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Maternal microbiome and the impact in pre- and post-natal life

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Abstract

The maternal organism, including the microbiome of the oral cavity, vaginal and intestinal microbiome, influences the risk of pregnancy outcomes related to fetal health even after birth.

Recent research reveals that it is not only the vaginal cavity, blood circulation, placenta or amniotic fluid that contain bacteria. While the interaction of bacteria or their metabolites with the fetus or newborn has serious consequences by causing diseases or malformations. An alternative for women undergoing cesarean section is vaginal seeding, a practice that involves transferring vaginal fluids into the body of the newborn. The purpose is to provide beneficial maternal bacteria to babies.

Moreover, factors such as probiotics, oral hygiene and nutrition have been shown to influence the microbiome. The consumption of antibiotics during the gestational stage could lead to preterm delivery due to deficiency of the maternal gut microbiome. Some hypotheses suggest alterations in neurodevelopment, for example, in thalamocortical axonogenesis, where its deficiency is related to decreased limb sensitivity.

Research on the bacterial 16S rRNA sequence comparison makes it possible to establish phylogenetic relationships between prokaryotic organisms; this new identification method uses the 16S rRNA polyribonucleotide, makes it possible to distinguish individual bacteria, especially in the case of difficult ones. It consists of 3 steps: gene amplification from the sample, nucleotide sequence determination, and sequence analysis. As a result, it has been discovered that the fetus does not grow in a sterile environment.

Key words: Microbiome; Genetics; Fetus Development; Alterations; Vaginal Seeding.

1. Introduction

The human microbiome is the community of microorganisms that live on and in the human body, consists of upwards of 100 trillion cells, which outnumber human cells by a factor of ten and collectively contain 27 times more genes than the human genome [1]. The human microbiome comprises bacteria, viruses, fungi, protozoans, and archaea, which colonize primarily the gastrointestinal tract, but also the airways and the skin surface from the first days of life and gradually develop and diversify concomitantly with the physiological growth of the individual. The resident microbial communities in the human gut and other organs have been shown to modulate both the innate and acquired immune responses [2]. The maternal microbiome is recognized as a key determinant of a range of important maternal and child health outcomes, and together with perinatal factors influences the infant microbiome [1].

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Throughout pregnancy, diet, medications, weight gain, and smoking influence the maternal gut, vaginal and oral cavity microbiome, which may be related to complications such as preeclampsia and other diseases. Therefore, alterations in the gut microbiome during pregnancy are likely to have secondary effects that could play a role in the development of pregnancy-related diseases and important consequences for maternal and infant health [3].

1.1. Bacteria transmission of the mother to fetus

The comparison of 16S rRNA sequences allows phylogenetic relationships between prokaryotic organisms to be established. This fact has had an enormous impact on bacterial taxonomy, giving rise to the current classification system and allowing the rapid and accurate identification of bacteria, including those that are part of the microbiome. With the discovery of 16S rRNA sequencing (a rapid bacterial identification technique), the belief that the fetus grows in a sterile field was discarded because amniotic fluid, umbilical cord blood and fetal membranes are known to contain bacteria. This technique consists of analyzing the 16S rRNA macromolecule that is present in all bacteria, whose objective is the identification of strains that are difficult to isolate or cultivate, as well as to identify with commonly used methods, and it is also used for the discovery of new bacteria that do not biochemically match the characteristics of already known genera. Sequencing includes three stages: a) gene amplification from the sample, b) determination of the nucleotide sequence and c) sequence analysis, and then a phylogenetic tree is made to compare the differences and similarities between bacteria [4]. Relating to the method of identification of the bacteria that make up the maternal microbiome, different hypotheses are put forward to explain how the bacteria or their waste products are transmitted to the fetus. The first hypothesis stated that bacteria from the maternal intestine are picked up by dendritic cells and then migrate to the fetus through the blood. Similarly, a second hypothesis refers to intermammary transfer whereby breast milk transfers large amounts of micronutrients, macronutrients, immune factors and microbiota. A third theory called retrograde flow transfer mentions that microbiota from the maternal skin, the fetal oral cavity and the environment enter the mammary gland and thus transfer bacteria [5].

In addition, the maternal gut microbiome produces fatty acids, these molecules are passively and actively transferred into the bloodstream to the fetus. Moreover, on the membrane surface of the syncytiotrophoblast there are ATP-binding cassettes that are responsible for the bidirectional flow of metabolites that are produced by the maternal gut microbiome [6].

1.2. How does the probiotics contribute on the maternal microbiome

Various probiotic products claim to support the health of gut microbiome. Meanwhile, other areas of the body where bacteria and microorganisms also reside, such as the vaginal microbiome, have a significant impact on the future well-being of the fetus [7].

