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Chapter 13

Human Gut Microbiota and Obesity During Development

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Additional information is available at the end of the chapter

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Abstract

Obesity, particularly in children and adolescents, has become a significant public health problem that has reached "epidemic" status worldwide. The etiology of obesity is complex and involves lifestyle factors that are challenging to modify. The intestinal microbiota contribute to protection against pathogens, maturation of the immune system, and metabolic welfare of the host but, under some circumstances, can contribute to the pathogenesis of certain diseases. Over the last decade, novel evidence from animal and human studies has identified associations between human intestinal bacteria and host metabolism and obesity. Infancy is a critical period in the development of the gut microbiota: initial colonization is influenced not only by a number of early-life exposures, including birth mode, infant nutrition, or antibiotic use, but also by maternal factors during pregnancy, including maternal BMI, nutrition, gut microbial composition, and drug exposure, among others. Thus, an adequate nutritional and microbial environment during the perinatal period and early life may provide windows of opportunity to reduce the risk of obesity and overweight in our children by using targeted strategies aimed to modulate the gut microbiota during early life.

Keywords: obesity, gut microbiota, early life, pregnancy, prebiotics, probiotics, antibiotics

1. Introduction

Obesity has become a major global health challenge because of the established health risks and substantial increases in prevalence. Urgent global action and leadership is needed to help countries to more effectively intervene [1]. This increase runs in parallel to an increase in the

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obesity during pregnancy; moreover, due to the adverse effects that this condition has on both the mother's and offspring's health, infant obesity has become a highlight topic of study [2].

It is well known that the physiology during pregnancy differs between obese and normal-weight women. Obesity is associated with increased insulin resistance, adverse effects in implantation and placentation processes, growth, development and metabolism alterations of the fetus, and even impact on the offspring gut microbiota [3].

Until now, studies focused on the origins of obesity were oriented towards dietary excesses (processed sugars, fat, and proteins) [4] or host genes [5]. But recent studies have shown changes in gut microbiota associated to different diseases, like obesity, metabolic syndrome, or type I [6] and type II diabetes [7]. The community of microorganisms living in a specific environment is known as microbiota. These microorganisms include bacteria, Archaea, viruses, and some unicellular eukaryotes [8]. The collective genomes of the microorganism that constitute the microbiota are known as microbiome [9]. The normal gut microbiota imparts specific function in host nutrient metabolism, xenobiotics, and drug metabolism, maintenance of structural integrity of the gut mucosal barrier, immunomodulation, and protection against pathogens [10]. In fact, some of these microorganisms residing in the gut encode proteins involved in functions important for the host's health, such as enzymes required for the hydrolysis of otherwise indigestible dietary compounds, and the synthesis of vitamins [9]. Since the 1990s, our knowledge of the complexity of this ecosystem has increased due to the advances in culture-independent techniques. These new techniques are fast, facilitate high throughput, and identify organisms that are uncultured to date and present in the gut microbiota; recently, by using these techniques, it has been shown that alterations in the gut microbiota composition and function are associated with certain disease states, such as obesity [11]. With the increase in knowledge about gut microbiome functions, it is becoming increasingly more possible to develop novel diagnostic, prognostic, and most important therapeutic strategies based on gut microbiota manipulation.

Focused on obesity, it has been shown that certain bacteria metabolize different nutrients more efficiently than others, increasing the absorption of calories from the diet and the amount of energy usable for the host, which contributes to fat deposition [12]. Many studies have been performed in order to link this disease with changes in the composition of the intestinal microbiota [13]. Several studies have shown increased ratio in the proportion of *Firmicutes*/*Bacteroidetes* in genetically obese mice (ob/ob) and obese humans [14, 15]. However, other studies have failed to confirm these findings and showed variable patterns in the composition of the microbiota in obese humans [13]. Within the studies cited above, it is clear that the gut microbiota plays a role in obesity and metabolic disease, but it is difficult to draw definitive conclusions about the importance of certain bacterial groups. It is therefore very important to identify the active bacteria that cause dysbiosis in the gut microbiota in order to design therapeutic strategies for long-term protection against obesity. Quantitative and qualitative alterations in the composition of the gut microbiome could lead to pathological dysbiosis.

