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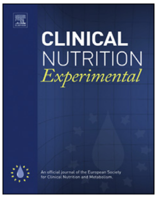

Perinatal nutrition: How to take care of the gut microbiota?

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S U M M A R Y

Perinatal and postnatal nutritional environments can result in long-lasting and/or permanent consequences that may increase the risk of chronic diseases in adulthood. The impact of perinatal nutrition on infant microbiome development has been increasingly gaining interest, however scarce information can be found about nutrition on maternal microbiome. The infant microbiome plays an essential role in human health and its assembly is determined by maternal offspring exchanges of microbiota. Microbial colonization runs in parallel with the immune system maturation and has a decisive role in intestinal physiology and regulation. This process is adversely affected by several practices, including caesarean section, antibiotics, and infant formula, which have been related to a higher risk of non-communicable diseases. Limited research has been performed to assess whether nutritional status and diet lead to changes in the maternal microbiota and thus affect the infant microbial colonization process during the critical frame of life. Early microbial colonization has a decisive role on human health, and alterations in this process have been lately associated with specific diseases in the future. The aims of this review are, firstly, to update nutritional recommendations for the perinatal period and, secondly, to analyse the influence of both maternal microbiome and nutrition on infant gut microbiota development.

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1. Microbiome, diet and human health

Recent research has revealed the importance of our gut microbiome for an optimal health status. The overuse of antibiotics, unbalanced diets, caesarean-sections (C-section) deliveries, excessive hygiene, and continuous stress are permanently changing our microbiome [1–3]. There is a clear relationship between what we eat and the balance and diversity of the community of bacteria we harbour, which has repercussions on our health status. Therefore, balanced diets would promote a well-structured microbiota. It is known that a long-term diet is able to affects the gut microbiota composition and activity, however, it is still unclear if the microbiota changes and responds to short-term interventions [4]. Disturbances in the microbiota composition and reduction in microbial diversity have been described as strong risk factors for the development of life-style diseases such as allergies, diabetes, obesity and metabolic syndrome, and irritable bowel syndromes [5]. It has also been reported that reduced microbial diversity and functional richness are related to alterations in the metabolism and a prolonged low-grade inflammation state [5,6]. Dietary intervention improved low gene richness and clinical phenotypes, although it seemed to be less efficient for inflammation variables in individuals who presented lower gene richness from the beginning.

Recently published studies reported that animal-based diets increased bile-tolerant bacteria while decreasing bacteria able to metabolize dietary plant polysaccharides [4]. Consequently, there are significant differences in microbiota between people who follow a Western-type diet and those who follow a more ancestral diet and lifestyle. In fact, the more balanced is the diet, the more diverse is the microbiota. Specific dietary components may promote disorders in the gut microbiota, which can be involved in the pathogenesis of many disease states [7].

Some studies suggest that high microbial enterotypes ratios have been strongly associated with several dietary components related to protein and animal fat-sources (*Bacteroides*), compared to carbohydrate-related diets (*Prevotella*) [8,9]. Other experts, however, did not find this relation [7]. An alternative study [10] demonstrated that vegetarians diets were related to less trimethylamine N-oxide (TMAO) levels from dietary L-carnitine – present in red meat – compared to animal and omnivorous diets using a microbiota-dependent mechanism. This study reported a relationship between elevated serum and plasma levels of TMAO and the presence of specific microbes, significantly increasing the risk of developing atherosclerosis.

In contrast to excessive dietary compounds, a recent study [11] focused on the influence of undernutrition, particularly amino acid deficiency, in gut microbiota composition leading to intestinal inflammation. Another study suggested that kwashiorkor disease in twins was related to a specific response of the gut microbiome [12].

Additionally, geography has a strong influence on the composition of gut microbial populations, probably due to lifestyle. It has been examined how gut microbes differ in the human population through the characterisation of faecal samples from 531 healthy Amerindian, Malawian and USA metropolitan inhabitants. It was reported significant differences in the microbial diversity between USA and the other two countries [13]. This study revealed that differential microbial traits were also evident in early life, suggesting that it would be needed to take into account specific factors as life period, diet and nutrition, physiological variations, and also, the impact of Westernization [13]. Additional studies [14] have demonstrated the Carbohydrate Active enzyme (CAZyme) profile shifts according to geography and is age-specific according to the 448 human gut microbiome databases analysed from nine geographies including Europe, America, Asia and Africa. This study revealed a core 89 CAZyme families present across 85% of the gut microbiomes analysed suggesting a more precise understanding of the role of carbohydrate active enzymes in human diet and nutrition.

