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Introductory Chapter: Impact of First 1000 Days Nutrition on Child Development and General Health

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1. Introduction

The concept of the first 1000 days refers to the period from conception through the age of 2 years. This period is very crucial for the growth and development of the fetus and child and its long-term health outcomes. Many factors influence this period, including maternal health, breast and complementary feeding, and socioeconomic factors. Biological and metabolic development might be affected permanently by nutritional interventions, leading to adaptive pathophysiological alteration later in childhood and/or adulthood, such as noncommunicable diseases like diabetes mellitus, cardiovascular and chronic respiratory diseases, cancers and neurodegenerative disorders [1], as well as obesity and its adverse consequences [2]. In other words, children's and adults' health risks may be programmed by the nutritional status during this period. The first scientist who raised the theory of the possible effect of inherited genes and environmental factors during this critical period as an origin for the adult disease was Professor David Barker during the 1980s of the last century [3]. Barker affirmed, "Much of human development is completed during the first 1000 days after conception." His theory was later evolved in the Developmental Origin of Health and Disease (DOHaD) theory [4].

This introductory chapter aims to discuss the effects of nutrition, during pregnancy through the age of 2 years, on the health and development of the child and adult and the potential underlying mechanisms.

2. First 1000 days and overweight and/or obesity

Overweight and obesity are defined as an abnormal or excessive accumulation of fat that may impair health. It is a very common problem worldwide, and according to WHO an estimated 38.2 million children under the age of 5 were overweight or obese in 2019 and 340 million children and adolescents aged 5–19 were overweight or obese in 2016 [5]. Obese children are more likely to become obese adults, and in 2016, more than 1.9 billion adults aged 18 years and older were overweight and of these 650 million adults were obese. The problem is increasing and the worldwide prevalence of obesity nearly tripled between 1975 and 2016 [5]. There is increasing evidence that the origins of obesity are within the first 1000 days of life [6]. Prevention of childhood obesity is a public health priority and as it the source for adult obesity, early intervention is recommended. Effective and affordable preventive strategies that are embedded in the existing health system are needed.

These strategies should start early in life, should not be resource intensive, and can be maintained for the long term [7–10].

Risk factors' list for childhood obesity is wide, and antecedents are multifactorial, including genetic/epigenetic, social, biological, environmental, dietary, and behavioral influences. Among these, the most important modifiable risk factors during pregnancy and early childhood are maternal overweight/obesity, gestational weight gain, feeding practice during the first 2 years of life, in addition to maternal general health and smoking during pregnancy, physical activity, and sleep duration [6].

Although the fetal origin of the disease is an old theory dating back to about 40 years ago [3], focusing on its role in the prevention of childhood overweight/obesity is recent. Aspects of nutritional programming are variable, and some aspects may result in a modification in organs or endocrine structures and their function, resulting in irreversible lifelong consequences, and other aspects can be corrected with repeated learned exposure as in early flavor programming for later acceptance of taste/flavor [6]. Childhood obesity is a multifactorial problem. Both acquired and environmental factors can induce effects on genetic expression, and with appropriate interventions, some of the epigenetic changes can be reversed or modified [11]. Several of these modifiable factors have been identified and well studied at the individual level. The most important are maternal feeding behavior during pregnancy and feeding practice behavior during the first 2 years of life. Generally, these factors can be categorized as food and diet behavior (maternal BMI and the rate of increase weight during pregnancy, breastfeeding, age of introduction of complementary feeding, fruit and vegetable intake, sweetened beverage consumption, and the rate of infant weight gain) or feeding and associated lifestyle behavior (maternal smoking, maternal diabetes mellitus and gestational diabetes, sleep duration or screen watching time, use of a pacifier, physical activity, parental inattention to child hunger and satiety, and the parental use of rewarding, controlling, and restrictive feeding practice behavior) [12–14].

A good example of how maternal diet affects the nutritional and metabolic programming of infants as well as his food preference is flavor programming, in which shaping infant food preferences is rooted to fetus exposure via amniotic fluid, and after the development of taste bud, it is from maternal diet preference during pregnancy. As such, the infant shows preference to carrot-flavored cereal in his complementary food when his mother consumed carrot-flavored water during the latter part of pregnancy [15].