The microbiota colonization of the maternal intestine influences offspring's metabolic and immune system development [16]. Besides, although the microbiota-gut-brain axis is not a new concept [17], in the last years there are growing interest in studying the influence of the microbiota

in children neurodevelopment by analyzing the microbiome impact on eating behavior, infant cognitive function, and brain structure and function [18]. However, the mechanisms by which maternal microbiota may contribute to health programming in the offspring are still unknown. The type of delivery (vaginal or caesarean section), diet [breast milk or formula], and antibiotics exposure have an influence on the offspring's immune system that may promote the development of chronic inflammation, leading to allergies, autoimmune diseases, like diabetes mellitus or rheumatoid arthritis, or noncommunicable diseases such obesity and their comorbidities in children [19–21].

In the present chapter, we aimed to update the knowledge about the factors involved in gut microbiota establishment during perinatal life, infancy and early childhood, and the relationship to obesity development.

2. Maternal environment

There is evidence for the importance of the prenatal period in the health and development of offspring throughout childhood and adult life [22].

In the periconceptional period, and during pregnancy and lactation is necessary to acquire the total nutrient requirements, which are associated with mother's lifestyles and health [23]. These requirements include specific amounts of iron, vitamins (D, C, and B), calcium, folic acid, essential fatty-acids, and others, which will increase along pregnancy [24]. Furthermore, it has been demonstrated that bad habits like smoking, use of illegal drugs, consumption of caffeine and alcohol, or overweight/underweight are related to conceiving problems [25].

During the first trimester of pregnancy, the mother is under anabolism, increasing maternal fat and nutrients storage to meet the fetus-placental and maternal requirements during gestation and lactation [26]. When a deficit or overabundance of nutrients arrives to the fetus, it has to adapt itself to the new metabolic status, changing its physiology and metabolism constantly [27].

It is noteworthy that due to fetal programing, obesity may become a self-perpetuating problem, because children of obese mothers may themselves be vulnerable to becoming obese and more likely to have offspring who share this vulnerability, but the mechanisms behind this association are not fully elucidated [28].

One hypothesis to explain the influence of the mothers' weight on their children is the transmission of obesogenic microbes from mother to her offspring; in this situation is also very important the etiology of such maternal obesity and others factors like socioeconomic status or environmental factors [29].

On the other hand, a meta-analysis including nine studies has shown an increased risk of stillbirth in obese pregnant women compared to normal-weight pregnant women [30].

It has been demonstrated that a high body mass index (BMI) and an excessive weight gain during pregnancy are associated with disturbances in the maternal gut microbiota, which will influence the development of gut microbiota in the infant [31].

Infant gut microbiota will not be only influenced by mother's BMI, but also by the mode of delivery [32]. A study indicated that excess maternal prepregnancy weight is associated with differences in neonatal acquisition of microbiota during vaginal delivery, enriched in genus *Bacteroides* and depleted in genus *Enterococcus, Acinetobacter, Pseudomonas*, and *Hydrogenophilus* [33].

Subsequent to delivery, it has been shown that the type of feeding is one of the major factors modulating infants gut microbiota and it will be discussed in Section 4.

The establishment of the microbial community allows the maturation of the immune system as it has been demonstrated in germ-free (GF) animal models, where commensal microorganisms are required for the development of a fully functional immune system, which affects many physiological processes within the host [34].

In conclusion, the mother environment influences the offspring phenotype of her offspring, independently of his genotype. So, not only genetics will influence offspring gut microbiota development, but also mother's lifestyle before, during, and after pregnancy.

3. Gut colonization and microbiota establishment in infancy

The first few weeks of life are very important for the gut colonization in the infant. This process will be influenced by maternal factors (weight gain during pregnancy, BMI, nutrition, microbiome composition), intrauterine state (microbiota of amniotic fluid), type of delivery (caesarean or vaginal), type of feeding later (breast milk or infant formula), and antibiotic exposure, among others (**Figure 1**).

