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The evolving microbiome during pregnancy, early infancy and its complications. A comprehensible multidisciplinary review

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Abstract:

Pregnancy induces a number of immunological, hormonal and metabolic changes in the physiology of women. Those changes are necessary for the mother to adapt her body to this new physiological situation, for the labor onset, and for the fetus to have a normal growth. It has been described that the mother, the placenta and the fetus microbiome influences the development of these processes, as well as the adequate development of the newborns. Microbiome modulates inflammatory mechanisms related to physiological and pathological processes that are involved in perinatal progress. Different metabolites derived from microbes and modulated by the diet, especially short chain fatty acids, might be involved in these stages.

The present review tries to summarize the knowledge about changes in the microbiota of the different tissues of the mother, the fetus, the newborn and childhood, as well as in some specific physiological and pathological situations during the perinatal periods, as well as the influence of the type of delivery and feeding. A number of factors influencing the discrepancy of data are also revised.

Keywords: Microbiome, pregnancy, fetus, placenta, newborn, infancy, sepsis, allergy.

Introduction

Pregnancy induces a number of immunological, hormonal and metabolic changes in the physiology of women. Those changes are necessary for the mother to adapt her body to this new physiologic situation and for the labor onset, and also for the fetus to have a normal growth [Newbern et al., 2011]. Gut microbiome contributes to maternal metabolic adaptations and supports the development of the fetus during the normal pregnancy [Koren et al., 2012]. During the *in utero* period, the mother, her microbiota, and the baby coexist as one interconnected metaorganism. However, there is a lack of consensus about the real nature of microbiome changes during pregnancy, since discrepant not predictable findings have been described [Koren et al., 2012; DiGiulio et al., 2015; Peelen et al., 2019]. These differences could be explained by the heterogeneity in gestational age, genetics, ethnicity, and the diet of the participants included in those studies. Indeed, it seems that maternal microbiota composition during pregnancy is affected by the mother diet [Flint et al., 2012; Garcia-Mantrana et al., 2018], and by pre-pregnancy weight and weight gain over the course of pregnancy [Collado et al., 2008; Santacruz et al., 2010; Collado et al., 2010; Gomez-Arango et al., 2016]. The amounts of anti-inflammatory butyrate-producer commensal bacteria associated with the non-pregnant microbiota decreased with pregnancy progress, whereas certain bacteria associated with proinflammatory responses, such as *Proteobacteria*, increased in a majority of the women [Koren et al., 2012]. Similarly, vaginal microbiota tends to reduce bacterial diversity during pregnancy, increasing vaginal *streptococci* along with several specific *lactobacilli* strains, which are thought to prevent the growth of pathogenic bacteria, to help human digestion, and to shape host innate and adaptive immune system responses [Aagaard et al., 2012]. On the other hand, the classical belief of the fetus as a sterile organism is no longer considered, since a characteristic microbiome has been identified in the placenta, the amniotic fluid and the fetus in healthy pregnancies [Aagaard et al., 2014; Prince et al., 2016].

Gut microbiota influences the immune function [Guinanne and Cotter, 2013], and thus may modulate the response through different microbial-derived metabolites, especially short-chain fatty acids (SCFAs) such as butyrate [Furusawa et al., 2015], acetate, or propionate [Smith et al., 2013], which are key drivers of T-cell subset, proliferation and activity. Gastrointestinal bacteria generate SCFAs from complex dietary carbohydrates fermentation. These SCFAs not only down-regulates pro-inflammatory responses at the specific site where the allergen is located, which typically precedes asthma in childhood [Havastad et al., 2014], but also influences bone marrow stimulation by reprogramming the immunological tone of the mammalian ecosystem [Lynch, 2016].

Finally, it is important to consider that the discrepancies of the data obtained until date could be influenced by the methodology of works. Given the large percentage of bacteria from meconium that are not culturable, new molecular methods are used to characterize the microbiota with their own limitations, as reagent and laboratory contamination. Therefore, new studies are needed to confirm the evolution of microbiota during pregnancy and its influence in healthy and complicated labors and newborn [Adak et al., 2018].

The present review tries to summarize, in an easy way to understand, the knowledge about changes in the microbiota of the different tissues of the mother, the fetus, the newborn associated to normal and altered development, as well as the influence of the type of feeding.

Changes in the microbiome during pregnancy

During pregnancy, the female body undergoes hormonal, immunological, and metabolic changes to preserve the health of both the mother and the offspring. These changes alter the mother microbiota at different sites such as the vagina, the oral cavity and the gut, although published data are not consistent. A number of factors might influence the microbiota profile such as the diet, antibiotic or other supplement intakes, as well as the methodology of works.