Prevention of childhood obesity is also related to infant feeding during the first 2 years of life. Healthy growth of infants requires breastfeeding started as early as possible after birth and the introduction of nutritious complementary food at an appropriate time. Weight gain during the first year of life is one of the best predictors for later obesity [16]. When compared with formula feed counterparts, infants on breastfeeding have a lower percentage of body fat accumulation and in turn lower weight gain and risk for obesity [17]. Three meta-analyses of observational studies found that the obesity risk at school age was reduced by 15–25% with early breastfeeding compared with formula feeding. Additionally, 4% lower obesity prevalence at a later age for each additional month of breastfeeding had been reported [18].

There is no consistent evidence that the introduction of complementary feeding before the age of 4 months is associated with higher later risk for obesity when compared with the introduction of infant complementary feeding between 4 and 6 months or at 6 months age. A study involving a systematic review of the literature investigating the relationship between the introduction of complementary feeding time and overweight or obesity during childhood concludes that the risk of childhood overweight

and obesity has no clear association with the timing of the introduction of complementary foods, although some evidence suggests that very early introduction (at or before 4 months), rather than at 4–6 months or more than 6 months, may increase the risk of childhood overweight [19].

Complementary diet quantity and quality, and in turn energy intake, may also play a role in the acquisition of subsequent childhood obesity. A large study that followed 881 infants in the United Kingdom shows that a higher prevalence of greater weight gain between birth and 1–3 years of age can be predicted in infants who were provided with solid foods at the age of 4 months [20].

Higher dietary protein intake during infancy, in particular from infant formula, had been found to be associated with a higher risk of obesity during the first 6 years of life [18, 21]. One explanation is given through early protein hypothesis, which describes the increasing level of insulin and insulin-like growth factor-1 as a result of high protein intake in early life, resulting in increased fat deposition and weight gain [18]. Apart from sweetened beverage intake, total carbohydrate intake during complementary feeding seems not to be associated with a higher risk of later childhood obesity [22]. Most of the studies about the role of fat intake during infancy in the development of childhood obesity failed to show a positive relationship. Although, one large study from China concludes that fat intake as fish liver oil is associated with a higher risk of childhood overweight [23, 24].

Measures to decrease the risk of obesity through the behavioral changes and nutritional education are found to be most effective during early life. Furthermore, human biology is the most pliable and amenable to changes during this period [25, 26].

3. First 1000 days nutrition and respiratory diseases

Susceptibility to the development of respiratory disease and its progression is affected by nutrition and feeding during the first 1000 days through epigenetic mechanisms [27]. Additionally, nutrition might affect the development of microbiota, which in turn can impress inflammatory, allergic, and immune mechanisms, rendering some individuals more susceptible to the various respiratory diseases of various mechanisms [28]. A study by Mayor et al. in 2015 shows that placental developmental and fetal growth is affected by poor maternal nutrition, resulting in increased susceptibility to noncommunicable diseases. This study in particular revealed that a high maternal fat diet intake before and during pregnancy increased glucose and insulin levels, leading to placental inflammation resulting in placental insufficiency, intrauterine growth restriction, and alteration of fetal lung development [29]. Fetal lung maturation impairment predisposes the neonate to an increased risk of respiratory distress syndrome at birth and chronic lung disease later on [30]. Furthermore, intake of diets rich in vegetables and fruit in the first and second trimesters is associated with a lower risk for allergic respiratory diseases such as allergic rhinitis and asthma in contrast with a diet rich in vegetable oil, margarine, and processed food [31]. This is very important when we compare Western diet (rich in oil, fast food, and processed food) to the Mediterranean diet (rich in fruit and vegetable, olive oil, fish, cereals, and other fiber diets) as a maternal dietary risk factor for the development of respiratory diseases. The adherence to the Mediterranean diet has been found to be associated with the normalization trend of gut microbiota, making it a good preventive choice for allergic diseases [32]. Some studies show that maternal supplementation with fish source Omega-3 polyunsaturated long-chain fatty acids during pregnancy is associated with a lower risk of allergic sensitization like allergic rhinitis, asthma, and atopic

dermatitis [31, 33, 34]. Additionally, maternal supplementation during pregnancy with micronutrients as Vitamin D and E and zinc is associated with a lower risk for childhood wheezes [35].