Traditionally, the placenta had been considered a sterile organ but current studies have reported the existence of a placental microbiome [35–37]. Although the origin of the bacteria colonizing the placenta is unclear, it has been shown that the microbial community is represented by members of nonpathogenic bacteria from the phylum *Proteobacteria, Firmicutes, Bacteriodetes, Fusobacteria*, and *Tenericutes* [38].

Recently, placenta microbiota has been associated with preeclampsia development during pregnancy and with preterm birth, which highlights the importance of the close relationship between the microbiota and pregnancy [39]. A placental dysbiosis during pregnancy as a consequence of excess weight gain could have a major influence on the colonization and establishment of gut microbiota community on the infant [40].

Because these findings are very recent, the effects of the bacterial profile modification by probiotic supplementation during pregnancy and the effects on placental microbiome modulation are still unknown and further studies are needed.

After birth, it is known that meconium is not sterile and harbors a particular microbial community, characterized by a higher abundance of *Firmicutes* compared to *Proteobacteria* in early fecal samples [41].

A study showed that the mode of delivery (caesarean or vaginal) did not affect the diversity of the microbiota from meconium, in contrast, these samples presented a lower species diversity

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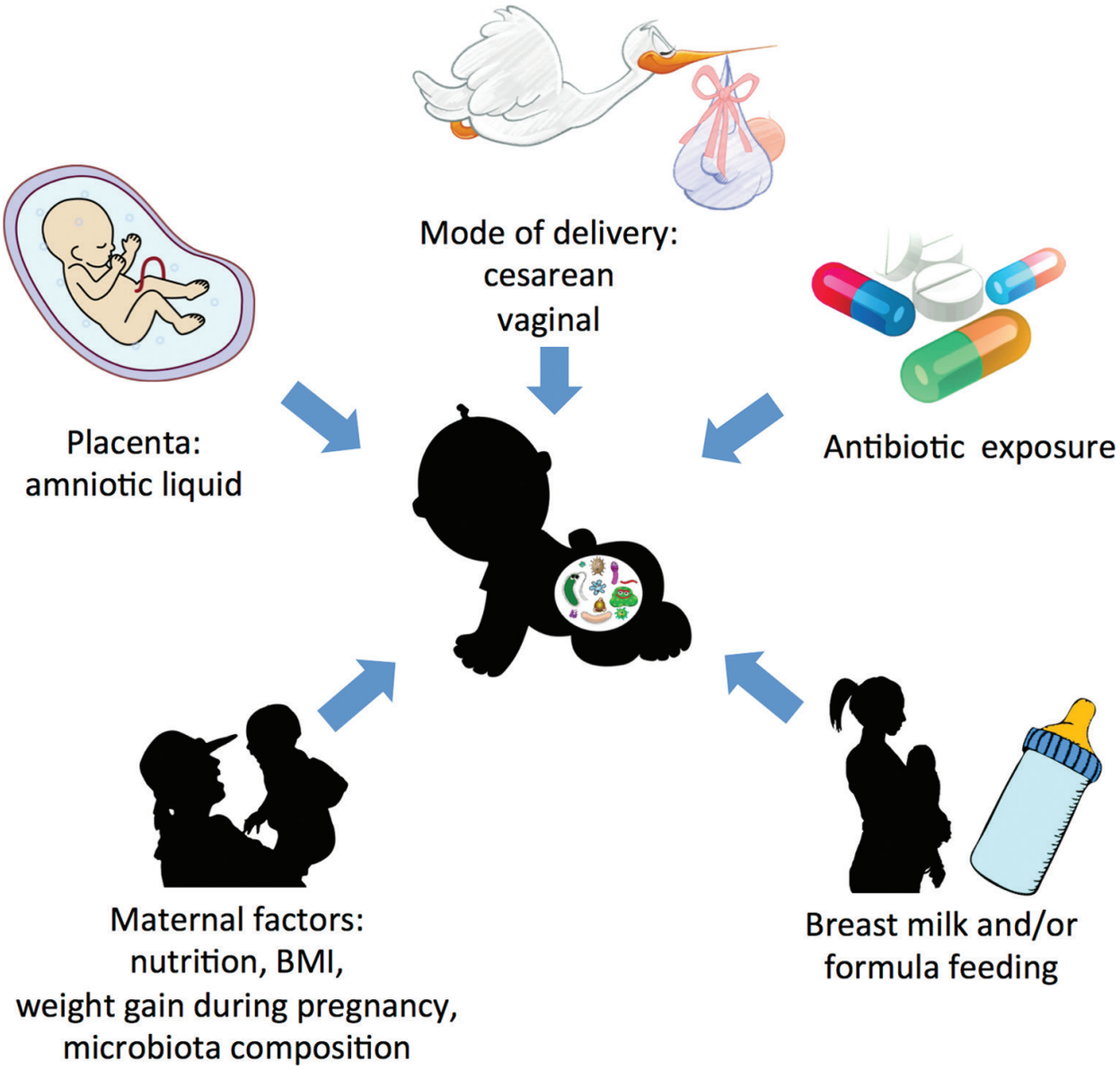

