Nutritional and metabolic programming during the first thousand days of life

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Abstract

The latest scientific acquisitions are demonstrating what has already been hypothesized for more than twenty years about the development of the state of health/illness of individuals. Indeed, certain stimuli, if applied to a *sensible phase* of development, are able to modify, through epigenetic mechanisms, gene expression of DNA, resulting in adaptive modifications of phenotype to the environment, which may reflect negatively on the health of every individual. This concept, applied to nutrition, has opened up important prospects for research in this area. The nutritional history of an individual, linked to the development of a healthy state, would begin very early. In fact, since the pregnancy and for the next two years (for a total of about 1000 days), the maternal eating habits, the type of breastfeeding and then the main stages of nutrition in the evolutionary phase represent those *sensitive* moments, essential for the development of important endocrine, metabolic, immunological alterations, better known as *metabolic syndrome*. This condition would represent the physiopathogenetic basis for explaining a series of disorders, known as non communicable diseases (NCDs) such as obesity, diabetes, hypertension, cardiovascolar disease and all those conditions that today affect the health of most industrialized countries and through the years are emerging especially in developing countries (South America, Asia), where new environmental conditions and increased food availability are changing food habits, with far-reaching public health impacts. This paper analyzes these new nutritional perspectives and the main implications of what has been termed the *1000-day theory*.

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Introduction

The origin of any individual metabolic pathway takes place early in life. If the genetic information stored in DNA sequence cannot be modified by environment, on the contrary epigenetic changes induced by exogenous stimuli can heritably affect genes' expression by altering the structure of proteins of DNA sequence or its interactions with other molecules.

The recent literature and many international scientific and human societies (*i.e.* UNICEF) have focused their attention on the *first thousand days* theory, that is the period from conception to two years of age. According to this concept, the period from the first day of pregnancy and the two years of life is crucial for the individual later development. Environmental factors may play a key role in this unique period and influence long-term health outcomes. Particularly, nutritional interventions may permanently affect the individual biological and metabolic development and lead to adaptive pathophysiological alterations later in childhood and/or adulthood, such as the non-communicable diseases (NCD) (*i.e.* diabetes, cardiovascular diseases, cancer, chronic respiratory disease, neurodegenerative disorders). The developmental adaptation due to the plastic interaction between inherited genes and environment/exogenous factors during the critical stages of life is defined *programming*. Programming concept traces back to the 80's when Professor David Barker developed his famous *Fetal Origin of Adult disease* theory that later evolved in the *Developmental Origin of Health and Disease theory (DOHaD)*.

The consequences of nutritional errors

Impaired quantity and quality of nutritional support in early developmental period (including pregnancy) may be responsible for an increased risk for morbidity and several chronic diseases in later life. According to UNICEF data, the health of more than 200 millions of children around the world is currently influenced by their nutritional status, with inevitable consequences on the quality of their growth and development.[1,2] Imbalanced nutritional intakes are still one of the more controversial and critical causes of paediatric morbidity. Indeed, if malnutrition is the main responsible for infant mortality in the most of the poorest countries, the deleterious effects of over nutrition in more developed states are more and more evident: diabetes, cardiovascular diseases, obesity.[3]

In addition to metabolic consequences, imbalanced nutritional intakes may also influence brain and neurocognitive development,[4] particularly neuronal multiplication, the later dendritic arborization and myelination, as shown by the modern neuroimaging techniques.[5]

Furthermore, nutritional support may also modulate the immune development and the composition of intestinal microbiota, leading to autoimmune deregulation or allergic diseases.[6,7]

Nutritional support during pregnancy

In addition to other well-known features of mother's behaviour (smoke, alcohol or drugs consumption, pollutants exposure, stress), increasing evidence suggests that one of the environmental factors that mainly contributes to fetal and later human development is maternal nutrition, starting from pregnancy throughout breastfeeding period.[8]

Evidence from literature supports the association between offspring's metabolism and maternal nutrition during the gestational period. Both maternal under nutrition and maternal over nutrition during pregnancy have been found to lead to impaired programming and consequent higher risk for childhood obesity.[9,10]

Indeed, in addition to fetal growth restriction, gestational starving may also cause a fetal adaptive tendency to later increase fat deposit, as a defence compensatory mechanism.[11] Similarly, an excessive availability of nutrients during intrauterine life programs the fetus to be more disposed to an impaired metabolic development and obesity.[9,11]

Moreover, pre-pregnancy BMI and excess maternal gestational weight gain are critical risk factors for impaired metabolic development in childhood and adulthood. Optimizing the nutritional support for mothers is mandatory, starting from the pre-conceptional period. The estimated ideal weight gain during pregnancy ranges from 7 to 15 kg in normal-weight women while a significantly lower increase is recommended for overweight and obese women (5 kg).[9]