The short- and long-term benefits of breastfeeding are beyond doubt. Breastfeeding reduces childhood morbidity and mortality from infectious diseases, including respiratory, because it contains secretory IgA antibodies, anti-inflammatory cytokines, galacto-oligosaccharides, and lactoferrin [36]. The American Academy of Pediatrics reported, in 2012, a 72% reduction of risk of first-year hospitalization in exclusively breastfed infants for the first 4 months of life. Additionally, the severity of RSV bronchiolitis was reduced by 74% when compared with infants who are never or only partially breastfed [37]. WHO, on the other hand, reports that human milk can reduce the rate of hospital admission, severity, and mortality of lower respiratory tract infection by around 50, 30, and 60%, respectively [38].

The increasing incidence of various types of allergic diseases, including allergic rhinitis and asthma, in the last decades, is well documented all over the world, especially in developed countries. Many theories for this raise of incidence have been suggested, such as the urbanization of the population and following of the western lifestyle. Hygiene hypothesis (decreased rate of infectious burden is associated with the increased incidence of allergic disease), tobacco smoking, pollution, sedentary lifestyle, and reduced rate or absence of breastfeeding in the first months of life are thought to be important contributors [31]. In the first year of life, exposure to a wide range of food antigens is associated with a lower incidence of asthma, allergic rhinitis, and atopic dermatitis. So, the inclusion of food allergen in the first year of life might be protective against allergic diseases especially asthma [31]. Furthermore, maternal diet during pregnancy might have an impact on health even before delivery, and some interventional studies report immunomodulatory effects of specific nutrients on the neonate and a reduction of early sensitization to allergens [39, 40]. The proposed mechanisms are mainly immunological, suggesting the key role of diet in the hemostasis of the immune system, leading to oral tolerance and preventing excessive reactions to innocuous antigens which lead to allergic disease.

The role of breastfeeding in preventing allergic respiratory disease is controversial. Some studies have addressed the protective effect of breast feeding on the development of allergic diseases during childhood by facilitating the development of host immune mechanisms especially against allergic rhinitis in the first 5 years of life, while the evidence for the association between breastfeeding and wheezing and asthma was inconclusive [41, 42]. On the other hand, a protective effect of exclusive breastfeeding during the first 3 months of life against the development of asthma in children from atopic families has been demonstrated by other recent studies [29].

Many studies have investigated the role of complementary foods' introduction during infancy as a risk factor for developing allergy. Delayed introduction of solid foods has no effects on the prevalence of allergy, a result found by many studies [43, 44]. Recently, many studies investigated the protective effect of early introduction of highly allergenic foods (cow's milk, egg, fish, and peanuts) after at least 3–4 months of exclusive breastfeeding against food allergy [30]. In general, the results of these studies and many others [31, 45, 46] are inconclusive, and further studies, especially in children with a positive family history of atopy, are required to investigate the role of timing of introduction of high allergenic food in the development of atopy.

The effect of type of the diet on the susceptibility to asthma and atopy in children also has been studied. It has been found that Mediterranean type of diet (rich in fruit, vegetable, fibers, seafood, and olive oil) has a protective effect against

asthma and atopy when compared to the western style of diet (rich in saturated fats, red meats and poor in fruit, vegetable, whole grain, and seafood) [33, 47].

The micronutrient also has an important protective effect against respiratory diseases. Those with a potent antioxidant activity may delay the onset, severity, and outcome of asthma. Recent studies conclude that asthma is associated with the boosted production of reactive oxygen and reactive nitrogen species (ROS and RNS) and the pathogenesis of this disease is enhanced by changes in enzymatic antioxidant activity in lung and blood. Furthermore, both ROS and RNS increase systemic oxidative stress and subsequently increase the oxidative burden due to the alteration of systemic and blood antioxidant systems, which is typical of bronchial asthma. Wherefore, improvement of antioxidant activity may represent a successful strategy for delaying the onset, decreasing the severity, and improving the outcome of asthma. The most important antioxidants in this regard are vitamin E, vitamin C, selenium, coenzyme Q10, and carotene [48]. Zinc and iron have an important role in the immune system. Zinc is thought to inhibit the viral replication or intracellular adhesion and boost immune response at mucosal surfaces and hence may have a protective effect against the upper respiratory tract infections. Iron, on the other hand, has an important role in cytokines secretion, T cell proliferation, and bactericidal activity. Iron deficiency might impair these functions [48].