Figure 1. Maternal and environmental elements affecting the onset and modulation of the gut microbiota in the newborn infant. A plethora of factors during pregnancy can negatively influence the neonate's gut microbiota composition and function. Furthermore, environmental factors, such as mode of delivery and feeding modality can significantly drive the neonate's gut microbiota.

and a higher variation among samples in comparison with adult feces [42]. These results indicate that the microbial contact during perinatal life may imprint the offspring microbiota and immune system in preparation for the much larger inoculum transferred during vaginal delivery and breast-feeding.

As mentioned in the previous section, the mode of delivery is going to favor the establishment of a specific microbiota. Previous studies have demonstrated that gut microbiota of infant born through vaginal delivery is similar to maternal gut and vaginal microbiota; conversely, the infants born by caesarean section have a gut community more similar to bacteria from maternal skin or the hospital environment [43].

Regarding the mode of delivery, epidemiological studies suggest that caesarean delivery is associated with increased risk of overweight and obesity later in life [44]. A study has found that caesarean section delivery was associated with adiposity at 6 weeks of age, being this association stronger in children born from obese mothers and having higher risk of obesity and overweight at 11 years old [45]. Although the mode of delivery may affect the colonization of the intestinal microbiota in the baby and will increase the risk for later obesity development, it has been found that perinatal exposition of the infant born by caesarean section respect to the vaginal discharge, can partially restore its gut microbiota and resembles to babies born by vaginal delivery avoiding the problems that this entails [46].

The microbiota of the babies by the end of the first year of life presents a different microbial profile in comparison to adults. The initial gut composition of the infant is simple, dynamic, and very unstable and undergoes marked fluctuations influenced by external factors [47]. At the beginning, the gut environment is aerobic, but through colonization, the oxygen level is reduced generating a suitable environment for the growth of anaerobes [48]. The intestinal microbiota of neonates is characterized by low diversity and a relative dominance of facultative anaerobes of the phyla *Proteobacteria* and *Actinobacteria* [49]. After birth, the phyla *Firmicutes* and *Bacteroidetes* increase their diversity and dominance, reaching over 3 years old a total resemblance to the adult in terms of composition and diversity [50]. These results indicate that dietary intake during the first 1500 days of life is a critical factor in the establishment of gut microbiota community and its role in the development of obesity is a matter of research and discussion.

4. Type of infant feeding

Another important factor modulating microbial colonization in infants is the type of feeding. The diet during early life will influence on the establishment and composition of the gut microbiota during childhood and even adult life [51]. Breast milk meets the infant's needs by providing nutrients appropriate to the infant's developmental stage, as well as growth factors, antimicrobial peptides, and proteins to support their developing immune system. Even though breast milk provides all the necessary nutrients for a suitable development of the baby, many babies cannot take it for several reasons and they are fed with infant formulas. Infant formulas provide a greater weight gain and increase the risk of obesity, hypertension, and diabetes [52]. Therefore, it is necessary to continue studying the composition and the positive effects of breast milk versus milk infant formula in order to better understand the beneficial role of breast milk on offspring's health to improve the outcomes in the formula-fed infants.