Gut microbiota

The gut microbiota shifts substantially throughout the progression of the pregnancy. This evolution is characterized by reduced individual richness (alpha-diversity), increased between-subject beta-diversity, and by changes in the abundance of certain species [Koren et al., 2012]. These changes are not related to diet, antibiotic treatments, gestational diabetes, or pre-pregnancy body mass index, but are vital for a healthy pregnancy. Therefore, it suggests that other factors, such as the state of the host immune and endocrine systems, may actively contribute to the observed changes [Neuman and Koren, 2017]. During the first trimester, gut microbiota pattern is similar in many aspects to that of healthy non-pregnant women, showing a predominance of *Firmicutes*, mainly *Clostridiales*, over *Bacteroidetes* [Walters et al., 2014]. Then, maternal gut microbiota declines in butyrate-producing bacteria (with anti-inflammatory effects), while *Bifidobacteria*, *Proteobacteria*, and lactic acid-producing bacteria increase from the first to the third trimester, when the microbiota resembles a unpredictably disease-associated dysbiosis that differs greatly among normal pregnancies [Koren et al., 2012]. Indeed, changes in the gastrointestinal mucosa host immune system together with metabolic hormonal changes may trigger to the inflammation, weight gain and dysbiosis occurring during normal pregnancies, and the microbiota changes may contribute to this evolution. In addition, dysbiosis during the third trimester may affect host metabolism in order to provide energy supply for the fetus [Koren et al., 2012]. On the other hand, it has

been reported that some alterations may contribute to pregnancy metabolic complications [Gomez-Arango et al., 2016], and that the gut microbiota during pregnancy is a critical determinant of offspring health: evidences suggest that the maternal gut microbiota during pregnancy potentially determines the development of atopy and autoimmune phenotypes in offspring [Nyangahu and Jaspan, 2019]. However, to our best knowledge, no studies on the relationship among the immune system, the gut microbiota, and metabolism in pregnancy currently exist.

Vaginal microbiota

The composition of the vaginal microbiota is dynamic, corresponding with hormonal fluctuations throughout the woman's reproductive life, and also during pregnancy. A number of protective lactic acid-producing *Lactobacillus* species dominates the healthy vaginal microbiota in most reproductive-age women. These bacteria protect against vaginal dysbiosis and inhibit opportunistic infections through different mechanisms. In addition, the degree of protection varies according to the predominant *Lactobacillus* specie [Smith and Ravel, 2017]. Vaginal dysbiosis is comprised of a wide array of strict and facultative anaerobes that correlates with increased risk of infection, diseases, and poor reproductive and obstetric outcomes [Kroon et al., 2018].

During normal pregnancy, the composition of the vaginal microbiota changes as a function of gestational age, with an increase in the relative abundance for *Lactobacillus spp*, as *L. crispatus, L. jensenii, L. gasserii, L. vaginalis*, and a decrease in anaerobe or strict anaerobe microbial species, as *Atopobium, Prevotella, Sneathia, Gardenerella, Ruminococcaceae, Parvimonas, Mobilincus* [Romero et al., 2014]. Those authors reported for the first time, that the composition and stability of the vaginal microbiota of normal pregnant women is different from that of non-pregnant women. In fact, low risk pregnant women have more stable vaginal flora throughout the pregnancy than non-pregnant women do. Normal changes in the vaginal flora during pregnancy are transitions to another *Lactobacillus* community, and this stability would protect against ascending infections through the genital tract. In addition, they reported a different presence of some *Lactobacillus* communities depending on the ethnicity of the women [Romero et al., 2014]. In 2015, DiGulio et al. [3] confirmed those data and found a stronger association between an altered vaginal microbiota and preterm birth that remains significant after adjusting by race, and suggested that pregnancy outcomes might be predicted by features of the microbiota in early gestation. Later, Stout et al. [2017] confirmed that vaginal community richness and diversity remained stable during the first and second trimesters of gestation in pregnancies ended at term, whereas in woman with preterm birth the richness and diversity decreased early in pregnancy. These data suggest that the preterm birth-associated vaginal microbiome may be less stable than that associated with termed birth, and that early pregnancy may be an

important ecological time for events that ordain subsequent term or preterm birth outcomes. In fact, a meta-analysis has reported significant differences (in diversity measures) in vaginal microbiomes at the first trimester, between women with term and preterm outcomes, indicating the potential diagnostic utility of these measures [Haque et al., 2017]. In addition, dysbiosis in the vaginal microbiota by pathogens is associated with complications of pregnancy, in particular with an increased risk of preterm birth and spontaneous abortion [Peelen et al., 2019].

Oral microbiota

An increase in the microbial load in the oral cavity during pregnancy has been described. The presence of pathogenic bacteria Porphyromonas gingivalis and Aggregatibacter actinomycotemcomitans in gingival sulcus were significantly higher during early and middle stages of pregnancy compared to non-pregnant women [Fujiwara et al., 2017]. In addition, a recent work has concluded that the alpha-diversity index is higher in the third trimester compared to non-pregnant women due to the increase of progesterone and oestradiol. Therefore, it is hypothesized that pregnancy creates a nutrient oral environment that is more favorable to some sensitive strains [Lin et al., 2018].