Taken together, cumulative data suggests that over- and under-nutrition have an impact on microbial community that favours specific microbial alterations, leading to increasing inflammation and metabolic related problems. This fact remarks the relevance of diet/dietary components and the nutritional status on the microbiota composition and activity. Overall, it is being suggested that the specific microbial functional fingerprint would play a key role in health status, and thus experts are currently focussing on this area in order to develop new strategies of personalized medicine and individual nutritional interventions.

2. Relevance of perinatal nutrition and microbial environment for human health

The combination of perinatal nutrition and a microbial environment may cause long-lasting and/or permanent modifications in the foetal physiology, leading to an increased risk of developing obesity, diabetes and cardiovascular diseases in adulthood [15,16]. Cumulative data highlights the potential role of microbes in the metabolic, immunological and microbial programming [17]. Microbes are among of the most important environmental factors providing the specific signals involved in immune system development and maturation [18]. Recent work suggests that shifts in microbiota composition and activity are related to adverse human health outcomes [19].

Dietary strategies have been described to modulate either the gut microbiota composition or the metabolic/immunological activity [20,21]. Then, adequate perinatal feeding and microbial ecosystem may provide a window of opportunity to reduce the risk of diseases. In this scenario, the maternal microbial environment may impact the immune system maturation and infant development, affecting the infant's health during life.

Maternal microbiota is being recognized as one of the essential factors determining maternal-child health outcomes [22,23], which would also be affected by specific perinatal factors that have an influence on infant microbiome development [1–3].

Thus, it is mandatory to identify the key environmental exposures in order to develop new nutritional strategies targeted at modulating the associated microbiota and aimed at reducing the risk of disease. Overall, it is necessary to establish how to take care of microbiota during the perinatal period in mother and infants, in order to assure an adequate microbial exposition in the critical and frail human period of early infancy. Further understanding is needed over how diet and/or eating practices through Western-diets impact on maternal microbes in order to use specific food and/or dietary compounds, designed to enhance the capacity of reducing the harmful effects of inadequate diets and stimulate the growth of “healthy and equilibrated” microbiota that mothers would transfer to their infants during perinatal period (from gestation to lactation) [24].

The following paragraphs summarize nutritional recommendations for the perinatal period and, subsequently, establish the relationship between both maternal microbiome and nutrition and infant gut microbiota development.

3. Nutrition in pre-gestational, gestational and lactation stages

3.1. Preconception nutrition

Preconception nutrition care is a part of the overall preconception care defined as “any intervention provided to women of childbearing age, regardless of pregnancy status or desire, before pregnancy, to improve health outcomes for women, newborns and children” [25]. One of the areas addressed is nutritional intervention, which could be particularly effective for women living in low-income countries as many of them could be undernourished, and this circumstance could negatively influence foetal growth and the nutritional, immune and neurologic status of the future infant. Pre-pregnancy weight and height predicts both low birth weight and intrauterine growth restriction, particularly in adolescent women [26]. For Prentice and colleagues, adolescence could be an additional critical window during the life cycle for nutritional intervention in order to reduce offspring consequences [26]. In this regard, it is extremely important to assess nutritional status, promote fortification of foods and to consider nutritional supplementation for these women with macro and micronutrients that help prevent severe deficiencies (iodine, iron, vitamin A, folic acid, etc.) [25–27].

The nutritional status should be evaluated in order to establish specific interventions before pregnancy. It is known that maternal underweight increases the risk of preterm babies and low gestational age; on the other hand, maternal overweight and obesity augment the risk of hypertension, preeclampsia and diabetes, increasing by approximately 1.5 times the probability of delivering by caesarean section [25].

Specific supplementation should be considered in preconception age in order to reduce health consequences. WHO guidelines recommend iron and folic acid weekly supplementation in all women of reproductive age for 3 months, followed by 3 months of no supplementation (60 mg of elemental iron and 2.8 mg of folic acid) [27]. Regarding iodine deficiency in middle-income countries, cross-sectional studies have reported intellectual and motor dysfunctions; in this regard, WHO/UNICEF recommend a childbearing women to take supplementations in the form of a single annual oral dose of 400 mg as iodized oil, or a daily oral dose of iodine as potassium iodide to meet the intake of 150 μg de iodine/day [28].

