



Infant growth, neurodevelopment and gut microbiota during infancy: which nutrients are crucial?

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Purpose of review

To update the role of specific nutrients during infant development.

Recent findings

Several bioactive nutrients such as long-chain polyunsaturated fatty acids (LC-PUFAs), iron, vitamins, proteins, or carbohydrates have been identified to exert an important role during the first 1000 days of life on infant growth, neurodevelopment, and gut microbiota establishment and maturation. LC-PUFAs are structural constituents of the central nervous system (CNS), being essential in retinal development or hippocampal plasticity. Recently, components of the milk fat globule membrane (MFG) are being added to infant formulas because of their key role in infant's development. A high intake of proteins induces a faster weight gain during infancy which correlates with later obesity. Digestible carbohydrates provide glucose, crucial for an adequate functioning of CNS; nondigestible carbohydrates [e.g. human milk oligosaccharides (HMOs)] are the main carbon source for gut bacteria. Iron-deficiency anemia during infancy has been associated with alterations of mental and psychomotor development. Folate metabolism, closely related to vitamins B6 and B12, controls epigenetic changes, whereas inadequate status of vitamin D affects bone development, but may also increase intestinal permeability and alter gut microbiota composition.

Summary

LC-PUFAs, proteins, carbohydrates, iron, and vitamins during early life are critical for infant's growth, neurodevelopment, and the establishment and functioning of gut microbiota.

Keywords

early nutrition, first 1000 days, growth, gut microbiota, neurodevelopment

INTRODUCTION

Historically, emphasis has been placed on the impact of early nutrition on growth patterns and children body fat composition. Compelling evidence shows that excessive energy intake and rapid or slow growth patterns in early life are associated with adverse developmental outcomes [1]; in fact, a rapid weight gain during infancy is a significant predictor of adiposity in later life [2^{*}]. However, early nutrition implications on neurodevelopment, brain structure and function, and on the establishment and maturation of gut microbiota need further research [3]. New approaches are trying to demonstrate that what we eat as infants and children is associated to long-term consequences. Here we will review the importance of type of feeding (breast milk vs. infant formula) and several bioactive nutrients during lactation and complementary feeding on infant's growth patterns, neurodevelopment and the establishment of gut microbiota, and their long-term impact on health.

TYPE OF FEEDING AND COMPLEMENTARY FEEDING DURING EARLY LIFE

Type of feeding is associated with significant differences in growth patterns and body fat composition. Babies fed with infant formula more frequently show a rapid growth pattern during the first

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KEY POINTS

- Exclusive breastfeeding is recommended during the first because it is considered as the gold standard of infant nutrition.
- When breastfeeding is not possible, infant formula should provide correct amounts of key bioactive nutrients facilitating an optimal infant growth pattern, neurodevelopment, and gut microbiota establishment and maturation.
- Around 6 months of life, it is necessary to introduce solid foods to meet infant's nutritional requirements for a correct growth and development. Complementary feeding should be quantitatively and qualitatively adequate for each infant.
- Nutrition during the first 1000 days of life has a key role in the programming of future health, being of special importance for neurodevelopment, growth patterns, and the colonization and establishment of gut microbiota.

6 months of life compared to breastfed ones. Pre-term babies fed with unfortified human milk present a catch-up growth slower than infants fed with preterm formula or fortified human milk, while that preterm infant fed with preterm formula present a rapid weight growth [4]. Type of infant formula also exerts a different impact on early rapid weight gain, independently of maternal feeding style, highlighting infants' self-regulatory capabilities [5].

Child cognitive development differs in relation to the food they receive during the first 1000 days of life, whether exclusive breastfeeding or infant formula, but also the type and quality of complementary feeding [6]. This important period of development coincides with the establishment and colonization of gut microbiota, when genome encodes proteins necessary for the hydrolysis of indigestible dietary compounds and synthesis of vitamins, for maintaining the structural integrity of the intestinal mucosal barrier and for the development of immunomodulation and protection against pathogens [7,8]. These processes take place in the gut during the first years of life, simultaneously with the intense synaptogenesis and the great neuronal plasticity, and bidirectional interactions have been shown, leading to the concept of 'brain-gut-microbiome axis' [9]. The functioning of this axis seems to be influenced by the diet at different stages of infant's development.