Placental microbiota

The placenta is an organ that has been considered sterile in the absence of clinical infection. However, several findings using both culture and metagenomic techniques suggest the presence of a low biomass microbial community in the healthy placenta [Nuriel-Ohayon et al., 2016; Pelzer et al., 2017]. When characterizing the placental microbial community, the presence of non-pathogenic commensal microbiota from the *Firmicutes*, *Tenericutes*, *Proteobacteria*, *Bacteroidetes*, and *Fusobacteria* phyla has been demonstrated. Specifically, the major phylum was *Proteobacteria*, including species such as *Prevotella*, *Tannerae* and *Neisseria*. Curiously, these authors described that the placental microbiome profiles are most akin to the human oral microbiome. In addition, an association of the placental microbiome with a remote history of antenatal urinary infection, particularly during the first trimester has also been reported [Aagaard et al., 2014]. The oral and intestinal transmission might be explained by epithelium gaps which allow the transference of bacteria into the placenta by hematogenous spread of those microorganism [Aagaard et al., 2014]. Some of those oral microbes, such as *Fusobacterium nucleatum*, may be transmitted hematogenous during placentation as a result of their ability to bind vascular endothelium, and modify its permeability. Therefore, these bacteria function as an "enabler" for other common commensals, such as *Escherichia coli* [Fardini et al., 2011]. Additionally to this classical hypothesis, a new theory has been proposed related to the role of the endometrial microbiome prior to conception. Franasiak et al. [2016] observed that *Flavobacterium* and *Lactobacillus*

represent the majority of endometrial bacterium at the time of embryotransfer. This fact should support the new paradigm of the endometrial environment, although its implication remains unclear.

The abundance of *Lactobacillus* sp, *Propionibacterium* spp. and members of the *Enterobacteriaceae* family have been proved by DNA-based studies in placental tissue of pregnant at term [Prince et al., 2016]. In addition, other authors have confirmed a distinct microbiota in the placenta and amniotic fluid of healthy woman at the time of elective caesarean, characterized by low richness, low diversity and the predominance of *Proteobacteria* [Collado et al., 2016]. These authors propose that the stepwise microbial gut colonization process may be initiated already prenatally by a distinct microbiota in the placenta and amniotic fluid. Similarly, several studies have found microbes in amniotic fluid and umbilical cord blood in healthy asymptomatic women, as well as in those with pregnancy complications [DiGiulio et al., 2010a, 2010b; Romero et al., 2015].

Microbiome fetal colonization

The classical paradigm of fetal environment as a sterile harbor has traditionally explained that microbes, and thus microbiome, are acquired both vertically [from the mother] and horizontally (from other humans or from the environment) during and after birth, but recent data has questioned the traditional accepted dogma of human microbiome acquisition, proposing that neither the fetus, the placenta or the amniotic fluid are sterile [Jimenez et al., 2005; Wassenaar and Panigrahi, 2014]. According to the literature, the colonization of the fetus gastrointestinal tract starts during the intrauterine life. The presence of bacteria within placental tissue was confirmed by cultivation-dependent techniques and, more recently, "healthy" placental microbiota has been demonstrated by modern sequencing technologies [Aagaard et al., 2014]. This placental niche of bacteria is not related with adverse outcomes of pregnancy or symptoms of clinical infection [Jiménez et al., 2005]. Animal but not human studies have hypothesized that the previously mentioned similarity between placental and oral bacteria may be due to bacteria passing from the oral cavity to the placenta through an unknown mechanism [Aagaard et al., 2014].

Once we know that colonization starts during fetal life, the challenge is to understand how this process develops. Microorganism may pass through the placenta and colonize the fetus ascending from the vagina, from the oral cavity, from the urinary track or from the intestinal lumen of the mother. These microorganisms may reach hematogenously the placenta and then be transmitted to the fetus [McClure and Goldenberg, 2009]. However, it is unclear where the fetal microbiota comes from, and which is the first fetus exposition. The presence of a different placental microbiota compared to the vagina raise the possibility that the infant

may be first seeded *in utero* by a common shared low abundance source, such as the placenta, and this seeding may vary by length of gestation [Aagaard et al., 2014].

Different studies have detected microbiome in the first baby fecal sample, the meconium, suggesting *in utero* exposure to bacteria [Jimenez et al., 2008; Hansen et al., 2015]. *Staphylococcus* has been reported as the most prevalent bacteria in meconium samples, followed by *Enterobacteriaceae*, *Enterococcu*s, *Lactobacillus* and *Bifidobacterium* even in infants born by caesarean. These findings suggest that colonization by certain bacteria might start before birth [Hansen et al., 2015; Martin et al., 2016]. Indeed, those authors has reported an increase in the chance of detecting *Bifidobacterium*, *Bacteroides fragilis* group, *Enterococcus*, *Staphylococcus*, *L. gasseri* subgroup, and *B. adolescentis* when delaying the collection of meconium samples by one day. This may be due to the impact of the type of feeding or the environment after the birth that may be more determinant to establish the intestinal microbiome during the childhood [Martin et al., 2016].

