

The controversial role of placental microbiome in preterm birth

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ABSTRACT

The correlation between the maternal and neonatal microbiome helps to understand the mechanisms that govern the metabolic and immune processes of the newborn. The literature of recent years brings pros and cons regarding the role of the placenta as a microbial residence and its involvement secondary to microbial colonization in premature birth. Additional multi-omics research will be needed to establish the role of this transient organ in elucidating the processes that govern premature birth. DNA sequencing has made it possible to identify microbial species in the human microbiome. Thus, the role of the maternal microbiome in pregnancy and related complications are partially elucidated. This article aimed to identify the diversity of species in the maternal placental microbiome, the possible association with the newborn microbiome, and the influence of dysbiosis in spontaneous premature birth (PTB). In pregnancy, the changes in the microbiome are multifactorial, and the analysis performed demonstrating the continuous intervention of the body in order to adapt the intestinal microbiota to have a positive maternal-fetal result.

Keywords: maternal microbiome, preterm birth, placental microbiome, pregnancy

INTRODUCTION

Premature birth (PTB) before 37 weeks of completed pregnancy continues to be an intense public health issue debated due to the high rate of morbidity and mortality of these newborns [1]. The incidence of PTB is estimated at about 11.1% of all live births globally, accounting for 5% in Europe [2,3]. Several studies have highlighted the role of the microbiome in the development and maintenance of a healthy pregnancy through metagenomic sequencing techniques. Disorders in the constitution of this microbiome can occur in the etiopathogenic mechanisms of premature birth [4,5]. Therefore, the influence of the maternal microbiome in the etiology of premature

birth requires a thorough study of the intestinal, vaginal, cervical, and placental microbiomes [6].

In the multi-omics studies in the last decade, the NIH Human Microbiome Project (HMP) was carried out, which included in the second phase the Integrative Project of human microbiomes focused on knowing the mechanisms related to the role of the microbiome in premature birth, in the etiopathogenesis of inflammatory bowel diseases and in interpreting stressors in people with prediabetes [7,8].

Research on microbial diversity has led to the idea that each person has in his constitution an individualized microbiome formed at the beginning of life and which shows rapid dynamics during it. For example,

dysbiotic conditions due to the influence of immune mechanisms can cause side effects in the female genital tract [9,10]. Franzosa et al. highlighted a series of algorithms on building the metagenomic code by connecting microbial theories with computer codes based on microbiomes and individual differentiation [9].

The Consortium achieved a role in defining the concept of a healthy microbiome for the human microbiome project by identifying maternal influences on the placental microbiome and possible modeling the neonatal microbiome. Several studies have sought to establish how the maternal microbiome can alter the microbiome in the formation of the newborn and how it can interfere with the normal course of pregnancy through the risk of premature birth [4,11].

Complementary studies are needed to see how the microbiome intervenes in metabolic and immune changes. In fact, the alteration of the microbiome has been observed in some medical conditions such as obesity, diabetes, hypertension, inflammatory bowel disease, and digestive cancer (e.g., colorectal) [4,12].

THE ROLE OF THE MICROBIOME IN PREGNANCY

Maternal adaptative physiological changes during pregnancy determine a series of morphophysiological and biochemical transformations secondary to hormonal influences and implicitly of the microbiome. The studies examined the evolution and changes of the microbiome related to pregnancy in the following sites: vagina, gut, lung, placenta, oral cavity [13,14]. Over time, a continuum of microbiota has been shown in the vagina, cervix, endometrial mucosa, and fallopian tubes of women of reproductive age, demonstrating that the intrauterine environment is unsterile even before conception [15].

Hypervascularization and hyperemia of the vaginal mucosa, cellular hyper-trophy, increased volume of cervical secretions, and decreased vaginal pH by excess lactic acid produced by *Lactobacillus acidophilus* are factors will significantly influence the microbiome and the continuous transformation during pregnancy [16,17]. Stout et al., in a study of a predominantly African-American population, found that early pregnancy was associated with a significant decrease in vaginal microbial diversity, being an essential moment in the chronology of events leading to premature birth [18].

The dynamics of changes in the microbiome can influence the immune status through the level of cytokines and thus increase the risk of infection. The microbiome component in pregnancy undergoes a series of transformations highlighting a decrease in species diversity, followed by the increased presence of other species such as *Lactobacillus*, *Bacteroidales*, and *Clostridiales* [19]. The vaginal microbiome in pregnancy shows the growth of four types of *Lactobacillus* spp (*L. jensenii*, *L. gasseri*, *L. crispatus*, and *L. vaginalis*) and a decrease in the number of anaerobic species [19,20].

Lactobacillus species, *L. jensenii* and *L. crispatus*, which inhibit sexually transmitted infections by producing hydrogen peroxide with decreased pH, had an increased biological significance. *L. johnsonii* produces Lactacin F to destroy germs from the gastrointestinal tract and in the digestion of milk by infants through the neonatal microbiome [21]. Another study revealed that the main role is to reduce the risk of ascending infection (chorioamnionitis) and premature birth [22].

The vaginal microbiome undergoes transformations related to gestational age and the vicinity of the cervix. Rarely a dominant species of *Lactobacillus* spp. can pass to one dominated by anaerobes (CST IV-A or CST IV-B) [20], a possible explanation would be due to the hormonal changes in pregnancy [23].