3.2. Maternal nutrition during gestation

Pregnant women are particularly receptive to dietary counselling [29,30], and such guidance, combined with provision of appropriate food products, has been shown to be effective in modifying food and nutrient intake with potential health benefits. In addition, diet is a key factor in determining our gut microbiota composition. Some of these dietary patterns are associated with different bacterial combinations, that might generate or favour the risk/onset of several diseases [4].

To assess the nutritional status in pregnant women, it is very important to measure weight, height and Body Mass Index (BMI) from the early weeks of pregnancy. The weight gained during pregnancy is dependent on preconception nutritional status. The determinants of this weight gained during pregnancy are: mother changes in body composition, maternal tissues (uterus, breast, blood and extracellular fluid), amniotic fluid, placenta and foetal growth. Additionally, pregnant adolescent women (2 years postmenarche) should gain more weight for pubertal growth spurt than adult women [31]. Guidelines for weight gain during pregnancy are shown in Table 1. These recommendations are established for women in United States (US), where prevalence of overweight and obesity is excessive [31].

Recently, the Dietary Guidelines Advisory Committee 2010 [32] reported that in industrialized countries, obesity before pregnancy and excessive weight gain during gestation are considered deleterious for the mother and the foetus. Maternal complications (preeclampsia, type 2 diabetes, etc.) increase during pregnancy and are connected to the rise of BMI. Most studies have demonstrated a direct relation between excessive weight gain during the first stages of pregnancy and gestational diabetes [33]. Moreover, one-fifth of American women are obese before they become pregnant and often put on much more weight than is healthy during pregnancy, having trouble losing it after delivery and placing their offspring at increased risk of obesity and type 2 diabetes later in life [32]. It has also been speculated that excess fat formed at birth may cause obesity in the medium and long term and influence foetal epigenome, negatively affecting the genes that control body fat accumulation or the associated metabolism [34]. Differently from women in industrialized countries, health complications experienced by undernourished women in developing countries include disorders of the immune system with high prevalence of infections, increased risk of preterm deliveries, malformations of the

Table 1
Recommendations for gaining weight during pregnancy by pre-pregnancy BMI.

Pre-pregnancy BMI	BMI[a] (kg/m^2)	Total weight gain range (kg)
Underweight	<18.5	12.5–18
Normal weight	18.5–24.9	11.5–16
Overweight	25.0–29.9	7–11.5
Obese (includes all classes)	≥30.0	5–9

From [31].

[a] BMI: Body mass index; calculations assume a 0.5–2 kg weight gain in the first trimester.

central nervous system, and neural tube birth defect as spina bifida, as a consequence of folic acid deficiency [35]. When the foetus does not get enough essential nutrients, it presents a poor growth rate and low body weight. The immune system is also damaged, increasing the risk of diseases and infections. Moreover, the foetus will present cognitive impairment, low IQ and stunted growth, together with a delay and a decrease in the development and size of the brain.

Regarding specific supplementations during pregnancy, the WHO published in 2012 the guidelines for iron and folic acid supplementations during pregnancy, defining them as one of the Millennium Development Goals to reduce child mortality and to promote maternal health [36]. WHO strongly recommended iron and folic acid daily oral supplementation as part of the antenatal care to reduce the risk of low birth weight, maternal anaemia and iron deficiency. More specifically, the dose recommended for iron is 30–60 mg of elemental iron and 0.4 mg (400 μg) of folic acid [36]. Vitamin A deficiency is also a major public health problem affecting 19 million pregnant women, mainly in Africa and South-East Asia (15.3% of pregnant women worldwide) [37]. This deficiency can result in night blindness, foetal growth retardation, increase of the infections severity, etc. Therefore, in high-risk areas this supplementation is absolutely necessary in childbearing women [37]. Concerning iodine supplementations, the WHO recommends a single annual oral dose of 400 mg as iodized oil, or a daily oral dose of iodine as potassium iodide to meet the intake of 250 μg de iodine/day [28].

Regarding PUFA (Polyunsaturated Fatty Acids) supplementations, these have been proposed during the last trimester of pregnancy, as this period is when the growth of the brain and accumulation of DHA in neural tissues is highest. In this regard, the Perinatal Lipid Intake Working Group of several nutrition societies has proposed the intake of a minimum 200 mg/day of DHA [38]. Nevertheless, in their recently published a randomized controlled trial of maternal DHA supplementation during pregnancy, it was concluded that this supplementation does not enhance attention in term-born pre-schoolers [39].