Microbiome in pathological and adverse pregnancy outcomes

There are some studies comparing the fetal or mother microbiome according to the presence of adverse pregnancy outcomes such as prematurity or low birth weight. However, the results remain under discussion since some microorganisms related with altered perinatal outcomes have also been observed in women with correct perinatal results. Ardissone et al. [2014] compared the meconium microbiome in newborn before and after 33 weeks of gestation, and they concluded that *Enterococcus* and *Enterobacter* were negatively correlated with gestational age, while *Lactobacillus* and *Phortorhabdus* had a greater abundance in newborn with less than 33 weeks of gestation. This indicates that the composition of the microbiome may be involved in the inflammatory response that leads to premature birth more than the colonization alone. Specifically, preterm subjects with severe chorioamnionitis had high abundances of *Ureaplasma parvum*, *Fusobacterium nucleatum*, and *Streptococcus agalactiae* [Prince et al., 2016]. Among women with spontaneous preterm birth, the placental microbiome varies by virtue of excess gestational weight gain, but not obesity, and this placental dysbiosis affects different bacterially encoded metabolic pathways that may be related with pregnancy outcomes [Antony et al., 2014]. It has been reported high abundance of *Burkholderia*, *Actinomycetales* and *Alphaproteobacteria* in placental samples from gravidae delivered preterm, and an enrichment of *Streptococcus* and *Acinetobacter* in placental samples from patients with a history of antepartum urinary infection. In contrast, *Paenibacillus* predominated in term placental specimens [Aagaard et al., 2014]. Other authors have proposed that the fetal intestinal microbiota derives from swallowed amniotic fluid, and that it may develop inflammatory response that leads to premature birth [Ardissone et al., 2014]. Considering that some strains of *Lactobacillus* may possess potential

anti-inflammatory activities, and could regulate blood glucose levels in diabetic human [Ejtahed et al., 2012], the low abundance of *Lactobacillus* in placentas of low birth weight neonates reported by Zheng et al. [2015] might be related with a pro-inflammatory status in pregnancy. Thus, the higher sensitivity of fetal intestinal tissue to inflammatory stimuli may induce the labor due to an immune reaction. In addition, a correlation between periodontitis and the risk of spontaneous abortion or miscarriage [Chanomethaporn et al, 2019]. On the other hand, Liu et al [2017] analyzed gut microbiome in pregnants affected by preeclampsia. They showed an overall increase in pathogenic bacteria such as *Clostridium perfringens* and *Bulleidia moorei* and a reduction in probiotic bacteria *Coprococcuscatus*. Finally, a number of bacteria, viruses, and protozoa infections have been associated with pregnancy complications. Therefore, identification of these placental infections might help the prediction of spontaneous abortion, stillbirth, premature delivery, growth retardation, and the sick newborn [Heerema-McKenney, 2018]. However, more research is needed to confirm these observations that can results in a future opportunity for new fetal therapeutic targets in adverse obstetrical conditions.

Changes in the microbiome related to the type of delivery

There is great controversy in the scientific community about the relationship of the meconium and infant gut microbiota profile and the type of delivery. Microbiome studies on early infancy have demonstrated a significant influence of the mode of delivery on the microbiome composition, suggesting the likely association of the infant gut bacteria with maternal vaginal or skin microbiome habitats. It is important to clarify the influence of factors commonly accompanying caesarean delivery on the microbiome, due to the potential influence on some non-communicable diseases, such as neonatal skin infection, asthma, allergies, obesity, inflammatory bowel disease, or type I diabetes mellitus [Montoya-Williams, et al. 2018; Stinson, Payne et al. 2018].

Vaginally delivered newborn have shown bacterial communities resembling their own mother's vaginal microbiota, dominated by *Lactobacillus*, *Prevotella*, or *Sneathia* spp. On the other hand, caesarean-born infants harbored bacterial communities similar to those found on the skin surface nicho, dominated by *Staphylococcus*, *Corynebacterium*, and *Propionibacterium* spp. [Dominguez-Bello, Costello et al. 2010] or potentially pathogenic microbial communities such as *Klebsiella*, *Enterococcus*, and *Clostridium* [Montoya-Williams, Lemas et al. 2018]. Other authors have reported that *Bifidobacterium* [Biasucci, Rubini et al. 2010; Rutayisire, Huang et al. 2016], and *Bacteroides* [Rutayisire, Huang et al. 2016] seems to be significantly more frequent in vaginally compared with caesarean delivered infants, which were mainly colonized by *Clostridium* and *Lactobacillus*