Decreased levels of lactobacilli in the vaginal microbiome cause bacterial vaginosis involved in PTB [24]. This was demonstrated by Joo et al. through the role of *Lactobacillus johnsonii* HY7042 in suppressing *Gardnerella vaginalis* by inhibiting the expression of COX-2, IL-1 β , and TNF- α by regulating NF- κ B activation, with beneficial action on bacterial vaginosis [25].

Another important component of the microbiome is the intestinal one, whose bacterial density increases during pregnancy and whose component undergoes a continuous change [26].

Collado et al. identified an increase in *Bacteroides* and *Staphylococcus aureus* species in the microbiota composition related to weight gain in pregnancy. In addition, the decrease of the maternal inflammatory process and the improvement of glucose tolerance are based on the action of the *Bifidobacterium* species that can actively intervene in the gut microbiome of the newborn [26].

that the possibility of reagents contamination is high [47].

The potential biological relevance of the similarities of the placenta and oral microbiome still raises questions. The bacteria of the placental microbiome play different functional roles when compared to other microbiomes. The roles of oral bacteria are in connection with carbohydrate, and amino acid metabolism, and the placental bacteria are enriched with genes regulating tryptophan, fatty acid metabolism, and benzoate degradation. Tryptophan metabolism is involved in the neurodevelopment in the fetus and the maintenance of feto-maternal tolerance, placental circulation, and antimicrobial activity. The fatty acids supply the energy for the fetus, and benzoate is considered a carbon source for many microorganisms [46].

Amos et al. proposed standardization of microbiome analysis methodologies as extremely important for the knowledge and correct description of microbial populations in the microbiome. To differentiate the microbial population of the host organism from the degree of exogenous bacterial contamination, they proposed a series of reference reagents produced by the National Institute for Biological Standards and Control (NIBSC) for microbiome analysis by DNA sequencing, as international reference reagents of the World Health Organization [48].

PRETERM BIRTH AND MATERNAL MICROBIOME

Premature birth continues to be an important element of public health due to the high rate of perinatal morbidity and mortality [5]. However, the etiopathogenic mechanisms underlying PTB have not been elucidated, with approximately 50% being idiopathic and 30% associated with premature rupture of membranes (PPROM) [49].

Chorioamnionitis is frequently associated with premature birth and is most likely caused by an increase in the germs of the vaginal flora with a placental pro-inflammatory effect. The inflammatory reaction caused by prostaglandins and cytokines in chorioamnionitis is the trigger for uterine contractions and local changes in cervical collagen. Steel et al. revealed that the presence of bacteria is common in most preterm tissues and not sufficient to cause preterm labor or PPRM, unrelated to delivery mode [50].

In the cervix, the production of cytokines IL-6 and IL-8 can be reduced by the use of corticosteroids, without influence on soluble E-cadherin level [51]. Currently, the role of the microbiome is related to the inflammatory aspects that can occur in addition to PTB, intrauterine growth restriction, and fetal deaths in utero [52].

Romero et al., in a case-control study showed by techniques based on 16S RNA gene sequencing on the composition of vaginal microbiome taxa that there were no differences between pregnant women who delivery at term and prematurely [20]. Kacerovsky et al. presented a possible explanation in PPRM of the association of high levels of *L. crispatus* in the cervical microbiota with a low risk of intraamniotic complications and a low rate of early neonatal sepsis [53].

Arbolea et al. revealed that the microbiome of the premature newborn is less diversified compared to that of the full-term newborn. These differences may be due to lack of exclusive breastfeeding, admission to the NICU and sterile isolators, and antibiotic treatment [54].

Baker et al., in case of preterm infants, identified low levels of strict anaerobes (*Bifidobacterium*, *Bacteroides*, and *Atopobium*) and elevated levels of facultative anaerobic microorganisms. In addition, larger amounts of pathogenic bacteria such as *Klebsiella*, *Enterobacteriaceae*, *Clostridium*, *Streptococcaceae* have been identified in the microbiota of the premature newborn [55]. Other studies showed a significant similarity between the placental microbiota and that of the newborn meconium [26,56].

Another possible influence in PTB can be given by the microbiome determined by the oral, gastrointestinal, vaginal triangle [20].

The dissemination of oral pathogenic bacteria in periodontitis is a factor causing adverse outcomes of pregnancy (fetal loss, preeclampsia, preterm birth, low birth weight, fetal growth restriction). The dissemination is done by a hematogenous spread of the bacteria or the inflammation mediators or colonization from the vaginal microbiome [33]. The amniotic fluid of women with preterm birth includes disseminated oral bacteria, and the presence of periodontal disease carries a 7-fold increased risk of preterm birth [57].

Several bacteria have been identified in PTB-associated infections, such as: *Ureaplasma urealyticum*, *Mycoplasma hominis*, *Bacteroides spp.* and *Fu-*

sobacterium nucleatum, the latter being a cofactor in the colonization of other potentially pathogenic organisms (*Escherichia coli*) [58].

CONCLUSIONS

The microbe of the newborn is acquired during birth and postpartum through a possible uterine colo-

nization in which the involvement of the placental microbiome has not yet been proven to have a predominant role. The connection between the maternal microbiome at all levels (oral, intestinal, vaginal, and possibly placental) and the immune system is different depending on the mode of birth, the time of birth; many studies demonstrating the role of the maternal microbiome in the mechanisms of premature birth.

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