Breast-feeding brings clear short-term benefits for child health by reducing mortality and morbidity from infectious diseases. There is evidence on the effects on child health and growth of exclusive breast-feeding for 6 months. Kramer et al. showed that infants who were exclusively breast-fed for 6 months experienced lower morbidity from gastrointestinal and allergic diseases, while showing nondeficits in growth rates to non–breast-fed children [53]. Based on such evidence, WHO and UNICEF recommend that every infant should be

exclusively breast-fed for the first 6 months of their life; continued breast-feeding for up to 2 years or longer is also recommended [54]. Also, there is evidence of long-term benefits of breast-feeding such as increased school achievement and performance in intelligence tests, reduced mean blood pressure, lower total cholesterol, and a lower prevalence of overweight and obesity leading to lower incidence of inflammatory bowel diseases, type 2 diabetes, and obesity later in life [54, 55].

Human milk is a dynamic fluid that contains many hundreds to thousands of distinct bioactive molecules that confers beneficial properties for infants. Human milk changes in composition from colostrum to late lactation, and varies within feeds, diurnally, and between mothers [56].

The composition of this complex mixture differs also during the lactation period, from colostrum through transitional to mature milk. Colostrum is produced during the first days of postpartum, it contains high amounts of secretory IgA, lactoferrin, leukocytes, and epidermal growth factor. Transitional milk typically occurs from 5 days to 2 weeks postpartum, it shares some of the characteristics of colostrum but there is an increase in milk production to support the nutritional and developmental needs of the rapidly growing infant. By 4–6 weeks postpartum, human milk is considered fully mature and it remains stable in composition over the course of lactation [57–59]. Thus, infant formula should adapt to different physiological and nutritional needs of the growing baby.

Regarding the gut microbiota acquisition, the first colonizers of the infant gut are facultative anaerobes including *Staphylococcus, Streptococcus, Escherichia coli*, and *Enterobacteria* that will be later replaced by strict anaerobes that dominate the gastrointestinal tract, primarily *Clostridium, Bifidobacterium spp*., and *Bacteroides* [60]. This change in dominant taxa representation can be attributed to the introduction of breast milk or formula-feeding, signifying the first diet-related colonization event in the infant gut microbiome [61, 62]. Breast milk has been shown to be an excellent and continuous source of potentially beneficial and commensal bacteria, including *Staphylococci, Streptococci, lactic acid bacteria*, and *Bifidobacteria*, with bacterial cell numbers reaching 103–105 ml^{-1} of breast milk. Although the commensals' origin is unknown, it is inevitable that bacterial from mother's skin are transferred to the baby during breast-feeding, but there is also other hypothesis wherein bacteria from the maternal gut may reach the mammary glands via maternal dendritic cells and macrophages [63]. More than 700 species of bacteria have now been identified in human colostrum and breast milk, including multiple species of lactic acid bacteria as well as species typically colonizing the oral cavity of infants [64].

The presence of *Bifidobacteria* in breast milk is important for the colonization of the infant gut, since it mediates the activation of IgA-producing plasma cells in the human neonatal intestine. It is well established that a gut microbiota dominated by *Bifidobacteria* typifies that of the healthy breast-fed infant [65]. There are conflicting results regarding differences in the relative abundance of these bacteria between breast- and formula-fed infants. Many studies have reported that formula-fed infants display dominance of *Bifidobacterium spp*. similar to what has been observed in breast-fed infants [61, 66]. However, another study reported approximately double the count of *Bifidobacterium* in breast-fed infants compared to those formula-fed [67].

Comparisons between breast-fed and formula-fed infants show that breast-fed infants tend to contain a more uniform population of gut microbes dominated by *Bifidobacteria* and *Lactobacillus* [67], whereas formula-fed infants exhibit higher proportions of *Bacteroides, Clostridium, Streptococcus, Enterobacteria*, and *Veillonella spp*. [66–69].