316 [Rutayisire, Huang et al. 2016]. The high abundance of *Bifidobacterium* species in infants is
317 considered to promote the development and maturation of the immune system to sustain
318 health, while high presence of *Clostridium difficile* is considered as one of the major
319 intrahospital dangers causing severe gastrointestinal infections during the infancy
320 [Rutayisire, Huang et al. 2016]. Another study proposed that *Propionibacterium* species
321 were most abundant in the meconium of vaginally delivered chinese infants, whereas the
322 caesarean-born children had higher amounts of *Bacillus licheniformis*. In addition, the
323 diversity of the microbial composition was also higher in vaginal than in cesarean deliveries,
324 although no correlation with maternal microbiome was reported [Shi, Guo et al. 2018].
325 Similarly, a metagenomic analysis concluded that *Propionibacterium* was enriched in the
326 meconium from the vaginal delivery group, and that it may reach from skin or fecal microbes
327 through contact during the natural labour [Backhed, Roswall et al. 2015]. Therefore, there is
328 no consensus regarding the most colonizable pattern of the first microbiota community in the
329 first 3 days of the newborn, although it seems that according to phyla, vaginally delivers are
330 more related to *Actinobacteria* and *Bacteroidetes*, while caesarean are more related to
331 *Firmicutes*. Indeed, it has also been suggested that the transfer of maternal vaginal microbes
332 play a minor role in seeding infant stool microbiota since the overlap of maternal vaginal
333 microbiota and infant faecal microbiota is minimal. However, the similarity between
334 maternal rectal microbiota and infant microbiota was more pronounced [Sakwinska, Foata et
335 al. 2017].

336 The discrepances of the results obtained could be due to different factors associated to
337 caesarean delivery such as antibiotics administration, or to breastfeeding, maternal obesity,
338 labor, gestational diabetes mellitus and even the methodology of work. In addition, the
339 diversity from *Firmicutes* and *Bacteroides* colonization levels on infants gut microbiota may
340 be influenced by geographical variation such as the latitude [Escobar, Klotz et al. 2014].

341 Some authors have proposed that the lower presence of *Bifidobacteria* and *Bacteroides*,
342 and the abundance of *Clostridia* and *Lactobacillus*, in infants delivered by caesarean could be
343 explained by the perinatal antibiotics administration [Rutayisire, Huang et al. 2016]. Mothers
344 delivering by caesarean use antibiotic prophylaxis before the beginning of surgery or, in
345 some countries, after the cord are clamped, to minimizes direct neonate exposure to antibiotic
346 [Seedat, Stinton et al. 2017]. In addition, Azad et al. determined that intrapartum antibiotics
347 in caesarean and vaginal delivery are associated with infant gut microbiota dysbiosis,
348 although breastfeeding modifies some of these effects [Azad, Konya et al. 2013].
349 Nevertheless, Martinez et al. performed antibiotic-free caesarean in mice and determined that
350 these mice did not have the dynamic developmental gut microbiota changes observed in
351 control natural born mice, evidencing the involvement of maternal vaginal bacteria in a

proper metabolic development even in absence of antibiotics [Martinez, Devlin et al. 2017]. It is worth to take into account that perinatal antibiotic administration may be associated with increased risk of developing morbidities as asthma, allergies and obesity, which may be influenced by dysbiosis. Epidemiological data show that atopic diseases appear more often in caesarean infants than after vaginal delivery [Laubereau et al., 2004; Negele et al., 2004]. Therefore, the composition of enteric microbiota in early days of life seems to be a very important factor for achieving and maintaining good health in the years to come [Neu et al., 2011].

In addition, the mode of delivery had a large impact on the microbiota composition of colostrums and milk [Cabrera-Rubio, Mira-Pascual et al. 2016; Toscano, De Grandi et al. 2017], what also may be influenced by antibiotics administrated during caesarean. It has been proposed that caesarean-born infants lacked the early provision of breast milk stimulated for a proper gut microbiota, that contains microbes such as *Lactobacilli* and *Bifidobacteria,* what can be a direct source for the higher colonization rates of these genera in vaginally than in caesarean-delivered infants [Neu and Rushing 2011]. In fact, Sakwinska et al. [2017] reported that only vaginally delivered and fully breastfed infants had gut microbiota dominated by *Bifidobacteria*. Importantly, caesarean may decrease colonization of milk-digested bacteria including the genus *Lactobacillus* in newborn during the first months of life [Dominguez-Bello 2010].

On the other hand, bacterial richness and diversity were lower in infant gut after elective caesarean born infants and higher in emergency caesarean, suggesting that colonization may be affected differently in both situations. It is important to highlight that emergency cesarean and vaginal delivery labor are frequently accompanied by rupture of fetal membranes, exposing the fetus to maternal vaginal bacteria [Azad, Konya et al. 2013], what could be related to the diversity of vaginal microbiota that increases by the time of labor onset [Avershina, Slangsvold et al. 2017]. In fact, infants born by elective caesarean had particularly low bacterial richness and diversity at 4 months of age [Azad, Konya et al. 2013]. Additionally, due to absence of labor, a different inflammatory levels and immune-mediating cytokines in caesarean-born infants may be related to some of the observed differences in neonatal microbiome colonization and health outcomes [Stinson, Payne et al. 2018]. The healthy gut microbiota is considered to promote development and maturation of the immune system, while abnormal gut is considered as the major cause of severe gastrointestinal infections during the infancy. A systematic review has concluded that the diversity and colonization pattern of the gut microbiota were significantly associated to the mode of delivery during the first three months of life, which is a critical period of life for immunological programming [Rutayisire, et al 2016]. However, the observed differences

disappears after 6 months of infants life, when solid foods are included in the diet [Stinson, Payne et al. 2018].

