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Pregnancy, embryo-fetal development and nutrition: physiology around fetal programming

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Abstract

The purpose of this brief narrative review is to highlight the role of nutrition during the gestation period. We focused on the possible effects of imbalance of some nutrients in normal course of pregnancy and embryonic development. We discussed about changes in nutritional and/or hormonal embryonic microenvironment, which represent the basis of a phenomenon known as "fetal programming". We strongly believe that the understanding of these events can be a valuable tool in order to prevent the onset of disorders and diseases in postnatal life.

Keywords: Infant feeding, malnutrition, nutritional support, nutritional surveillance, pregnancy

Introduction

Experimental observations clearly indicate that during pregnancy, the pre-implantation phase is the period of the greatest vulne rability for the future embryo in relation to several endogenous and/or exogenous factors, including those nutritional ones [1-3]. In mice, the nutritional stress, during the pre-implantation phase, is often responsible of blastocyst death and pregnancy block [4]. Reduction, deprivation or imbalance of nutrients in the very early stages of pregnancy, before implantation, results not only in an obvious impaired somatic development at birth [5,6], but also in the profound alterations of endocrine and metabolic functions [7] and, often, in the impaired maturation of reproductive system in postnatal life [8]. In addition, observations from clinical, epidemiological and experimental studies *in vivo* and *in vitro*, showed that different nutrients seem to be able to influence both the normal course of pregnancy and the embryo-fetal development in different animal species, including humans (**Figure 1**) [1-3]. Experimental results showed that undernutrition during pregnancy significantly reduces the number of infants in mice, by increasing the phenomenon of fetal resorption and neonatal mortality [9]; in sheep, it defers intrauterine development of the fetus [10] and in rats, it reduces the weight of pups at birth [8] (**Table 1**). In case of a severe maternal undernutrition, due to reduced caloric intake, there is a proportional increase in catabolic activity of maternal tissues that results in the release into the maternal-fetal circulation of many amino acids, vitamins and minerals, which are able to balance the insufficient "diet" of the fetus. Instead, when we consider the selective essential micronutrients during the embryo-fetal development, the insufficient intake of some of them is clearly associated with some malformation syndromes, such as neural tube birth defects related to insufficient amounts of folic acid and vitamins C, B6 and B12 [11,12]. The purpose of this brief narrative review is to emphasize the importance of nutrition before and during pregnancy, as the mother is the source of all the molecular elements that help to regulate growth and development of the embryo until birth.

Review

Nutritional deficiencies in preconception period

Sexual reproduction is a phenomenon that begins before fertilization. It can be realized thanks to the existence of the germ line and the subsequent gametogenesis, which takes place during the puberty. The literature provides more and more information about the consequences of nutritional deficiencies in parental germ cells, even before the fertilization of the egg

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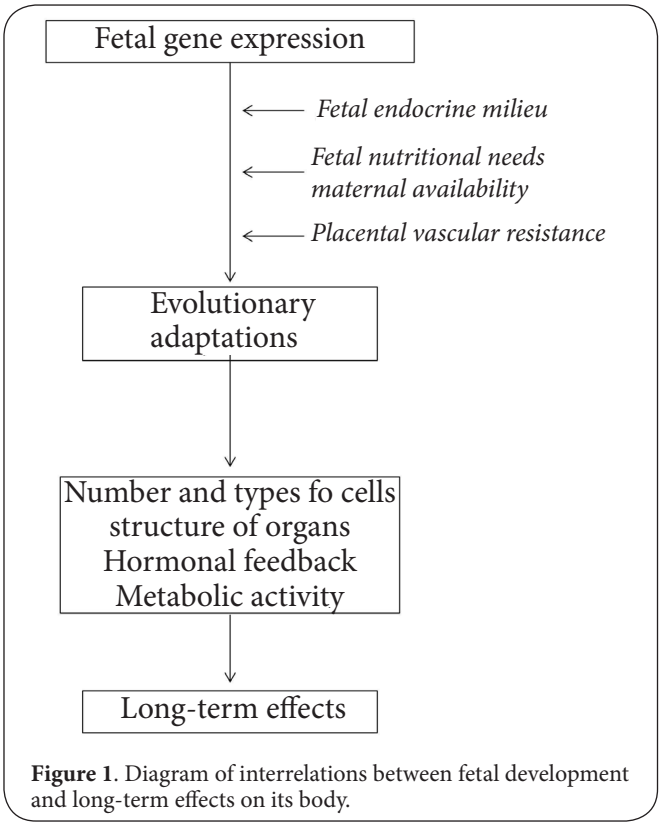

Figure 1. Diagram of interrelations between fetal development and long-term effects on its body.