Although infant formulas have evolved greatly during last years, a formula providing exactly the same benefits than human milk has not yet been developed. Among others, human milk contains substantial quantities of complex nondigestible oligosaccharides (known as human milk oligosaccharides, HMOs). HMOs are considered a type of prebiotics as they promote the growth and proliferation of beneficial commensals and, consequently, prevent pathogen colonization of the infant gut and exert positive health effects [70]. Thus, the chemical composition of breast milk does influence the gut microbiome through supplying oligosaccharides that are selectively utilized by specific bacteria in the gut [60].

Another way to modify the gut microbiome is by the administration of probiotics. Probiotics are defined as "live microorganisms which when administered in adequate amounts, confer a health benefit to the host" [71]. *Lactobacillus* and *Bifidobacterium* species isolated from human milk are the most commonly used probiotic strains. They exert beneficial properties in the gut by suppressing the proliferation of pathogenic microbes, has been extensively studied [72]. For this reason, another area of research regarding formula enrichment is in HMOs and probiotics and their effects on the infant gut microbiota.

Certain gut-associated bacterial populations such as *Bifidobacterium spp*. possess gene clusters dedicated to the metabolism of HMOs [73, 74]. Degradation of these compounds produces lactate and short-chain fatty acids (SCFA), which in turn generates an acidic environment that prevents pathogen invasion [75]. Besides *Bifidobacteria*, HMOs may be consumed by other species such as *Bacteroides spp*. (e.g., *Bacteroides* fragilis and *Bacteroides vulgatus*) that consumes a broad range of HMO glycans [76]. Thus, HMOs play an important role in the gut colonization of the infants.

Among the most common prebiotics are fructo-oligosaccharides (FOS), galacto-oligosaccharides (GOS), inulin, and lactulose. The prebiotic mixture of 90% GOS plus 10% FOS has been assessed to be safe when added to infant formula [77]. Several randomized controlled trials have been made to evaluate the efficacy and safety of prebiotic supplementation in infant formulas [78, 79]. After compiling data of these trials into a meta-analysis, weight gain [weighted mean difference 1.07 g/day] was significantly higher among formula-fed infants supplemented with prebiotics compared to the placebo group [80]. In addition, a large number of clinical trials in term of infants have shown controversial results related to the increase in *Bifidobacteria* in feces due to supplementation of infant formula with GOS and FOS. A systematic review published by Rao et al. [78] reported that some of the randomized controlled trials (RCTs) showed a trend of increasing *Bifidobacteria* counts in formula supplemented fed infants, and another systematic review published by Mugambi et al. [81] failed to show the increase in *Bifidobacteria* or *Lactobacillus* or the decrease of pathogens in infants fed with prebiotic supplemented formula.

Nonetheless, there are promising results from studies which have assessed the effect of prebiotic supplemented formulas on the gut microbiota of infants. Prebiotics are able to change gut

metabolic activity, bring stool consistency, and defecation frequency closer to that of breast-fed infants. Other outcomes included better weight gain and softer stools, and a significant reduction in stool pH for infants who received prebiotic supplementation [78, 81]. Moreover, prebiotics have been used to prevent or treat obesity. Compared to probiotics, human studies with prebiotics have shown more promising results in obesity management, with reductions in body weight and fat mass in adults [82–84] in contrast with results from meta-analysis mentioned above, where the supplementation with prebiotics was significantly associated to a higher weight gain [80].

In the last years there is a growing interest in the simultaneous administration of prebiotics and probiotics, what is termed "symbiotic." There are a few recent studies which have assessed the effect of symbiotic supplementation on the infant health. The ESPGHAN Committee on Nutrition showed an increase in stool frequency for three types of symbiotic (*B. longum* BL999 plus GOS/FOS, *B. longum* BL999 plus *L. rhamnosus* LPR plus GOS/FOS, and *L. paracasei* subsp. paracasei plus *B. animalis subsp. lactis* plus GOS) [79]. Also, Ringel-Kulka et al. showed that a yogurt with the probiotic bacteria *Bifidobacterium* animalis subspecies lactis (BB-12) and the prebiotic inulin significantly reduced days of fever, improved social and school functioning, and increased frequency of bowel movements in healthy children attending child care centers [85]. Regarding to obesity interventions with symbiotic, Safavi et al. [86] found that treatment of overweight children with a symbiotic mixture of the prebiotic, FOS, in combination with seven probiotic strains was associated with a decreased BMI *z*-score compared to placebo.