During pregnancy, only a slight increase (10%) in caloric requirement is suggested, while higher intakes for micronutrients and oligoelements are required: folic acid and vitamins A, B and D necessities increase 50% and iron requirements double.[12]

Pregnant women require additional iron and folic acid to meet their own nutritional needs as well as those of the developing fetus. It is estimated that large part of pre-pregnant women worldwide has insufficient levels of folic acid.[13] Deficiencies in folic acid during pregnancy can potentially negatively impact the health of the mother, her pregnancy, as well as foetal neuronal development. Supplementation is therefore mandatory and it should be begun at least two months before conception.[14]

Evidence has shown that the use of iron and folic acid supplements is associated with a reduced risk of iron deficiency and anaemia in pregnant women. Iron deficiency has also been associated with later child cognitive and behavioural development.[15]

Long-chain saturated fatty acids play a key-role for fetal and infants' development. Boosting the consumption of omega 3 fatty acids during pregnancy seems to limit the risk of preterm delivery and to enhance cognitive development.[16,17]

Finally, low adherence to a Mediterranean diet in early pregnancy seems to be associated with decreased intrauterine size, lower birth weight and higher risk for preterm delivery and fetal malformations.[9,12,13]

Role of epigenetics

As previously described, cellular DNA can not be modify in its unique sequence, however genes expression patterns can be affected by an organism's environment throughout its lifetime, leading to potential origin of NCD.[17,18]

Epigenetics describes a variety of reversible modifications to the individual genome that are heritable and may take origin during the fetal life. Epigenetic changes include DNA methylation, histone modifications, chromatin remodelling and micro-RNA arrangements.[19,20] These epigenetic mechanisms can provide the link between environmental exogenous factors and phenotypic changes of genes expressions. The crucial interaction between gene expression and environmental factors (such as malnutrition, stress, hypoxia, hormonal levels), in the specific critical stages of life characterized by tissues' rapid growing (fetal and first two years of life), can produce detrimental adaptive effects in the developing organism.[21,22]

Intrauterine growth restriction as a model for programming

Nutrients' availability inevitably influences fetal growth, which represents an indicator of fetal health status.[23] According to his fetal growth trajectory, an infant can be classified as weight restricted (IUGR), small for gestational age – SGA (weight below the 10° percentile for gestational age, corrected for parity and gender) or large for gestational age (weight above the 90° percentile for gestational age, corrected for parity and gender).[24]

Intrauterine growth restriction (IUGR) refers to a condition in which a fetus is unable to achieve its genetically determined potential size because of environmental (particularly nutritional) factors.[25]

The terms IUGR and SGA are often used alternatively, actually they applied to different condition: SGA is diagnosed according to birth weight, while IUGR is a clinical definition for fetus and newborn with clinical evidence of malnutrition.[24,26]

IUGR births represent an important cause of neonatal morbidity (high risk for preterm birth, hypoglycaemia, neurological complications, asphyxia) and mortality. Their incidence is extremely elevated and estimated to be around 50:1000 newborns in USA and 110:1000 newborns in the poorest countries.[27]

In these latter, maternal undernutrition is the main responsible for fetal IUGR, while placental abnormalities are the leading causes in the more developed countries.

IUGR could be symmetric, when it affects all the anthropometric parameters (in this case it usually takes places in early gestational period) or asymmetric.[28] In this condition, there is first a restriction of weight and then length, with a relative *brain sparing* effect.[29] This asymmetric growth is more commonly due to extrinsic influences that affect the fetus later in gestation. Postnatal growth after IUGR depends on cause of growth retardation, postnatal nutritional intake and social environment.[26,29]

While a large number of aetiologies for IUGR are not identified, the known associations involve fetal, placental, and/or maternal factors. Particularly, placental insufficiency is one of the most common causes. Imbalanced levels of crucial mediators such as arginine and nitric oxide and polyamines, may play a key role by modulating angiogenic mechanisms and cellular proliferations in placental development.[30] When the placental nutrients' (including oxygen) supplies are insufficient, an intrauterine growth restriction is established: the fetus, in order to spare nutri-

tional resources, irremediably limits its growth pattern and modulates its metabolic pathways with potential detrimental outcomes for the later life (obesity, cardiovascular diseases, diabetes)[31,32].