Breastfeeding is strongly recommended during the critical period of the first 6 months of life [10,11]. Human milk is a complex fluid and its composition continuously changes, adapting to

infants' needs, even in circumstances of maternal malnutrition [12]. Human milk is also a continuous source of probiotics, which intervene in the correct development of infant's gut microbiota. The predominant genus is *Bifidobacterium*, which delays the implantation of *Enterobacteria* [13] and fungi [14], and *Lactobacillus*, which ferments lactose, creating an acid medium that suppresses the growth of some pathogenic microorganisms [15]. Other microorganisms are added from the areola and the nipple, and several studies indicate that bacteria from mother's intestine can reach the mammary glands through the macrophages to finally reach the infant's digestive tract [16]. Furthermore, human milk provides prebiotics that promote the growth of intestinal microbiota, and growth factors, cytokines, and immunoglobulins that stimulate the immune system with a very positive impact on infants' growth, neurodevelopment, and metabolism [17]. Importantly, prebiotics are not present (or not in the same amount) in infant formulas, which likely affect gut colonization [18].

From 6 months of life onwards, exclusive breastfeeding no longer covers infant's energy and nutrient requirements; therefore, the introduction of solid food is strongly recommended [19,20]. The composition of the complementary diet is likely to affect child's future health. A high intake of proteins, together with a low intake of fruits, vegetables, and fish, and an unfavorable distribution between polyunsaturated and saturated fats are associated to health risks later in life, for example obesity, type 2 diabetes, and dyslipidemia [21].

The energy intake will be increased by the introduction of cereals, which constitute the main energy source in the form of complex carbohydrates; this will affect growth and functional development of the central nervous system (CNS), and promote gut colonization by phylum *Firmicutes*, which will lead to diversification of the gut microbiota community [22,23]. Fruits and vegetables are introduced after cereals and represent an excellent source of vitamins, minerals, and macronutrients. An excess of dietary fibers should be avoided because they can interfere with the absorption of micronutrients such as iron or zinc, leading to a deficit that may be detrimental to neurodevelopment [24].

The gradual addition of meat, egg yolk, and fish will help to cover protein needs and to ensure a proper neurodevelopment and the colonization of several bacteria (namely from the *Lachnospiraceae* and *Ruminococcaceae* families); this results in a more mature gut microbiota composition, which will be definitely established around the age of 2.5 years [25,26].

IMPORTANT NUTRIENTS DURING THE FIRST YEAR OF LIFE

Macronutrients

Fats

Fatty acids are the major constituent of many lipids, and those which are essential must be provided through the infant diet for a healthy growth, neurodevelopment, immune system, and gastrointestinal function. During the first months of life, polyunsaturated fatty acid (PUFAs) requirements are increased, because rapid growth and neurological development [27]. Fat intake in infants, which is high during the breastfeeding period, is reduced gradually in the second half of the first year from the start of complementary feeding. Fats nutritional requirements of the total daily energy intake, from 0 to 6 months of life are 50–55%, from 6 to 12 months 30–40%, and from 12 to 36 months 35–40% [28]. Recently, different European Organisms have established that the intake of Linoleic acid should constitute 4% of total energy, whereas alpha linolenic acid 0.5% of total energy [28].

Long-chain PUFAs (LC-PUFAs), n-3 docosahexaenoic acid (DHA, 22:6n-3), and arachidonic acid (ARA, 20:4n-6) are functional components of cell membranes of CNS and have a key role in neurotransmission [29]. The European Food Safety Authority (EFSA) Committee has established as adequate DHA intake 100 mg/day from 0 to 24 months of age, whereas the ARA requirements are 140 mg/day from 0 to less than 6 months of age. There are no specific recommendations from 6 to 36 months of age for ARA [28].