Table 1. Effects of micronutrients intake on female reproductive activity.

Supplements	Significant effects
Calcium	Reduction of symptoms related to PMS
	Reduction of the preeclampsia effects in high-risk pregnancy
	The maternal intake of calcium improves bone mineral component of the newborn Reduction in the incidence of hip fractures from osteoporosis
Folic acid	Prevention of the incidence of NTDs in the fetus
Folic Acid+Zinc+ multivitamin preparations	Prevention of the incidence of NTDs and other birth defects
	Prevention of preterm birth
	Prevention of a low birth weight
Multivitamins	Reduction of the risk of premature birth and the consequences of hypo-weight at birth
	Minimization of the risk of fetal death and increase the plasma concentrations of immune cells in HIV-positive pregnant
Vitamin A/b-carotene	Reduction of maternal mortality
Vitamins C and E	Reductionof the risk of preeclampsia

PMS: Premestrual Syndrome; NTDs: Neural tube defects; HIV: Human immunodeficiency virus

cell [13-15]. Recently, it has been shown that damage to DNA in spermatocytes of adults, as a result of micronutrient deficiencies, can significantly increase the risk of congenital malformations and even carcinogenesis in descendants [16,17]. Some substances such as cigarette smoking and alcohol can aggravate deficiencies of crucial nutrients such as folate, zinc, vitamins C, E and A [11,12]. A condition of undernutrition during the folliculogenesis, a phase characterized by active angiogenesis and protein synthesis, results in a poor quality of the oocyte [18]. Therefore, both in the preconception period and in the earliest stages of embryonic development, the nutritional deficiencies and/or nutrient-gene interactions may be responsible for changes or complications of reproductive process.

Vascular and cardiovascular factors

Complications of reproductive process become more serious if mediated by vascular and cardiovascular factors [19]. Deficient or abnormal development of placenta and of its vascularization, both in the early stages of pregnancy and in the perinatal period, may also play a substantial role in the control of normal embryonic development [19,20]. In this case, many congenital defects are also related, at least in part, to the vascular damage of embryonic tissues [20]. A possible cardiovascular disease in the pregnant women, is often associated with a significant increase of the incidence of body weight reduction in infants [19]. This is related to the reduction of blood flow to the uterus and the consequent reduction in the supply of oxygen and nutrients into the embryo-fetal circulation (**Figure 2**) [19].

Endocrine and paracrine factors

A general or selective deficiency of essential nutrients is not the only cause of potential congenital defects. During embryonic tissue growth and differentiation, a number of important

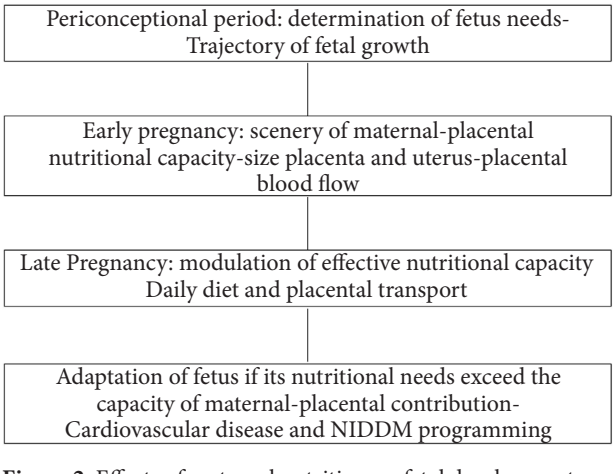

Figure 2. Effects of maternal nutrition on fetal development and its programming. NIDDM: non-insulin dependent diabetes.

