed that the integration, for a period of two years, with folic acid and vitamins B6 and B12 reduced their cognitive decline; in addition, in these patients a brain atrophy reduction of about 30% was observed by magnetic resonance imaging [23]. An appropriate supply of folate is essential during pregnancy. In pregnancy, there is a decrease in concentration of folate of about 50%, compared to the norm due to the increased folate request for rapid cell proliferation in uterus and placenta tissues and for the foetus' growth. Folic acid integration during pregnancy is necessary in relation to its protective role against possible neural tube defects [24,25], especially in the closing stages of neural tube. For this reason, it is strongly suggested the consumption of 400 µg of folic acid daily, from conception to the end of the first trimester of pregnancy [26]. Scientific data, even if not entirely consistent, suggest that the concentration of folate during pregnancy can affect the neurological development and behaviour of offspring. Moreover, it seems that the low concentration of maternal folate is linked to increased inattention, hyperactivity problems and emotional problems in the progeny [27], considerations that deserve further investigation. Few studies, however, investigated the status of maternal folate in the second and third trimester of pregnancy, to determine if the effect of folate is specific for some stages of pregnancy or if extended to the whole gestational period.

Tryptophan is an essential amino acid that cannot be synthesized by the body and so it had to be taken with food. It is the precursor of serotonin, a neurotransmitter synthesized by serotonergic neurons of the central nervous system and by enterochromaffin cells, involved in the regulation

of several body functions. Scientific data widely show the link between dietary tryptophan and serotonin production, in fact the abnormal tryptophan intake (in defect or excess) in the maternal diet has effects on different body areas of the progeny. For example, the strong decrease of serotonin, caused by a maternal diet deficient in tryptophan, causes alterations of both growth and maturation of specific developing brain regions [14] and secretion of hormones such as GH (Growth Hormone), TRH (Thyroid-Releasing Hormone), PRL (Prolactin), and gonadotropins [28,29]. In contrast, the excess of serotonin in the CNS could determine alterations, hindering the normal differentiation of the serotonergic neurons of the raphe nuclei of the brainstem and preventing the serotonergic processes from reaching the hypothalamus [30] with a consequent reduction in the production of GH by the pituitary gland [31] and, therefore, of IGF-1 by the liver [17,32].

It is important to improve knowledge on potential epigenetic mechanisms, during pregnancy and postnatal life, in order to provide information on important links between folate, B vitamins, tryptophan, and the status of brain health.

3.2. Myogenesis, Adipogenesis, and Fibrogenesis during Pregnancy and in Early Postnatal Life

Since skeletal muscle, fat, and connective tissue originate from mesenchymal stem cells, myogenesis, adipogenesis and fibrogenesis are mechanisms directly involved in foetal and neonatal development of the musculoskeletal system [33]. The commitment of mesenchymal stem cells to myogenic, adipogenic, or fibrogenic lines can be considered a competitive process and it is "due" to numerous inductive regulators. Since during embryonic and foetal development there is a controlled distribution of nutrients, skeletal muscle, and adipose tissue have a lower priority if compared to brain and heart, so that the development of the skeletal muscle and adipose tissue is particularly vulnerable to maternal nutritional deficiency [34]. The critical period for development of skeletal muscle, and connective and adipose tissues is mainly the foetal stage, therefore, just in this stage the maternal under-nutrition affects the proliferation of myogenic precursors reducing the number of muscle fibres. On the contrary, maternal nutrition has relatively minor effects on the development of skeletal muscle during the embryonic stage, since only a very small number of muscle fibres are formed during this stage. Even maternal over-nutrition influences foetal development of skeletal muscle, intensifying intramuscular adipogenesis and fibrogenesis. During foetal development of skeletal muscle, only a small portion of progenitor cells differentiate into adipocytes generating intramuscular fat, but at half gestation, maternal overnutrition can increase the expression of markers of adipogenesis, compromising myogenesis in favour of adipogenesis, which leads to a further increase of intramuscular fat, an event also associated with insulin resistance in skeletal muscle caused by paracrine effect of intramuscular adipocytes. In addition to myofibrils and adipocytes, mesodermal progenitor cells can also differentiate into fibroblasts, which can determine the increase of the connective tissue of endomysium, perimysium and epimysium in foetal skeletal muscle during late gestation [33]. Maternal over-nutrition increases the production of collagen and reticulation of skeletal muscle, heart, and large intestine of the foetus, suggesting an important role of maternal nutrition also in foetal fibrogenesis. The switching induced by over-nutrition, from myogenesis to fibrogenesis, leads to impairment of muscle function, including the oxidative capacity. Moreover, the attenuated myogenesis can reduce the number of muscle fibres, exerting permanent negative effects on muscle strength. Finally, during aging, a progressive loss of muscle mass, accompanied by an increase in adiposity and fibrosis with consequent decrease in structural integrity and functional capacity of muscle is evident, so that the proper differentiation of mesenchymal stem cells during foetal development is crucial for the individual's health over the long term.

A protein restriction during the gestational and neonatal periods alters the normal development of the neuromuscular system, and its effects on skeletal muscles seem to be permanent and not reversible, influencing, in the long term, the normal function of the muscle fibres and the neuromuscular junction. The molecular mechanisms by which protein restriction during pregnancy affects the morphology of

striated skeletal muscles remains to be clarified, but an alteration in the pathway of protein synthesis may be related to muscle fibre hypertrophy [35,36].