Human milk supplies both ARA and DHA. Infants' DHA status is provided through breast milk and it is dependent on maternal DHA status; nonetheless, ARA concentration in breast milk, always near 0.5% of total fatty acids and typically higher than DHA, is more stable compared with DHA [30–32]. Significant amounts of both n-3 and n-6 LC-PUFAs accumulate rapidly in the membranes of organs and tissues. In the last trimester of fetal life and exponentially during the first 2 years of life, DHA accumulates in brain tissue, particularly in the grey matter areas associated with attention, motor control and sensory integration, whereas ARA is responsible for hippocampal plasticity [33,34]. It has been shown that an elongation product of ARA, the adrenic acid (ADA, 22:4n-6), is a significant component in cell membranes. ADA constitutes nearly half of the n-6 LC-PUFA in the brain, and n-6 LC-PUFA far exceed n-3 LC-PUFA content [35]. A balanced intake of DHA and ARA is crucial for brain function, and healthy human development

[36]. In fact, higher DHA/ARA ratio during early life has been associated with better cognitive outcomes. It has been shown that the neurodevelopmental outcomes favor a ratio of 1:1 or 1:2 of DHA to ARA, whereas a ratio of 1.5:1 reduces ARA concentration in red blood cells during brain development compared to the 1:1 and 1:2 ratios [36,37[■]].

Studies trying to establish a relationship between fatty acid intake and linear growth show mixed conclusions; some of them suggested that essential fatty acids are important for optimal linear growth during infancy [38], and others found no associations [39[■]].

On the other side, fats' research efforts have suggested that milk fat globule membrane (MFGM) proteins represent a bioactive fraction of breast milk that provide some of its health benefits [40]. This membrane fraction is composed of different bioactive components (phosphatidylcholine, sphingomyelin, cholesterol, and cerebroside, gangliosides, ...), which positively influence brain development and immune functions [41,42] and protect neonatal gastrointestinal tract modulating gut microbiota composition [40].

Not only the excess of fat in the diet, but also the profile of dietary fatty acids, could change gut microbiota composition and obesity profile [43]. Recently, Jiang *et al.* [44[■]] have shown a significant association between sn-2 fatty acids in human milk and infant gut microbiota; they found that ARA and DHA were associated with the genus *Bacteroides*, *Enterobacteriaceae*, *Veillonella*, *Streptococcus*, and *Clostridium*, bacteria involved in short-chain fatty acids (acetate, propionate, and butyrate) production, which have important immunomodulatory functions and play a key role against the development of intestinal pathologies, among other functions, and significantly increased at 13–15 days after breastfeeding was initiated.

Proteins

Proteins are important during the first 1000 days of life because their role in cellular structure and as components of enzymes and neurotransmitters. During the first 6 months of age, proteins recommendations per kg body weight/day are: from 0 to 6 months of life 0.58 g and from 6 to 36 months of age, 0.66 g [28]. Human milk has over 400 proteins with a variety of functions, such as antimicrobial, immunomodulatory activities, or stimulation of nutrient absorption [45]. Protein deficiency can lead to poor growth outcomes and delayed motor and cognitive development [19]; however, high protein intake is known to induce a faster weight gain during infancy and correlate with obesity later in life [46[■]].

Normal infant growth pattern during the first 4 months of life has been demonstrated in babies fed with infant formula with a decrease in total protein up to 1.0 g/dl (similar to human milk) [47²²]. Tang *et al.* [48²³] demonstrated that protein sources and intakes from complementary foods can significantly affect infant growth and possibly overweight risks; they showed that meat- and dairy based complementary foods led to distinct growth patterns, especially for length. Meanwhile, associated types of protein-rich foods during complementary feeding have an effect on the gut microbial composition and metabolites in formula-fed infants; children fed with meat showed a gut community enriched in *Firmicutes* phylum and *Faecalibacterium* genus, and a decrease in *Proteobacteria* phylum and *Bifidobacterium* genus [49].

Carbohydrates and sugars

The total carbohydrate requirements of the total daily energy intake during the first 6 months of life are 40–45%, from 6 to less than 12 months 45–55%, and from 12 to less than 36 months of age 45–60%, just like adults [28].

Glucose has a key role for an adequate functioning of the CNS, because it is the main energy source for growth, nerve impulses, and synapses [19]. Glucose is provided to the baby by different carbohydrates such lactose, as the main sugar present in human milk (ranging from 6.7 to 7.8 g/dl), and a diversity of oligosaccharides, which comprise approximately 1 g/dl [50].

Human milk oligosaccharides (HMOs) constitute a significant fraction of breast milk carbohydrate indigestible by the infant [50]. HMOs have prebiotic function, nourishing the gastrointestinal microbiota and encouraging the growth of beneficial bacteria [45]; furthermore, they have been linked to multiple biological functions such as effects on gastrointestinal development and systemic immunity [51], bifidogenic activity and anti-infective [52,53], modulation of inflammation [54], activation of enteric neurons and gut motility [55], and enhancement of CNS functions [56].