Finally, there are different potential preventive intervention strategies to restore the gut microbiota after caesarean [Moya-Perez, Luczynski et al. 2017]. The intervention could be focused on maternal administration of probiotics and prebiotics during gestation. There is a great interest about "seeding approaches" as "vaginal seeding" to reverse the effects of caesarean delivery mode on the microbiome in early life, but at the same time there are critical voices that are concern about safety and efficacy of this practice [Moya-Perez, Luczynski et al. 2017; Stinson et al. 2018]. On the other hand, the intervention could concentrate on the neonate using "seeding" methods such as encouraging breastfeeding instead of formula feeding, or the use of infant enriched formulas. In these sense, supplementation with symbiotic, the combination of synergistic pre- and probiotics, might offer an innovative strategy to reestablish the delayed colonization of *Bifidobacterium* spp. in caesarean-delivered children [Francavilla et al., 2018-[70].

Microbiome and Obese Pregnancy

Epidemiological evidence shows that 50% of women of childbearing age and 20-25% of pregnant women in Europe can be affected by overweight or obesity [Stevens et al., 2012]. Consequently, maternal obesity is becoming a serious public health concern in developed countries, since it increases the risk of cardiometabolic diseases in mothers [Zhu and Zhang, 2016] and the susceptibility to metabolic diseases in offspring [73-Eriksson e al., 2015; 74-Hussen et al., 2015; 75-Gaillard et al. 2016; 76-Toemen et al., 2016]. Maternal obesity is associated to environmental factors, such as the diet and the reduction in physical activity [Murray et al., 2013]. However, further evidence relates obesity with a missing factor which has been identified as the alterations in gut microbiome due to its crucial role in energy balance and metabolism [Okeke et al., 2014; Sanmiguel et al., 2015]. It seems that maternal microbiota composition during pregnancy is affected by nutrition [Flint et al., 2012; Carcia-Mantrana et al., 2018], pre-pregnancy weight and weight gain over the course of pregnancy [Collado et al., 2008; Collado et al., 2010; Santacruz et al., 2010; Gomez-Arango et al., 2016].

Pregnancy-associated changes are different in overweight or obese women compared with normal-weight pregnant women. Overweight pregnant women reduce the number of *Bifidobacterium* and *Bacteroides,* whereas increase the number of *Staphylococcus, Enterobacteriaceae* and *E.coli* [Santacruz et al., 2010]. Additionally, higher levels of *Staphylococcus* and *Akkermansia muciniphila* and lower levels of *Bifidobacterium* were detected in women with excessive weight gain during pregnancy as compared with

normal-weight ones [Collado et al., 2012]. Consequently, this altered maternal microbiome will shape the composition of offspring [Ma et al., 2014; Mueller et al., 2016] and thus influence his or her future health.

Specifically, neonates born vaginally from overweight or obese mothers show increased numbers of *Bacteroides* and depleted in *Enterococcus*, *Acinetobacter*, *Pseudomonas*, and *Hydrogenophilus* [Mueller et al., 2016]. On the other hand, when specifically examining phyla level relative taxonomic abundance among preterm women by virtue of maternal weight gain, other authors have reported an appreciable and significant increased abundance of *Firmicutes*, *Actinobacteria*, and *Cyanobacteria*, and decreased relative abundance of *Proteobacteria* [Antony et al., 2015]. Furthermore, this altered maternal microbiota composition may be transferred from mother to fetus during the prenatal period [Gohir et al., 2015] and through lactation [Garcia-Mantrana and Collado, 2016]. Several routes may be involved in the transfer of maternal microbiota to offspring, but it is not clear which one plays the most important role for the transfer of maternal obesogenic microbiota to offspring.

In addition, gut microbiota can induce obesity in children by several mechanisms. For example, lower amounts of *Bifidobacteria* can affect weight gain in infants through mucosal host-microbe crosstalk, and immune and inflammatory dysregulation. Moreover, higher concentrations of *Bacteroides*, *Clostridium*, and *Staphylococcus* can stimulate greater energy extraction from food, combined with a reduced control of inflammation; this dysbiosis occurs during the first six months of life in infants of overweight mothers [Collado et al., 2010]. These first months of life are of great importance since rapid weight gain during this period is associated with an increased risk of obesity during childhood, even more than the birth weight [Taveras et al., 2009].

Microbiome and diet

Maternal diet establishes long-lasting effects on offspring gut microbial composition what may have important clinical implications [Clarke et al., 2014]. It has been described that dietary composition during pregnancy may also affect infant microbiota [Penders et al., 2006]. Therefore, regular exercise must be recommended as an effective way of weight control during pregnancy [Muktabhant et al., 2015], what could enhance the gut microbiota composition [Clarke et al., 2014]. In addition, complex interactions of cytokines and microbiota in breast milk guide the microbiological, immunological, and metabolic programming of infant health, what may explain the heightened risk of obesity for infants of overweight and excessive weight gain mothers [Collado et al., 2012]. Given that early infant weight gain can have lifelong consequences for metabolic health, further studies will provide evidences of the impact of maternal obesity on infant microbiota. On the other hand, data

458 supporting the notion of bacterial translocation from the maternal gut to extraintestinal sites
459 during pregnancy are emerging, and potentially explain the presence of bacteria in breast
460 milk [Nyangahu and Jaspan, 2019].