From the *Fetal origin of adult disease* to the *Developmental origin of health and disease* theory

Nutrients' availability is one of the environmental key-factors that could modulate and *program* the expression of genome sequence during the periods characterized by tissues' rapid growth rate.[17,33]

As previously mentioned, programming concept traces back to Professor David Barker's famous *Fetal Origin of Adult disease*/*Thrifty Phenotype* Hypothesis, also known as *Barker's hypothesis*, that later evolved in the *Developmental Origin of Health and Disease theory (DOHaD)*.[34]

First *Barker's hypothesis* arose thirty years ago from epidemiological findings of a correlation between birth weight and rates of adult death from ischemic heart disease. These observations led to the theory that undernutrition during gestation was an important early origin of adult cardiac and metabolic disorders, probably due to a fetal programming mechanism that permanently modified biological structures and metabolic function contributing to childhood and adulthood disease.[35]

The fetal/neonatal origin of adult disease theory gained increasing support from many scientists and led to the concept of the developmental plasticity adaptive responses of the fetus to adverse events in utero, not just as a short-term, compensatory response at birth but as a permanent, altered phenotype for a lifetime.[36] Therefore, the permanent effect of developmental programming limits the possibility of postnatal adaptability, creating disease vulnerability.[37] In the intrauterine nutrients' restriction model, because of limited nutritional supplies, fetus modifies his metabolic pathway (*i.e.* insulin secretion) and biological structures (vascularization) to spare the limited nutritional resources. However, when, after birth, the infant has to face a different, unrestricted, environment, the permanent changes established during fetal life make him more vulnerable to disease development.[38]

Thus, the mismatch between the pre- and postnatal environments is an important determinant of later diseases.

Human milk role

Human milk is the preferred feeding for newborns and infants in the first months of life. Increasing evidence suggests its beneficial role on immune and neurocognitive development and its protective effect from obesity, diabetes, and hypertension.[39,40] This could be explained by the endocrine modulation induced by bioactive nutrient composition of human milk. According to the American Academy of paediatrics and WHO recommendations, breastfeeding should be protracted at least for the first months of life. When human milk is not available, formula milk is needed.[41,42]

The most widely accepted evidence for the protective effect of breastfeeding is the difference in child growth rates and the different risk for obesity associated with human versus formula-fed feeding.[43] Indeed, in the first months of life, human milk-fed infants present a different growth pattern compared to formula-fed ones. Moreover, body composition differs according to type of feeding: in the first 4 months of life, human milk- fed infants show a higher fat mass compared to formula fed infants, while, after this time-period, formula fed infants present a higher fat mass and a subsequent higher risk for overweight and obesity. Accordingly, formula-fed infants show higher plasma Insulin-like Growth Factor (IGF)-1 levels.[44]

This might be potentially due to the different nutritional composition and to the presence of bioactive elements in human milk compared to formula one. Particularly, human milk's content is lower in energy and protein, and higher in fat.[43,44]

Moreover human milk contains bioactive regulating hormones, such as leptin, insulin, GLP-1 (glucagon-like peptide-1), peptide YY and adiponectin that play a recognized role in the pathogenesis of metabolic syndrome in humans, and lower leucine level, an aminoacid involved in adipogenesis regulation.[45,46]

Accordingly to programming mechanism, the higher protein consumption in infancy has been found in association with increased risk for obesity in childhood.[47] Furthermore, in the last decade, new National Recommended Energy and Nutrient Intake Levels (LARN) have been proposed in order to limit the consumption of proteins in formula-fed infants.[48,49]

In addition, type of feeding may influence intestinal microbiota. Neonatal intestinal microbiota seems to differ according to type of delivery (vaginal *vs* caesarean section) and to type of feeding (breast milk *vs* formula milk).[43] As known, microbiota is supposed to modulate metabolic pathway, particularly fatty acids metabolism and thus insulin-sensitivity, suggesting its potential influence on later metabolic diseases development.[41]

Finally, also feeding modality (breast *vs* bottle) and duration of human milk administration have been found in correlation with the risk of obesity in childhood, between the 2 and 9 years of life.[49,50]

Conclusions

Nutritional support plays a key role in modulating the metabolic pathway of fetus and infants with potential long-term outcomes for later health. In crucial life stages, particularly in the first thousand days of life, characterized by a rapid growing rate for the organism, epigenetic changes induced by environment can heritably influence genes' expression. This can permanently affect the individual biological and metabolic development and lead to adaptive pathophysiological alterations later in childhood and/or adulthood, such as chronic disease's development (diabetes, cardiovascular diseases, cancer, chronic respiratory disease, neurodegenerative disorders). Future researches and further clinical knowledge should be primarily focused on the nutritional intervention in critical period in early human development and public health efforts for effective preventive actions would be needed.

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