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endocrine and paracrine factors, whose action is crucial in the control of reproductive processes, are involved [3]. Among these, a crucial role, not only during embryonic development but also in the course of postnatal life, is played by insulin and insulin-like growth factors (IGFs), which are considered, as amply demonstrated in the experimental animal, the most potent regulators of cell proliferation, apoptosis (especially programmed apoptosis), oogenesis, embryogenesis and ovarian secretion (**Table 2**) [2,3,16]. The role played by serotonin in the diet of pregnant rats has been shown in recent data from literature [16,21-24]. Our recent studies showed that deficiency or absence of L-tryptophan (L-Tp), the precursor of serotonin (5-HT), could be responsible for altered growth and possible alterations in sexual development of descendants of pregnant rats fed with L-Tp free diet [8]. Even the excess of L-Tp in diet of pregnant rats, showed adverse effects on their descendants [25], in particular on muscle tissue development. Indeed, this amino acid has been shown to limit the production of IGF-I by the liver [26], therefore, we could hypothesize the existence of a real 5HT/growth hormone (GH)/IGF-I axis [27]. In humans, there are numerous clinical observations in pregnancy, which may confirm these experimental conclusions. It is known that IGF-I significantly influences the secretion of ovarian steroids (estrogen and progesterone) in human ovary [28]. Nucleotides such as cyclic adenosine monophosphate (cAMP) and guanosine monophosphate (GMP), as intracellular second messengers, may be responsible for mediation or control of the pituitary gonadotropic cells, with obvious effects on ovarian function, and in particular on folliculogenesis. During the intrauterine life, in particular IGF-I, but also IGF-II, play an important role in the regulation of nutrient metabolism (especially in the later stages of pregnancy). Instead, in the immediate neonatal life they promote the use of energy for growth and for the final differentiation of various tissues, especially those of musculo-skeletal and nervous systems, and their progressive adaptation to extrauterine environment [26]. Moreover, IGF-I is important for some essential functions such as the increase of protein synthesis and, at the same time, the limitation of catabolic process [29]. Alterations in the regulation of nutrients in prenatal life may be responsible for the onset of short or long-term endocrine-metabolic disorders such as postnatal insulin resistance, diabetes type 1, obesity and disorders in puberty [7,30]. This is the pathophysiological basis for numerous and detailed clinical studies on adults [31-33]. These studies start to highlight the mechanisms that are able to establish a link between the various critical moments of the embryo-fetal development, which are also represented by a rapid cell proliferation, and the eventual diseases of postnatal life.

Table 2. Effects on fetal and placental weight in mice in the last stages of gestation according to the distribution of genes that control the bioavailability of IGFs.

		% of normal weight	
Gene target	**Effects**	**Fetus**	**Placenta**
Igf1	Absence of IGF-I in tissues and plasma	60	100
Igf2	Absence of IGF-II reduction of placental	60	75
Placental PO Igf2	IGF-II normal fetal IGF-II	75	65
IGF-Type I	No response from the receptors for the IGFs	45	100
Receptor (*IGFIr)*	IGF1r	--	--
IGF-Type 2	No clearance of IGF-II	140	140
Receptor (*Igf2r*)	Increase of plasmatic IGF-II	--	--
H19	No suppression of maternal IGF-II Increase of tissue IGF-II	130	140
Igf2 e*H19*	Increase of tissue and plasmatic IGF-II	200	230

Fetal programming and immune system

Nutritional or/and hormonal changes in the embryo-fetal microenvironment, can alter the fetal genomic expression and exert permanent effects on a wide range of physiological processes [34]. This phenomenon is known as "fetal programming" (**Table 3**). Results from recent researches confirmed that maternal-fetal malnutrition (both hypo- and hyper-nutrition) exerts a suppressive effect on the immune response of both mother and fetus, with inevitable consequences on the deveopment of the immune system of the latter [35,36]. Hyponutrition, in fact, evokes a significant hypotrophy of both primary and secondary lymphoid organs. Also hyper-nutrition, especially if characterized by the abundance of fat, may have a suppressive effect on the immune response [29,35]. The consequences of

Table 3. Tissues and systems for which there is evidence, in humans, of fetal programming.

Tissue/systems	**Examples of programming**
Cardiovascular system	Vascular compliance Thickness of the wall of the left ventricle Endothelial function
Respiratory system	Volume of each lung
Endocrine system	Hypothalamic-pituitary-adrenocortical axis Insulin metabolism of glucose GH-IGF-I axis Hypothalamic-pituitary-gonadal axis
Musculo-skeletal system	Insulin resistance Glycolysis during exercise
Bone	Bone mineral content
Kidney	Renin-angiotensin system
Liver	Cholesterol metabolism Synthesis of fibrinogen and factor VII
Immune system	Thyroid autoimmunity