3.3. *Maternal nutrition during lactation*

Regarding maternal nutrition during lactation, it is unequivocally necessary to consider the mother-child binomial. Human milk constitutes the main source of energy and nutrients adapted for an infant's needs, but at the same time, breastfeeding inevitably puts mothers under the need of supplementary nutritional demands to synthesize this milk, as that can hinder their own nutritional status. During lactation, the energy and nutrients 'invested' by the mother in nourishing her baby is even higher than during pregnancy. In fact, the result of nine months of pregnancy is a newborn of about 3,3 Kg of weight, consisting mainly of water and liquids. Nine months later however, this infant reaches a body weight of around 2.5 times its weight at birth, with a body composition presenting lower percentage of water and higher in fats [40]. Breastfeeding has no sustained impact on maternal weight gain or loss, but has numerous benefits for both the mother and the infant, and thus should be encouraged [32].

Human milk is considered to provide the ideal food for infants; it is the source of abundant biocomponents that protects them against nutritional and infectious diseases (IgA, lysozyme, mucine, lactadherin, anti-inflammatory and antioxidant components, oligosaccharides, glycoconjugates and growth and anti-microbial factors) [41,42]. The effort put in promoting and securing feeding through human milk, even in those situations when mother-child direct feeding is not possible (absence of the mother, hospitalization of the infant, etc.) has encouraged the development of a variety of cold storage methods, in an aim to preserve milk properties until usage [43]. Regarding human milk composition, three different stages of lactation can be differentiated: colostrum (1st–7th day), transitional (8th–15th day) and mature milk (16th day onwards). Mature human milk composition remains surprisingly constant regardless of maternal nutritional status and only decreases in cases of acute malnutrition production, dropping below the average daily rate of 780 mL [44]. Nevertheless, a series of maternal factors may influence the composition of specific nutrients, with special attention to the relation between maternal diet and percentage of fat in the milk. Lipids constitute a major nutrient of human milk; they are directly related to brain development, being LCPUFAs (Long-Chain Polyunsaturated Fatty Acids) one of the main neuronal membrane compounds. Evidence shows that Docosahexaenoic Acid (DHA) PUFA content in milk can be influenced by the mother's diet, and it is higher in women that eat fish on a regular basis compared to those that do not eat fish [45]. Moreover, several studies have reported that supplementation of LCPUFAs omega-3 during gestation and lactation was advantageous for later mental development of children [46]. Regarding unsaturated fatty acids, previous reports demonstrate the impact of omega-3 on cognitive development [47,48]. Omega-3 alpha-linolenic acid and DHA acid, as well as omega-6 linoleic acid were recognized as the most abundant unsaturated fatty acid both in term and preterm samples during lactation with high variability in DHA levels, according to recent studies [49]. Trans-fatty acids contained in industrial goods also affect milk composition, therefore it is recommended to control the intake of these products to prevent its negative effects on the infant [50]. Concerning other nutrients such as micronutrients, a longitudinal study comprising 144 milk samples evidenced that zinc content decreased significantly with maternal age (over 30 years of age) and lactation The average zinc concentration decreased sharply from 7.99 to 3.3 mg/L on day 15; the rate of decrease slowed down gradually until 1.05 mg/L. However, the iron content varied from 0.56 to 0.40 mg/L by the 30th day, remaining constant until the end of the first trimester, and iron supplementation had no impact on milk composition [51]. It should be noted that the following quickly respond to changes in the maternal's diet: Vitamins A and D; several water-soluble vitamins including vitamin B6, vitamin B12, and folate; iodine and selenium [52–54].

From this viewpoint, an adequate nutrition is considered essential in the first major stages of the infant's life (pregnancy and lactation) in order to minimize risk to suffer short- and long-term diseases. The Dietary Reference Intake values for energy, water, macro and micronutrients for pre-pregnant, pregnant and lactating women are resumed in Table 2 [44,55–60].

Table 2
Dietary Reference Intake values for energy, water, macro and micronutrients for pre-pregnancy, pregnancy and lactation women.