HMOs include acidic oligosaccharides, mainly sialylated [e.g. 6'-sialyllactose (6'-SL), 3'-sialyllactose (3'-SL), or neutral oligosaccharides [e.g. 2'-fucosyllactose (2'-FL)]. Fucosylated glycans are the most abundant HMOs' form in breast milk (80–90%) [57].

Glycans are a source of carbon for microbes, and are crucial to recognition, signaling, and epigenetic regulation between host cells and microbes, being implicated in a wide range of immunological and metabolic disorders [58]. Bai *et al.* [59] observed a significant correlation between the levels of human milk N-glycans and the growth of *Bifidobacterium*

spp. and *Lactobacillus* spp. in the infants' gut during early and late lactation.

Several preclinical models have demonstrated HMOs effects on cognitive function [60,61] but, to our knowledge, clinical data in humans have not been published yet.

Regarding sugars, there are no specific DRI for sugars in infancy. The ESPGHAN Committee on Nutrition recommends avoid added sugars in the diet of children less than 2 years old [19,62]. It is also recommended to avoid fruit juices or sugar-sweetened beverages, because their early introduction has been associated with higher risk of developing type 1 diabetes later in life [19,24²⁴,62].

Micronutrients

Iron

During the first 6 months of life, infants use iron liver reserves build up during fetal life, as the iron content of breast milk is very low. Thus, at around 6 months, an exogenous source of iron from the diet is needed to meet the nutritional requirements [19,63]. From 0 to 6 months of life iron requirements are 0.3 mg/day and from 6 to less than 12 months of age, 6 to 11 mg/day, whereas from 12 to less than 36 months the requirements range from 3.9 to 9 mg/day [28].

Iron deficiency can affect brain, neurological, and psychomotor development, because iron is a component of enzymes needed for neurotransmitters. Iron deficiency causes a reduced oxygen-carrying capacity, which results in a limited conversion to glucose needed for growth and development; these limitations could lead to growth retardation, lower weight, and length for age, but unlike what happens with neurological development, they can be overcome by iron treatment [19,28,63,64²⁵].

Breast milk is the main source of *Bifidobacterium breve*, which can acquire luminal iron with the help of a divalent metal permease, and lactoferrin, promoting these beneficial bacteria growth, and sequestering iron from bacterial pathogens [65²⁶]. According to Paganini *et al.*, iron deficiency causes a dysbiosis in the gut microbiota community, which is reflected with an increase of the relative abundance in *Enterobacteriaceae* and *Veillonellaceae* families, and reduced abundance of *Coriobacteriaceae* and *Bifidobacteriaceae* / *Enterobacteriaceae* ratio compared to healthy controls [66²⁷].

Vitamin D

Exclusively breastfed infants receive below the minimum recommended intake of vitamin D and much lower than the DRI. To avoid possible pathologies

derived from the deficit of this vitamin, such as inadequate bone mineralization or rickets, maternal supplementation with 400 to 2000 IU per day can increase levels of vitamin D in breast milk; sunlight exposure and vitamin D supplementation are recommended for exclusively breastfed infants [67].

Vitamin D nutritional requirements from 0 to less than 36 months of life are 10 $\mu\text{g/day}$ [28]. Vitamin D induces the nerve growth factor, promotes neurite growth and inhibits neuronal apoptosis in the hippocampus. Thus, a deficiency during critical neurodevelopmental periods, has been observed to cause behavioral, memory, and learning disorders later in life [68].

Recent systematic reviews have shown some association between vitamin D and the gut microbiome in rodent models and humans [69]. Low levels of vitamin D can lead to increased intestinal permeability, producing a state of chronic low-grade inflammation [70]. Some differences have been observed in the gut microbiota composition of ethnically diverse infants at 3–6 months of age, whose mothers were supplemented with vitamin D during pregnancy to prevent asthma and allergies in their offspring [71].