Vitamins also play a role in the defense mechanisms against respiratory diseases. Vitamin A is important for the enhancement of immune function and may limit the severity of respiratory infections in children older than 5 years of age [30]. Vitamin D, on the other hand, probably affects the onset, severity, and exacerbation of asthma, respiratory tract infections, and chronic obstructive airway diseases. Many theories have been adopted to explain this effect of vitamin D, including modulating immune mechanisms [49] and its influences on fetal lung maturation and airway smooth muscle cell proliferation and differentiation per via paracrine [50]. The role of vitamin C in the prevention and treatment of common cold is well known. By its potent antioxidant proprieties, vitamin C counteracts oxidants and decreases the external attacks of bacteria, viruses, toxins, and xenobiotics in the lung and hence modulates the development of bronchial inflammation and the impairment of pulmonary function [30, 51]. Contrary to the positive effects of the above vitamins, some studies show that folic acid (commonly used as a preventive measure for neural tube defects) in high dose given after the first trimester has been associated with an increased incidence of childhood asthma and eczema [30]. This relationship has not been documented by many other studies [52, 53].

4. First 1000 days nutrition and brain development

Throughout life, the first 1000 days represent the most vulnerable period for brain development and growth. During this period, the brain grows more rapidly than any other time, and it is the period where the neuronal connection and proper cognitive functioning occurs. Nutritional needs should be met during this period to ensure proper growth and development of the brain. A lifelong deficit may result from failure to provide key nutrients during this critical period despite subsequent nutrient repletion [54].

Development of the brain started 16 days after conception, growing throughout pregnancy, and taking adult form by 7 months of gestation [55]. Protein, fat and fatty acids, zinc, iron, folate, and iodine are required for neuronal creation, myelination, and synapses formation. Inadequate intake for these nutrients and micronutrients might impair the neurodevelopmental process [56].

Nutrition during the first 2 years of life is essential for this critical period of brain development and growth. Motor functions such as posture, balance, and coordination and the child's ability to create and recall memories (hippocampal—prefrontal connection) are well known to develop during this period [57]. Breastfeeding is the idealistic food for brain growth and development during the first 2 years of life as it contains hormones, growth factors, and a variety of nutrients that are essential for this process. Deoni et al., in their cross-sectional study in 2013, conclude that infant breastfeeding is associated with improved developmental growth in late-maturing white matter association regions, and extended breastfeeding duration is associated with improved white matter structure and cognitive performance [58]. Furthermore, extreme preterm infants fed predominantly with breast milk in the first 28 days of life show a greater deep nuclear gray matter volume, and by the age of 7 years, they had higher IQs and better scores in reading, mathematics, working memory, and motor function tests [59]. Breastfeeding provides not only the first-class nutrition necessary for the shaping of the brain but also affects the quality of the experiences and interactions they have with caregivers, which is found to be critical for both the cognitive and socio-emotional development [60].

5. First 1000 days nutrition and probiotics

The term dysbiosis refers to the microbial imbalance inside the human, especially digestive tract. In the last two decades, there was a great interest in the human microbiome. Thousands of studies were conducted to highlight its impact on health and disease. More than 500 bacteria species were found harboring the digestive tract, representing about 25 times more genes than the human genome [61, 62]. These microbes are thought to play a vital role in human health through protection against pathogenic microorganisms, metabolic functions by fermentation of indigestible carbohydrates, and modulation of the human immune system. Furthermore, recently there is important evidence to link dysbiosis with many human diseases like allergy, asthma, obesity, and inflammatory bowel diseases [63–65]. The gut of newborns will be rapidly colonized by microbes immediately after birth from exposure to the mother's microbiota, especially from the vagina and fecal material. Later on, feeding, close physical contact like hugging and kissing, and the environment will be the source of microbes. The adult pattern of gut microbiota will be established by the age of 3 years [66]. The establishment of the gut bacterial patterns is greatly influenced by the type of feeding. Breast milk is rich in complex nondigestible oligosaccharides, with more than 200 different molecules [67]. These oligosaccharides are resistant to hydrolysis by human small intestine enzymes and reach the large intestine, acting as substrates for microorganisms there, promoting the growth of specific bacteria. Nowadays, most infant formulas are supplemented with oligosaccharides, in particular fructo- and galacto-oligosaccharides, with the aim to improve the intestinal microbiota in early life [68]. Early dysbiosis that resulted from different factors like cesarean sections, prematurity, and early exposure to antibiotics might be associated with a wide spectrum of diseases like obesity, allergic disease, and autism spectrum disorders as revealed by several epidemiological studies [68, 69].