Nutrient (day)/life state group	Prepregnancy		Pregnancy		Lactation	
	14–18 y	≥19 y	14–18 y	≥19 y	14–18 y	≥19 y
Energy 1st trimester (kcal)	2370	2400	2370	2400	2700[c]	2730[c]
Energy 2nd trimester (kcal)			2700	2740	2770[d]	2800[d]
Energy 3rd trimester (kcal)			2800	2850		
Protein (g/kg)[a]	0.85	0.80	1.1	1.1	1.3	1.3
Carbohydrate[a]	130	130	175	210	175	210
Fibre (g)[b]	26	25	28	28	29	29
Total fat (g)[b]	ND	ND	ND	ND	ND	ND
Linoleic Acid, n-6 (g)[b]	11	12	13	13	13	13
Alfa linoleic acid, n-3 (g)[b]	1.1	1.1	1.4	1.4	1.3	1.3
Water (L)	2.3	2.7	3.0	3.0	3.8	3.8
Calcium (mg)[a]	1300	1000	1300	1000	1300	1000
Phosphorus (mg)[a]	1250	700	1250	700	1250	700
Magnesium (mg)[a]	360	310	400	350	360	310
Iron (mg)[a]	15	18	10	9	10	9
Zinc (mg)[a]	9	8	13	12	13	12
Iodine (μg)[a]	150	150	220	220	290	290
Vitamin A (μg)[a]	700	700	1200	1300	1200	1300
Vitamin D (IU)[a],[e]	600	600	600	600	600	600
Vitamin E (mg)[a]	15	15	15	15	19	19
Vitamin K (μg)[b]	75	90	75	90	75	90
Vitamin C (mg)[a]	65	75	80	85	115	120
Vitamin B_6 (mg)[a]	1.2	1.3	1.9	1.9	2.0	2.0
Folate (μg)[a]	400	400	600	600	500	500
Vitamin B_{12} (μg)[a]	2.4	2.4	2.6	2.6	2.8	2.8

Y (years).
From [44,55–60].

[a] RDA (Recommended Dietary Allowance).
[b] AI (Adequate Intake).
[c] 1st 6 months.
[d] 2nd 6 months.
[e] Vitamin D: 1 μg = 40 UI.

4. Maternal microbiome and nutrition influence on the infant's early microbial colonization

Maternal microbiota influences health status considerably, as it represents the infant's first contact with microorganisms (Fig. 1). This first contact is a crucial step towards the correct development of the infant's immune system. Previous studies have suggested that early gut microbiota composition may be linked to development of specific health disorders. Therefore, shifts in microbiota composition depending on the mother's diet, health status and lifestyle may be transferred to the infant during this time, while in utero and after birth. Despite the critical role of the human microbiota in health, our understanding of microbiota compositional dynamics, during and after pregnancy, is incomplete. In addition, the effect of diet and specific nutrients on microbiome during pregnancy has not been reported widely [61]. Although there is recently published evidence from human studies on the benefits of using pre and probiotics during perinatal period, there is also a lack of studies on microbiota modulation of diet [30,62,63].

Pregnancy per se influences the gut microbiota composition [64–66] and promotes a number of physiological and microbial changes on the body. Consequently, differences in the microbiota due to nutritional status may disappear when an individual becomes pregnant [67]. In general, at the end of pregnancy there is an increase in Proteobacteria and Actinobacteria, and reduced bacterial richness [65]. Then, changes in the maternal gut microbiome have been implicated in contributing to metabolic adaptations during pregnancy. In general, a microbiota profile is typified as being related to inflammation, i.e. pro-inflammatory or responding to an inflammatory signal. Thus, it appears that those changes are related to inflammation and, when that microbiota was transferred to germ-free mice, adiposity and insulin insensitivity were increased [65]. In this respect, a study in Bangladesh [68] reported significant gut microbiota changes during first months after delivery followed by smaller changes maintained next 9 month after delivery. Furthermore, pregnancy also influences the vaginal microbiome, which is modified in terms of structure and composition [66,69]. Recent studies found that the pregnant vaginal microbiota is dominated by *Lactobacillus* spp and showed lower richness and