Studies suggest that pre-, probiotic, and symbiotic supplementation may be beneficial in the prevention and management of disease where the gut microbiota has a key role (e.g., necrotizing enterocolitis, gastroenteritis, or obesity). Although these studies show promising beneficial effects, the long-term risks or health benefits of pre- and probiotic supplementation are not clear as results from single studies need to be replicated in well-defined RCTs. Nonetheless, there is active research on functional food that contains pre-, probiotics, and symbiotics supplementation because they can influence not only the microbiota favoring the growth of beneficial microorganisms, but also the mucosal immune system associated to the gut [87].

5. Childhood exposure to antibiotics

Exposure to antibiotics during infancy and childhood use to begin very early. Two different studies showed that >30% of women with a delivery had done systemic antibiotic treatments during pregnancy [88, 89]. Although the effects of antibiotic exposure during pregnancy on acquisition of infants' microbiota have not been established, maternal antibiotic exposure is relevant since infants' microbiota is taken at least in part from their mothers. In addition, prenatal antibiotic exposure has been shown to have effects on the birth weight of neonates and is associated with increased risk of obesity and related metabolic sequelae later in life [90, 91].

After birth, a number of neonates, particularly premature infants, receive antibiotics to prevent or treat bacterial infections. Fjalstad et al. showed that 2.3% of all live-born term infants received intravenous antibiotics in the population, they analyzed from 2009 to 2011 [92].

Higher prescription rates were shown in preterm or term infants with relevant clinical problems. In a study involving neonates admitted to the neonatal intensive care unit in U.S. from 2005 to 2010, more than 88% of extremely low birth weight infants were administrated antibiotics [93].

Over the last decade, several national and international health institutions have made an enormous effort to decrease antibiotic use in the pediatric population by educating parents about the futility of treating viral infections with antibiotics and about concerns of antibiotic resistance [94, 95]. But, despite a recent reduction, widespread antibiotic use in infants and children remains a relevant health problem in the entire industrialized world, mainly because most prescriptions were frequently inappropriate [96].

However, even in countries in which the prescribing pattern usually adheres to national guidelines with respect to the choice of antibiotics, antibiotics are still largely prescribed to children, particularly to very young children [97–100].

In addition to antibiotic exposure for infection prevention and therapy, children could potentially be substantially exposed to antibiotics through the food supply chain or, more rarely, drinking water [101].

5.1. Evidence from animals

In last 50 years, farmers have been using low doses of antibiotics to promote growth and feed efficiency of pigs, cows, sheep, and poultry [102]. Different antibiotics have been demonstrated to have these effects independently of its class, chemical structure, and mode of action and spectrum of activity. Moreover, the effects on growth are greater when animals receive antibiotics early in life than if the exposure occurs later in life [103–105].

Also, studies in mice using multiple types of antibiotics have further confirmed this association, as well as identifying early life as the key period for microbe-mediated programing of host metabolism [106, 107].

Experiments with germ-free animal models have provided direct evidence of the key role of the microbiota in the association between low doses of antibiotics exposure and growth promotion. In 1963, Coates et al. showed that in germ-free chicken antibiotics alone have no growth promoting effects [108]. Recently, Cox et al. showed that germ-free mice who received the microbiota from mice treated with low dose penicillin gained more weight and fat mass than mice colonized with microbiota from control animals [107].

Then, there are two main findings from these experiments. First, early life is a critical time for metabolic development of the host, and second, the microbiome has a key role in this process and its disturbance duty to antibiotic exposure at this time affects the course of growth and development [109].