Vitamin B12 and folic acid

During the first 6 months of life, vitamin B12 requirements are 0.4 $\mu\text{g/day}$ and from 6 to less than 12 months 0.5 to 0.8 $\mu\text{g/day}$, whereas from 12 to less than 36 months are 0.6 to 1 $\mu\text{g/day}$ [28]. Folate nutritional requirements, from 0 to 6 months are 65 $\mu\text{g/day}$, and an adequate intake of 80 $\mu\text{g/day}$ is recommended by EFSA [72] for infants aged 6–12 months, whereas from 12 to less than 36 months the requirements are 100 $\mu\text{g/day}$; the upper intake level has been established between 200 and 800 μg of folic acid (FA)/day for children aged 1–17 years [73].

FA (the synthetic and most stable form of folate, also named Vitamin B9) and Vitamin B12 (cobalamin) play an essential role as cosubstrates and cofactors involved in a wide range of biological processes, such as nucleic acid synthesis, glycolysis, gluconeogenesis, and amino acid metabolism. Moreover, status with respect to folate and vitamin B12, and other micronutrient cofactors required for one-carbon metabolism cycle, may influence DNA methylation, leading to long-term health effects.

It is well known that FA deficiency during pregnancy results in higher risk of neural tube defects in the offspring. Nevertheless, a high dose of FA is not related to a better status, nor in the mother or the offspring; in fact, intakes higher than 400 $\mu\text{g/day}$ during pregnancy have no clear benefit. FA supplementation during breastfeeding can result in

modest increase of breast milk total folate [74]. In children, FA deficiency is related to impaired cognitive development [75] and increased diarrheal and respiratory disease [76]; however, FA supplementation does not help to decrease these pathologies [77].

FA excess consumption may have potential adverse effects, including an increased frequency of several diseases (e.g. cancer, neurological disorders, growth syndromes, respiratory disorders, and multiple sclerosis). Currently, high percentage of European children show high intakes of FA because of the consumption of supplements or fortified foods [78]; however, it is not known whether these intakes may cause harm, particularly during early development, whereas a substantial number of epigenetic changes are occurring in many tissues.

When maternal vitamin B12 status is poor, the content in breast milk is reduced and will affect their offspring vitamin B12 status. Vitamin B12 is essential for the CNS metabolism and maintenance, and together with folate plays a key role in homocysteine metabolism and the preservation of myelin. Thus, a deficiency of vitamin B12 can cause damage in the myelin sheath covering cranial, spinal and peripheral nerves, which can lead to the development of neuropsychiatric disorders [75].

In-silico genomic reconstruction and prediction of community-wide metabolic phenotypes for several B-vitamins suggest that a significant fraction of microbial gut communities are represented by auxotrophic species, whose viability is strictly dependent on acquiring one or more B-vitamins from the diet and/or prototrophic microbes via committed salvage pathways [79²²].

It is important to note that maternal methyl-group donor intake (choline, betaine, folate, methionine) can alter her offspring's DNA methylation. Pauwels *et al.* [80] observed that this intake, especially in the periconception period, can influence infant's buccal DNA methylation in genes related to metabolism, growth, appetite regulation, and maintenance of DNA methylation reactions. In addition to dietary intake, it is of specific interest bacterial folate biosynthesis. Kok *et al.* [81] proposed that bacterial folate biosynthesis provides an additional source of folate with important implications on health outcomes and/or DNA methylation. In a colonic model *in vitro*, supplementation with methylcobalamin and whey enhanced the proportions of *Firmicutes* and *Bacteroidetes* spp. and reduced those of *Proteobacteria* spp., which includes pathogens such as *Escherichia* and *Shigella* spp., and *Pseudomonas* spp. [82]. Moreover, Xu *et al.* [83] observed in

humans that methylcobalamin promoted lipid, terpenoid, and polyketide metabolism by gut bacteria, induced the degradation of exogenous substances, and inhibited the synthesis of transcription factors and secondary metabolites (vitamin B12).

CONCLUSION

An adequate diet during the first year of life with an appropriate supply of LC-PUFAs, proteins, carbohydrates, and micronutrients such as iron and vitamins are necessary for an optimal infant growth, neurodevelopment, and the correct establishment, maturation, and functionality of the gut microbiota to avoid long-lasting consequences.

New initiatives should be focused on the correction of infant bioactive nutrient deficiencies and gut dysbiosis for better long-term growth patterns, adequate body composition, and optimal neurodevelopment.

During the first 1000 days of life, nutrition has an essential role in all biological changes taken place during this period; new studies should evaluate the interaction of nutrition all together with gut microbiota, brain development, and growth patterns.

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Conflicts of interest

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