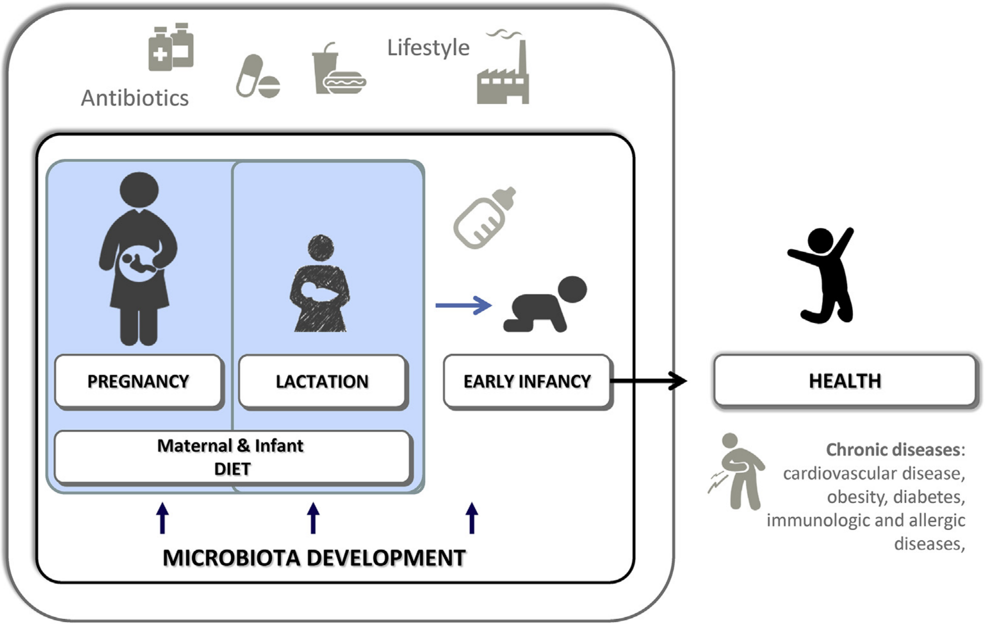

Fig. 1. Maternal environment, diet, and lifestyle influence microbiota development, and are linked with the risk of development of childhood chronic diseases that may persist in adulthood.

diversity than in non-pregnant vaginal microbiomes. Pregnancy also has an important effect on the subgingival oral microbiota [70] and is also associated to a high risk of oral inflammatory-related diseases, such as periodontal diseases [71].

It has been suggested that, during pregnancy, microbes may play a key role in health programming, potentially through serum biochemical variables, hormones and other metabolites related to nutritional and health status [72,73]. As mentioned above, there are several studies that have intended to elucidate the association of dietary variables and gut microbiota. In a recent study [74], the maternal gut microbiota from 20 lactating women from 2 days to 6 months postpartum was characterized in order to explore significant differences related to variation in energy intake, dietary constituents and nutritional status. It was observed that the gut microbiota (in terms of abundant bacterial taxa) of healthy lactating women was similar to that found in other healthy adult individuals, despite other significant differences. Moreover, an increase in the intake of some micronutrients such as, pantothenic acid, riboflavin, vitamin B6 and B12 resulted in an increased abundance of *Prevotella* and lower levels of *Bacteroides* genus. Mineral intakes such as copper, magnesium, manganese and molybdenum were positively correlated with Firmicutes and negatively related to Bacteroidetes. Unlike other authors [7], results from this study show inverse correlations according to macronutrients intakes, and negative correlation between protein intake and relative abundance of Bacteroidetes, while *Prevotella* members were not associated with carbohydrate intake. Thus, discrepancies still exist in the association microbiota-diet. More studies are needed to determine which dietary variables might impact an individual's gut microbiome and the degree of this impact.

There is a considerable lack of studies investigating the impact of diet on the establishment of the gut microbiome in early life. However, a recent study with *Macaca fuscata* (Japanese macaque) in a primate model revealed high fat maternal diet as having a significant impact on the neonatal intestinal microbiome [75]. Moreover, it has been reported that obesity also influences the maternal microbiota, probably due to the connection between gut microbiota and host metabolism [73]. High pre-pregnancy BMI and excessive weight gain during pregnancy have been linked with shifts in maternal gut microbiota composition, which could affect the infant's microbiota acquisition and development. The same study reported higher levels of *Staphylococcus*, Enterobacteriaceae and *Escherichia coli* and lower counts of *Bifidobacterium* and *Bacteroides* groups in overweight women in comparison with the lean pregnant women group [73]. Furthermore, associations between bacterial groups and metabolic biomarkers have been identified, potentially implying a connection between the gut microbiota and the host metabolism. It has been suggested that a gut microbiota with higher levels of *Bifidobacterium* spp and a lower levels of *Staphylococcus* genus would protect against maternal overweight. Normal weight gains over pregnancy were related to higher levels of bifidobacteria; mothers transferred those higher levels to their offspring, being this *Bifidobacterium* group protector of infant weight development [75]. All these changes in maternal gut microbiota are in agreement with results obtained in previous studies, which also showed lower levels of *Bifidobacterium* spp. in infants who were overweight by the age of 7 years old, compared with normal-weight children [76]. Then, higher concentrations of Bifidobacteria during infancy may provide protection against overweight and obesity development, and exclusive breast-feeding promotes a *Bifidobacterium*-dominated microbiota that differs from those who follow other infant feeding strategies.