An altered tryptophan intake in the mother's diet has an indirect effect on the regular development of skeletal muscle. In fact, as above mentioned, a deficiency or an excess of tryptophan causes hyposerotonemia or hyperserotonemia that, although with different pathways, induces alterations in the normal brain development with functional defects on the hypothalamus/pituitary axis, resulting in a lack of hormones such as GH, TSH (thyroid-stimulating hormone), T3, and T4. These deficiencies are associated with low body weight and alterations in the normal development of muscle tissue [28,37,38]. The reduced production of GH by the pituitary gland [31] will induce a deficient production of IGF-1 by the liver [17,32], and low levels of IGF-1 have negative consequences on the differentiation of muscle and bone tissue and, therefore, on body growth [17,32]. In addition, recent experimental data show that, in pregnant rats, even the hyperserotonemia causes alterations in the offspring such as lower body mass index (BMI) and a lower rate of survival [31,39,40].

The mechanisms behind the observed changes in foetal skeletal muscle, in cases of maternal malnutrition, remain largely unknown. In addition to the alteration of inductive regulators, it is likely that microRNAs are involved in myogenesis and adipogenesis regulation, although further investigations are necessary. Furthermore, it is thought that epigenetic changes, such as DNA methylation, may modify the cell line commitment during muscle and adipose tissue foetal development.

4. Conclusions

As we analysed in this narrative review, the DOHaD hypothesis is supported by both epidemiological evidence and animal experiments showing that, during pregnancy, maternal under- and over-nutrition can lead to anomalies in metabolism and body composition in adulthood. Nowadays, it is believed that a "programming" in the early stages of life could be important in the aetiology of diseases such as obesity, type 2 diabetes and cardiovascular disease, suggesting that these common diseases can be prevented through optimal development of both foetus and newborn.

The nutritional needs of the foetus depend on the intake of nutrients of the mother, their metabolism, and their distribution through maternal circulation and on the placental transport mechanism. Malnourished mothers may be limited in their ability to adequately support the foetus. Vitamin D helps gastrointestinal absorption of several nutrients, including calcium, phosphate, magnesium, iron, and zinc. Vitamin D is present in many foods although most of vitamin D is synthesized in the skin after exposure to ultraviolet light (sunlight). Antioxidants, such as vitamin E and C, help to protect cells by acting as free radical scavengers. Other scavengers of free radicals and antioxidant enzymes depend on essential nutrients such as magnesium, riboflavin and niacin for their activation. The vitamin B complex is essential for cellular function, synthesis of neurotransmitters and metabolism of glucose, lipids, proteins and alcohol. Phosphate and magnesium ions are essential components of the nucleic acids and a lot of enzymes require magnesium as a catalytic agent. Selenium is a cofactor for antioxidant enzymes and thyroid hormones. Potassium helps to maintain osmotic balance. The docosahexaenoic acid (DHA) is particularly important in cognitive development [41,42] and the eicosapentaenoic acid (EPA) promotes the development and function of the brain [43], its mechanisms on development processes reflect those of DHA [44,45].

Foetal nutrition is influenced by size and composition of the mother's body and by her diet. In humans, strong evidence that maternal nutrition programs the risk for disease in the progeny is limited, even if it seems to indicate that the accumulation of oxidative stress and the consequent rapid cell aging are the major molecular mechanisms. Several studies suggest that maternal antioxidant therapy could reverse some of the deleterious effects of oxidative stress suffered in the early stages of prenatal life. Nevertheless, studies both in animals and humans [46,47] show that a proper assessment can be possible only in postnatal life, so that further studies are necessary to deal with the potential beneficial effects of postnatal supplementation with antioxidants. Other data on specific nutritional

interventions do not always agree even if they show beneficial effects on vascular function, lipid concentrations, glucose tolerance, and insulin resistance. A proper control of glucose homeostasis during pregnancy and early postnatal life is crucial for development of the foetoplacental unit and for adaptive physiological responses at birth. Recent evidence indicates that apelin and its receptor (APJ), expressed in a wide range of tissues, such as lung, heart, brain, kidney, stomach, muscle, and testis, control the homeostasis of the foetal and neonatal glucose, and this function is altered by decreased foetal growth induced by maternal under-nutrition [48].

What has been observed clinically in humans has been confirmed in animal experiments, and this allows the use of new knowledge to reduce the onset of many diseases. Therefore, it is necessary to know both the factors that determine foetal growth and the conditions that limit the maternal-foetal supply of nutrients and oxygen to the foetus. Even if much has already been done, further investigations are necessary in order to better understand how the foetus adapts to a limited supply of nutrients from the mother, how these adaptations could influence structure and physiology of the body, and what are the molecular mechanisms by which nutrients and hormones could alter gene expression. We believe that it is necessary to develop dietary strategies to optimize nutrition, not only during pregnancy, but already when this is programmed in order to improve the outcomes of pregnancy, promote growth and healthy child development, reduce the risk of chronic diseases, and slow down the metabolic decline associated with aging.

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Abbreviations

EPA	Eicosapentaenoic Acid
CNS	Central Nervous System
DHA	Docosahexaenoic Acid
DTH	Delayed-Type Hypersensitivity
BMI	Body Mass Index
DOHaD	Developmental Origins of Health and Disease
GH	Growth Hormone
HIV	Human Immunodeficiency Virus
IHD	Ischaemic Heart Disease
IGF	Insulin-Like Growth Factor
IL-2	Interleukin-2c
PRL	Prolactin
NTDs	Neural Tube Defects
NK	Natural Killer
PMS	Premenstrual Syndrome
TSH	Thyroid-Stimulating Hormone
TRH	Thyroid-Releasing Hormone
T3	Triiodothyronine
T4	Tetraiodothyronine

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