461 *Gut microbiome and prematurity: the influence of the type of feeding*

462 Breast milk has been recognized as the gold standard for human nutrition [American
463 Academy of Pediatrics, 2012]. In preterm infants, breast milk has been associated with
464 improved growth and cognitive development [Belford et al., 2016] and a reduced risk of
465 necrotizing enterocolitis and late sepsis onset [Menzen-Derr et al., 2009; Collado et al., 2012;
466 Ballard et al., 2013]. Occasionally, the absence of mother's own milk (MOM) requires the
467 use of donor human milk (DHM). It has been observed that the type of feeding has an
468 important impact on gut microbial composition in preterm infants. A prospective cohort
469 study has been launched to determine the impact of DHM upon preterm gut microbiota
470 admitted in a referral neonatal intensive care unit. Despite the high variability, no differences
471 in microbial diversity and richness were found, although feeding type significantly
472 influenced the preterm microbiota composition and predictive functional profiles. Inferred
473 metagenomic analyses showed higher presence of *Bifidobacterium* in the MOM, a genus
474 related to enrichment in the glycan biosynthesis and metabolism pathway, as well as an
475 unclassified *Enterobacteriaceae* and lower unclassified *Clostridiaceae* compared with the
476 DHM or in the formula fed groups. After adjusting for gender, postnatal age, weight and
477 gestational age, the diversity of gut microbiota increased over time and was constantly higher
478 in infants fed MOM relative to infants with other types of feeding. Finally, DHM favors an
479 intestinal microbiome more similar to MOM despite the differences between MOM and
480 DHM [Parra-Llorca et al., 2018]. Using DHM could have potential long-term benefits on
481 intestinal functionality, immune system and metabolism [Bertino et al., 2009; Christen et al.,
482 2013; Madore et al., 2017]. However, available pasteurization methods cause changes that
483 may blunt many of the positives aspects derived from the use of MOM [Untala et al., 2009;
484 Sousa et al. 2014; Peila et al., 2016]. Further studies are needed to understand the complex
485 links between microbiome and DHM feeding, its impact on health programming, and to
486 develop sensitive methods capable of providing human milk as similar as possible to their
487 MOM, when the latter is not available.

488 **Microbiome and sepsis in the newborn**

489 In spite of variation in net incidence, neonatal sepsis remains one of the leading causes of
490 preventable neonatal morbidity and mortality throughout the world. The main agents
491 responsible for sepsis are group B Streptococcus (GBS), E. coli and coagulase-negative
492 Staphylococci (CONS). However, this scenario is susceptible to future changes depending on

493 the use of antibiotics and/or the implementation of non-culture diagnostic techniques [Özenci
494 and Schubert, 2018].

495 In recent years, there has been a growing interest on the role of commensal bacteria in the
496 individual´s susceptibility to infection. A few studies have evaluated the maternal vaginal
497 microbiota in relation to GBS carrier status. Although it seems that some specific taxa might
498 be associated with the presence of GBS [Rosen et al., 2017], there is no apparent parallel
499 reduction of the predominant commensal bacteria *Lactobacilli* [Kolter and Henneke, 2017].
500 Indirect evidence suggests that the neonatal gut microbiome might be of relevance in GBS
501 infection, since different colonizing species have been found in stool of infants from GBS
502 positive and negative mothers, while on the other hand, the protective effect of pre and
503 probiotics has also been suggested [Kolter and Henneke, 2017].

504 It seems that gastrointestinal microbiota might induce an increase in permeability,
505 modulating gut and systemic immune response and decreasing the tight junction integrity
506 [Berrington et al, 2013]. As a consequence, intestinal bacteria can promote the systemic
507 inflammatory response syndrome, facilitate bacterial translocation, and cause late-onset
508 sepsis and necrotizing enterocolitis, especially affecting the premature population. Most, but
509 not all, of the evidence suggests that premature newborns with low microbiome gut diversity
510 or with predominance of *Staphylococcus, Firmicutes* and *Proteobacteria* are associated with
511 increased risk for late-onset sepsis compared with those premature infants at lower risk
512 [Madan et al., 2012]. Furthermore, gut colonization with *Bifidobacterium* and increased
513 presence of prebiotic oligosaccharides in feces, has been related with less disruption of the
514 mucosal barrier and gut epithelial translocation, providing an improved gut development and
515 protection [Stewart et al, 2017]. It remains unclear if invasion of the bloodstream during
516 sepsis is caused by the same microorganisms identified in stool [Carl et al., 2014] or by
517 others [Madan et al., 2012], in which case the gut microbiota would act as a facilitating
518 mechanism by interfering with the gut barrier or intestinal immune function. Further and
519 bigger studies are needed to tease out if the differences observed in gut colonization in
520 intensive care units patients do predispose to sepsis or if they respond to other factors such as
521 the diet [Mai et al., 2013], site differences in initiating and advancing feeds, breastfeeding,
522 the use of antibiotics [Taft et al., 2015], or interpatient transmission within the neonatal
523 intensive care units [Carl et al., 2014].