Shifts in maternal gut microbiota composition have been associated with alterations of biochemical parameters in maternal blood (e.g., increased folic acid and ferritin levels and reduced transferrin and cholesterol levels) [73]. Higher plasma cholesterol was related to higher total bacteria and *Staphylococcus* group, while *Bacteroides* were related to higher levels of HDL-cholesterol and folic acid levels, together with lower levels of triacylglycerides. Then, pregnant gut microbiota would be related to weight gain and metabolic biomarkers, which would support individual management of health and have an impact on their offprings. It was also reported that *Bifidobacterium* group were linked to normal-weight women, compared to overweight women, and their levels correlated positively with folic acid and iron levels [73].

The composition of our microbiota evolves from birth and continues throughout the first year of life, when microbial abundance and diversity increase takes place and converges towards an adult-like microbiota [1–3]. Gut microbiota is the result of different environmental influences, and is significantly modified by mode of delivery, perinatal antibiotics and type of infant feeding.

Neonates receive the next major bacterial inoculation at the time of delivery, followed by the contact with bacteria from breast milk, influencing further intestinal microbiome development. At this point, the bacterial inoculation reflects the microbiota of the mother's vagina and gastrointestinal tract in case of vaginal delivery [1,2]. Vaginally delivered infants acquire a bacterial composition similar to that in their mother vagina, skin and faeces, including *Lactobacillus* and *Bifidobacterium* groups [1]. This early stepwise microbial colonization process, which presents alterations in infants delivered by C-section when compared to vaginally born infants [1–3], plays an important role in the development of the child. In fact, babies born vaginally present lower rats of asthma, allergy, respiratory problems, type-1 diabetes and obesity [77,78] compared to C-section babies, who show increased neonatal morbidity. Nevertheless, C-section delivered infants acquire different and less diverse bacterial communities [79]. A C-section delivery – one in three births – bypasses this critical early colonization step, partially causing an altered and less diverse gut microbiota. In addition, the abuse in hygienic measures and antibiotics exposure during pregnancy and during the first months of life of the infant also decrease our bacterial diversity, weakening our immune system and increasing the risks for a variety of chronic disorders in later life [17,80–82]. Postnatally, the transfer of bacteria from the mother to the infant continues via breastfeeding, further reinforced by breast milk and skin bacteria. Therefore, in infants, the microbiota colonization of the healthy, breastfed, vaginally delivered, full-term baby is considered the gold standard.

5. Breastfeeding impact on the infant's early microbial colonization

Exclusive breastfeeding practises are linked to infant healthy postnatal growth through optimal nutrition and health protection; this evidence has led to the 6-months exclusive breastfeeding recommendation by WHO [83]. Exclusive breastfeeding practices confer exceptional protective health effects and reduce the risk of diseases later in life [84–86]. Human milk provides the energy, nutrients, immunological components and bioactive substances, including metabolic hormones, necessary for the development of the newborn infants. Additionally, bioactive factors in human milk stimulate gut epithelial cell proliferation and contribute to the development of the intestinal mucosal barrier [87], together with helping in the neonate's endocrine maturation [88]. Moreover, it contains a complex and dynamic microbiome and a complex of growth-promoting substances, led by human milk oligosaccharides (HMOs) that sustain specific microbial establishment [89]. These HMOs represent the main players with a clear “bifidogenic effect”, having underweight mothers (BMI = 14–18) a significantly lower total HMOs concentration compared to higher BMI mothers [90]. Alternatively, maternal undernutrition may affect the bioactive compounds present in breast milk. In this regard, poor maternal health was linked to alterations in immunoglobulins and glycoproteins during lactation and with decreased lactoferrin [24,91].

Breast milk is also the microbial postnatal link between the mother and its infant [3,92,93], and continues driving infant microbiota colonization during lactation. Exclusive breast-feeding promotes the specific growth of *Bifidobacterium* spp. that differ from those who follow other infant feeding strategies [94]. Moreover, both the genotype and phenotype of the mother influence the composition and functionality of breast milk. In addition, breast milk composition is influenced by many perinatal factors (pre and postnatal factors) and changes over lactation stage. It is shaped by maternal health status, both maternal body mass index before pregnancy and weight gain over the pregnancy, mode of delivery and gestational age [3,92,93,95,96].