5.2. Epidemiologic evidence

There is epidemiologic evidence that exposure to antibiotics in early life is associated with increased risk of excess adiposity. Recently, epidemiological studies have shown that

this phenomenon can also occur in humans starting in the fetal stage of life. In that sense, Mueller et al. observed in a U.S. cohort that the administration of antibiotics to women in the last two trimesters of pregnancy increased 84% the risk of obesity in children at 7 years old compared to children born to mothers without antibiotics administration at the same period [110]. Also, Mor et al. observed similar results in a study performed in Denmark where they showed that prenatal exposure to systemic antibacterials was associated with an increased risk of overweight and obesity at school age, and this association varies by birth weight [111].

After birth, the exposure to antibiotics has been associated to obesity due to the analysis of different human cohorts in various countries. In a Danish mother-child pairs cohort, Ajslev et al. showed antibiotic exposure in children during the first 6 months was associated with an increased risk of being overweight at 7 years of age; the effect was stronger in boys than in girls. In a U.K. cohort, Trasande et al. showed that antibiotic use in the first 6 months of life was associated with increased BMI at 10, 20, and 38 months of age [19]. Both studies also determined that maternal BMI was a contributing factor for the development of obesity following exposure to antibiotics in early life, with increased effects seen in children with mothers of normal weight compared with children from mothers who were overweight. Also, Azad et al. in a study of Canadian infants showed that antibiotics administered in the first year of life increased the likelihood of a child being overweight at 9 years and 12 years of age being almost seen in boys [112], which was consistent with the previous results from Ajslev et al. In a U.S. cohort, Bailey at al. observed that repeated exposure to broad-spectrum antibiotics at ages 0–23 months was associated with early childhood obesity. Importantly, this observation was associated with the use of broad-spectrum antibiotics, but not with the use of narrow-spectrum antibiotics.

Finally, in a multicenter, multicountry, cross-sectional study (The International Study of Asthma and Allergies in Childhood Phase III) Murphy et al. observed a significant interaction between sex and early-life antibiotic exposure. Exposure to antibiotics during the first 12 months of life was associated with a small increase in BMI in boys aged 5–8 years but not in girls in this large international cross-sectional survey.

Colonization of neonate's gut microbiota relies on vertical transmission from the mother at the time of delivery; thus, during pregnancy or early-life exposure to antibiotics could have effects on weight later in life by disturbing the proper establishment of the gut microbiota.

5.3. Antibiotic exposure and dysbiosis in children

Prospective studies have showed that changes in gut microbiota in early life may precede the development of overweight and obesity [113, 114].

In particular, some bacterial taxa has been associated with the risk of obesity development, regarding to this, a high abundance of intestinal *Bifidobacteria* in early life appears to be associated with lower risk of overweight [114, 115], whereas high amounts of *Bacteroides fragilis* increase the risk of obesity development [113]. Thus, likely factors that exert an impact on gut microbiota composition and functionality in early life may also modulate the risk of obesity development.

Therefore, antibiotic exposure during childhood can reduce the phylogenetic diversity and microbial load of the gut microbiota [116].

Regarding preterm infants it has been shown that treatment with amoxicillin and gentamicin during the first week of life reduced the bacterial diversity and raised the relative abundance of *Enterobacter* in the second and third weeks of life compared to preterm infants not exposed to antibiotics [117].

Moreover, administration of penicillin, ampicillin, cephalexin, gentamicin, amikacin, erythromycin, vancomycin, clindamycin, and teichomycin to preterm infants has been associated with a decrease in the relative abundance of *Bifidobacteriaceae, bacilli*, and *Lactobacillales spp*., commonly linked with a healthy status and an increase in the presence of potentially pathogenic *Enterobacteriaceae* [117–119]. Besides short-term-effects, the dysbiosis produced by antibiotics administration in infants may produce long-term effects like the persistence of the risk of obesity development. It has been observed that 3 months after of antibiotics persists the microbiota disruption [120]. However, antibiotic administration to neonates has been linked to several critical clinical conditions in which modification of the microbiota composition is thought to play a relevant role, in diseases such as necrotizing enterocolitis and sepsis [121, 122].

Antibiotic treatments in early life can lead to long-term alterations in microbiota composition that result in changes to host metabolic functions, particularly during development, increasing the risk of obesity [109].

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