524 **Microbiome and allergic conditions**

525 Allergy disorders represent an important burden from worldwide diseases, with an
526 increasing prevalence in infants and children, mainly as food allergies, atopic eczema
527 [Dunlop et al., 2018], and respiratory pathology as rhinitis [Bousquet et al., 2008] or asthma

[Bousquet et al., 2007]. Their cause is multifactorial and contemplates interactions between genetic, environmental and socioeconomic factors leading to different symptoms or phenotypes [Johansson et al., 2004]. Among this heterogeneity, a restricted microbial exposure at early life seems to plays also an important role influencing allergic diseases, and consequently asthma onset [Abrahamsson et al., 2013].

Gut microbiome and atopy

Eczema or atopic dermatitis (AD) is the first typical allergic manifestation in newborns [Wopereis et al., 2017]. A recent study has reported high proportion of *Faecalibacterium prausnitzii* among gut microbiome in AD subjects, which are known to be deficient in Crohn's disease subjects, while anti-inflammatory faecal bacteria metabolites decreased in those subjects [Song et al., 2015]. Besides, literature has shown that infants with AD improved their condition in parallel with an increased abundance of faecal *Coprococcus eutactus*, a butyrate-producing bacteria [Nylund et al., 2015]. It has been proposed that dysbiotic gut microbiota and subsequent dysregulation of the gut inflammation may promote an aberrant Th2-type immune response to allergens altering the epithelial barrier in AD skin [Muir et al., 2016].

Gut microbiome and food allergy

Available literature on animal models suggests that gut microbiome may have an important role in the susceptibility to food sensitization and food allergy, mainly at early stages of life [Stefka et al., 2014]. Among the causes, the increasing use of antibiotics both in humans and in agriculture, and the lower intake of dietary fibre have had an impact on the gut microbiota [BerniCanani et al., 2015]. Chen et al. [2015] have recently shown that children with food sensitization in early life have both lower microbiota diversity and altered gut microbiota composition (an increased number of *Firmicutes* in detriment of *Bacteroidetes*) compared to children not having these condition.

Gut microbiome and asthma

Allergies are the strongest risk factors for childhood asthma development in western countries [Simpson et al., 2010], but the relationships between asthma and the microbiota is not clear. Although it has been indicated that the diversity of the gut microbiota in infancy is even more determinant for asthma development than the prevalence of specific bacterial taxa, those authors suggested that there might be specific bacterial species important for prevention of asthma, and that gut microbial diversity during the first month of life may be more associated with asthma development at school age than other allergic manifestations

[Abrahamsson et al., 2013]. The main cause of this lack of awareness may be that the available clinical follow-ups studies had been performed in infancy [Masoli et al., 2004], whereas allergic asthma is still uncommon [Abrahamsson et al., 2013]. Indeed, another study has indicated that the neonatal gut microbiota influences susceptibility to childhood allergic asthma, via alterations in the gut microenvironment that modulates CD4+ T–cell populations and functions. These authors have observed a characteristic depletion of dihomo-γ-linoleate, a precursor of anti-inflammatory ω-3 polyunsaturated fatty acid and prostaglandins, that may be related [Fujimura et al., 2016].

As described previously, different factors has been associated with infant microbiome and with risk of asthma, such as the furry pets exposure [Tun et al., 2017], gestational age, the mode of delivery (vaginal *vs*. caesarean), and antibiotic treatment (direct *vs*. indirect via mother), among others [Marques et al., 2010; Chong et al., 2018], but there is no doubt that a key issue is the type of feeding. A systematic review addressing the effect of breastfeeding in the development of asthma has found that children who were breastfed for longer time had a lower risk of developing asthma, mainly between the first two years of life [Dogaru et al., 2014], what may be mediated by the shape of the early gut microbiota [Groer et al., 2014]. However, longitudinal and multicenter studies are still needed to better understand if the dysbiotic microbiota is a cause or consequence of the atopic and allergic diseases [Muir et al., 2016]. Besides, interventional studies suggest that pre- and probiotics could prevent or down-regulate the severity of some diseases, such as asthma or allergies, but the biological mechanisms, as well as the best taxa or type of intervention, require further research [Mennini et al., 2017].

Conclusion

There are many data confirming the involvement of the microbiota in the development of pregnancy and the newborn, and how it influences the correct establishment of labor and all perinatal processes. However, despite the large number of studies, we are still not able to obtain adequate conclusions, due to the large number of factors that may influence these processes, such as the age, race, the type of feeding, the mother diet, the intake of antibiotics, as well as the presence of other pathologies. Recent developments in genome sequencing technologies, bioinformatics and culturomics will enable researchers to explore the microbiota and, in particular, their functions at more detailed level than before. Therefore, new studies are needed to confirm the evolution of microbiota during different conditions and its influence on healthy or complicated perinatal evolution.

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Author Contributions

All authors have contributed to the writing of the work. M.D.M. had primary responsibility for the final content. All authors read and approved the final manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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