6. First 1000 days and epigenetics

Epigenetic modifications of the expression of genes occur through several mechanisms including DNA methylation, histone modifications, and posttranscriptional

gene-silencing by noncoding microRNAs [1]. Modifications to the epigenetic profile by external and internal environments of the cell can have short-term and long-term effects on gene expression [70–72]. A range of environmental stressors have epigenetic effects that are associated with diseases [70]. Some of these stressors include tobacco smoke-related diseases, air pollution effects on immunity and inflammatory responses, endocrine disrupting compounds, and others [73, 74].

Studies of the impact of environmental stressors on the epigenome provide insights into the mechanisms that link those stressors with the subsequent manifestations of disease. Such studies are especially important in establishing a full understanding of the linkage between stressor-induced modifications of the epigenome during the initial 1000 days and maternal and neonatal nutrition. At this time, most human studies have been aimed at characterizing the degree of association between epigenetic modifications and environmental stressors. Many of these studies use methodologies that characterize changes in global DNA methylation patterns or methylation of a limited subset of specific genes of interest in cord blood or maternal or neonatal peripheral blood samples. The methylation patterns are then used as biomarkers to correlate with the developmental abnormalities and disease status. A few examples are summarized here.

Maternal folate nutrition during pregnancy has been implicated in several birth defects [75]. The mechanisms that underlie DNA methylation are dependent on dietary folate and one-carbon metabolism [76]. Methylation profiles of a number of genes, including some not normally associated with folate biology, have a significant association with the maternal plasma folate during pregnancy [77]. Maternal serum folate concentrations are associated with DNA methylation patterns of seven genomic regions observed in the neonatal cord blood, especially in a region upstream of a regulator of DNA methylation during development [78]. Methylation patterns of insulin-like growth factor-2 (*IGF2*) in children are associated with the maternal periconceptional supplementation of folic acid [79]. Others have observed that the methylation patterns of *IGF2* promoter regions are not associated with the folate concentrations in maternal blood or cord blood [80]. On the other hand, the latter study did report an association between the serum levels of vitamin B12 in maternal blood and methylation patterns in one of the *IGF2* promoters. Vitamin D supplementation of pregnant and lactating women also has been associated with differential epigenome-wide DNA methylation patterns in their breastfed infants [81]. Specific effects of folate and other nutrients on epigenetic alterations in the fetus or newborn continue to be the areas of active investigation.

Toxic metal (arsenic, mercury, cadmium, and lead) exposure during pregnancy is associated with epigenomic changes in the offspring [82, 83]. Similarly, epigenomic changes in the offspring have been found associated with the exposure to endocrine disruptors, such as bisphenol-a, dichlorodiphenyltrichloroethane, polybrominated diphenyl ethers, polychlorinated biphenyls, and phthalates [83]. The relationship between these types of observed associations of epigenetic changes and environmental stressors during pregnancy and early life and their relationship with the known effects of those stressors and childhood and adult health remain to be understood.

Prenatal exposure to famine is associated with less methylation of the insulin-like growth factor-2 (*IGF2*) gene observed in adults six decades later [84]. That study underscores the potential for early life environmental stressors to cause long-term epigenetic modifications. Prenatal exposure to other environmental stressors on the mother, such as smoking, asthma, immune stress during pregnancy, and obesity, are associated with differences in the DNA methylation patterns of peripheral blood cells when comparing children who develop asthma with those who do not develop the condition [85].

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