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malnutrition are more severe if present in particular stages of life. Malnutrition during pregnancy is a serious risk for the development of the immune defense of the fetus, both in the intrauterine life and in the postnatal one, when the infant is no longer protected by the maternal defenses [37]. Malnutrition during weaning and in early childhood may result in lasting effects that can affect important aspects of the entire postnatal life, such as the somatic and stature growth and defense against infectious diseases [35]. The gastro-intestinal immune system develops mainly on the basis of the reports that it contracts with the world of bacteria [38] and the development of bacterial flora begins from the moment of birth and continues, especially in humans, with a particular sequence of bacterial strains, that change with different stages of infant nutrition, from breast feeding to weaning [39]. The principle of succession of bacterial micro flora varies in different species of mammals [40]. In the human fetus, it begins with coliform bacteria and enterococci, and it is subsequently followed by bifid bacterium [41]. Some specific nutrients also seem to act as crucial co-factors in the immune response expression [35]. Moreover, the bacterial flora intervenes directly on the digestive function, and for this reason it acts as indirect supplier of nutrients in the gastro-intestinal tract [38]. This, in turn, has an impact on the development of the intestine immune system [37]. This has significant consequences for production of: immunoglobulin A (IgA), receptor mfolecules of the major histocompatibility complex (MHC) and intraepithelial lymphocytes [42] (**Table 4**).

Table 4. Effects of micronutrient intake on the immune response in pregnant women.

Supplement	Significant effects
Multivitamins	In healthy woman and in elderly they improve the response to delayed-type hypersensitivity test (DHT): keep the number of T-helper cells; reduce morbidity from infectious diseases; increase the antibody titer in influenza vaccination.
Vitamin E	Increase DTH; promotes the proliferation of immunocytes; improves the antibody titer in the vaccination against hepatitis B; increases the production of IL-2; reduces the production of MPEG2.
Vitamin C	Improves the response to the test of delayed-type hypersensitivity (DTH).
b-carotene	Block the UV-induced immunosuppression in both young and old patients; improves the function of NK cells

DTH: delayed-hypersensitivity skin-test; IL-2: Interleukin-2

Conclusions

What has been observed clinically in humans, has also been confirmed by experimentation on animals, and this allows us to use this new knowledge to reduce the onset of many diseases. Therefore, it is necessary to understand and know both factors that determine fetal growth and conditions that restrict the provision of maternal-fetal nutrient and oxygen supply to the fetus (**Figure 3**). So much has been already done, but further studies are needed to understand how the fetus adapts to the limited supply of nutrients from mother, how

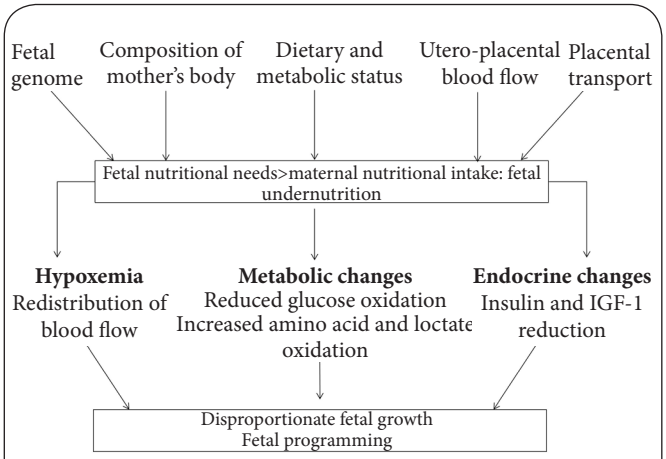

Figure 3. Diagram explaining the maternal regulation of the development and embryo-fetal programming.

these adaptations influence body structure and physiology, and by which molecular mechanisms, nutrients and hormones can alter the gene expression. We believe that, for the improvement of the pregnancy outcomes, the promotion of healthy growth and development, the reduction of the risk of chronic diseases and the slowing down of the metabolic decline associated with aging, it is necessary to develop dietary strategies to optimize the nutrition not only during the pregnancy, but already at the time in which it is planned, through the intake of adequate micronutrients, of complementary foods and also by the promotion of breast feeding.

List of abbreviations

5-HT: Serotonin
cAMP: Cyclic adenosine monophosphate
GH: Growth hormone
GMP: Guanosine monophosphate
IgA: Immunoglobulin A
IGFs: Insulin-like growth factors
L-Tp: L-tryptophan
MHC: Major histocompatibility complex

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Authors' contributions	GM	PC	FMT	RP	MAS	RI
Research concept and design	✓	✓	--	--	✓	✓
Collection and/or assembly of data	✓	✓	✓	✓	✓	--
Data analysis and interpretation	✓	✓	✓	✓	✓	--
Writing the article	✓	--	--	--	✓	✓
Critical revision of the article	✓	✓	✓	✓	✓	✓
Final approval of article	✓	✓	✓	✓	✓	✓
Statistical analysis	--	--	--	✓	✓	✓

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