Breast milk samples from 32 healthy mothers from Spain (15 vaginal deliveries vs 17 caesarean sections) were analysed [95]. The microbiota composition of colostrum, transitional and mature milk showed significant differences among the lactation stages in terms of total bacteria concentration, *Bifidobacterium* and *Enterococcus* spp. counts, increasing throughout the lactation period.

As mentioned previously, several studies have shown the differences in intestinal microbiota composition in infants depending on mode of delivery [1–3], but only a few focused on whether and how the delivery mode impacts on breast milk microbiota composition. Taking into account the hypothesis of the association between the stress and the hormonal signals related to labour, and the bacterial transfer to the mammary gland through the so-called entero-mammary pathway, we can imply that the breast milk microbiome may also be affected by mode of delivery. The same studies revealed higher bacterial concentrations in colostrum and transitional milk corresponding to vaginal delivery cases when compared to caesarean sections. Similarly, *Bifidobacterium* spp. was detected more frequently in breast milk samples from vaginal than caesarean deliveries [93,95,96]. Moreover, it has been shown that breast milk samples from mothers who gave birth by elective caesarean delivery – but not from non-elective – contained a different bacterial composition than breast milk samples from mothers who gave birth vaginally. On one hand, elective caesarean mothers showed a significant compositional shift compared to the other two mother groups. On the other hand, the non-elective mothers showed a more similar and comparable breast milk microbiota composition to that of mothers who gave birth vaginally, reinforcing the hypothesis of the role of a physiological stress or hormonal signals contributing to the microbial transmission process to breast milk [93].

Continuing to focus on breast milk composition and perinatal factors affecting it, an alternative study reported that maternal obesity, overweight and weight gain during pregnancy affect the immunomodulatory potential of breast human milk in terms of microbes and transforming factors (TGF-β2, sCD14 and cytokines) [92]. Moreover, obesity also affects the milk microbiota composition. In the same study, higher counts of *Staphylococcus* group bacteria and lower counts of *Bifidobacterium* spp. were detected in overweight subjects than in normal weight. Additional findings evidence that maternal BMI and weight gain during pregnancy have an impact not only on breast milk microbiome taxonomic composition, but also on its diversity, with obese mothers showing a lower diversity than normal-weight mothers [93]. All these results indicate once more the relationship between obesity and microbiota dysbiosis. Furthermore, breast milk microbiota composition is influenced by the gestational age, according to a study that recruited samples from prematurely ended pregnancies from a gestational age of 24 weeks onward [95].

Significant differences in breast milk microbiota were found between term and preterm groups and throughout the different lactation stages. Lower counts of *Enterococcus* spp., statistical difference in colostrum and higher counts of *Bifidobacterium* spp. were detected in milk samples from gestational term deliveries. Considering the milk of the mothers belonging to the preterm delivery group presents specific microbiota characteristics, as supported by several findings, we can imply that these microorganisms may have an important role in preterm infants.

Mothers of preterm infants produce breast milk that is slightly different in composition, at least during the initial weeks, and this difference is designed to meet their baby's particular needs. Necrotizing enterocolitis is one of the most common diseases in preterm infants and breast milk is known to help in the prevention of this disease [97,98].

6. Conclusions

Maternal nutritional status, environment, diet, lifestyle and microbes are associated with the risk of development of childhood chronic diseases that may persist in adulthood. An adequate energy intake and a balance diet, together with specific nutritional requirements, are needed during gestation and lactation to assure optimal growth and health. However, scarce information is available about the effects of these nutritional requirements, nor about the supplementation on the maternal microbiome and its influence on the infant. Recent evidence suggests that diet and nutritional status are useful tools in modulating gut microbiome. Therefore, we need to understand the pivotal relationship between nutrition and microbiome during pregnancy, lactation and early infancy, where diet would play an important role, and reach a higher level of understanding over the influence of maternal nutrition on microbiome and its role in infant development. This knowledge would enable the design of new and personalized dietary strategies based on microbial modulation, including probiotics and prebiotics. In conclusion, this review highlights the need for high-quality large-scale human dietary intervention studies aimed at the beneficial microbiological, immunological, and metabolic programming of infant health.

Conflict of interest

No conflict of interest.

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