Although research is still limited, studies have explored the use of probiotics during pregnancy as a strategy to enhance the maternal microbiome, potentially offering benefits for both the mother and fetus. Rutten and his team analyzed 341 mothers who reported consuming probiotics during pregnancy and compared them with 2150 mothers who had not used them. They found no difference in the incidence of respiratory and gastrointestinal infections in infants during their first year of life. On the other hand, [8] conducted a randomized controlled trial in which they administered probiotic milk or placebo to pregnant and lactating women, evaluating the development of atopic dermatitis in their children up to two years of age.

Research in rodents has shown that the administration of probiotics to mothers can offer several benefits to their offspring, such as preventing hypertension and cardiovascular problems, reducing respiratory inflammation caused by environmental pollution, stimulating intestinal and brain development, and exerting anxiety-relieving effects [3].

Studies indicate that most probiotic strains, including *Lactobacillus* and *Bifidobacterium*, are generally safe for long-term use. Nonetheless, some researchers are examining whether excessive intake of probiotic supplements could facilitate the transfer of resistance genes to infectious pathogens, heighten antibiotic resistance, and result in other negative health impacts [9].

1.3. Maternal Oral Cavity Microbes

The poor oral health in mothers is associated with an increased risk of preterm labor, preeclampsia and low birth weight for gestational age babies. Factors such as diet, smoking, immune system responses and oral hygiene impact both the microbiome and oral health. Also, areas with dental plaque and inflammation, including gingivitis and periodontitis, may contain up to one billion bacteria of more than 500 different species, which could influence the development of these fetal diseases [10].

About 60% to 75% of pregnant women have gingivitis; the disease occurs when the gums become red and swollen from inflammation that may be aggravated by changing hormones during pregnancy. If the inflammation is not treated, the gums can become infected and increase the risk of this fetal disease. Although the contribution of periodontitis to the development of fetal disease has not been fully determined, there is evidence that it could be the cause of preterm birth and low birth weight [11].

1.4. Allergy and asthma risk development

An appropriate gut microbiome and its intestinal metabolites are a protective factor for asthma development. The main factors involved in the development of allergic disease and asthma include psychosocial stress, consumption of unpasteurized cow's milk, farm environment, antibiotic use and dietary fiber. At birth, transmission of maternally derived bacteria likely leverages this in utero programming to accelerate postnatal transition from a T_H2- to T_H1- and T_H17-dominant immune phenotype and maturation of regulatory immune mechanisms, which in turn reduce the child's risk of allergic disease and asthma [12].

The microbiota interacts with the innate and adaptive defenses of the host's intestinal mucosal immune system, through these mechanisms it drives the differentiation of regulatory cells in the intestine, which is essential to maintain immune tolerance. In this sense, the microbiota can activate different tolerogenic dendritic cells in the intestine and, through this interaction, drive the differentiation of regulatory T cells. It is also important to mention that the microbiota drives TH1 cell differentiation, which corrects the TH2 immune skewing that is thought to occur at birth. If proper immune tolerance is not established early in life and is not maintained throughout life, this could represent a risk factor for the development of inflammatory, autoimmune and allergic diseases [13].

1.5. The endometrial microbiome on pregnancy

Lactobacillus delbrueckii and *Lactobacillus rhamnosus* modulate immune tolerance in early pregnancy by dampening lipopolysaccharide-induced expression of HLA-DR, CD86, CD80, CD83, and IL-12 from human dendritic cells. Pregnancy studies had demonstrated that the decremented endocervical and endometrial bacterial diversity of lactobacillus are enriched with pathogens, generating a local inflammation mediated by an immune response associated with disease states in woman [14].

A study examined the endometrial and vaginal microbiota of 47 women who had experienced two or more consecutive miscarriages; of these, 36 cases were classified as unexplained recurrent pregnancy loss (RPL). The findings revealed that, in patients with RPL, *Lactobacillus crispatus* was significantly less prevalent, while *Lactobacillus jensenii* and Gardnerella vaginalis were more abundant compared to the control group. No notable differences were observed in the presence of *Escherichia coli*, *Blautia spp.*, or *Faecalibacterium spp.*: *Lactobacillus iners*, however, emerged as the predominant endometrial bacterium in RPL patients. Furthermore, the fungal analysis indicated that *Candida parapsilosis* was exclusively found in the endometrial samples of RPL patients, with an average relative abundance of 18.2% [15].

1.6. Gut microbiome alterations over different diseases

The maternal gut microbiome changes drastically when antibiotics are administered, which affects the newborn with an early onset of sepsis or at least increased susceptibility. A study by Zhou Ping [16] showed that after administration of antibiotic treatment the load and diversity of lactobacillus decreased, and this was associated with a higher risk of preterm birth. On the other hand, the high-fat diet is associated with necrotizing enterocolitis and increased inflammation [17].

Deficiency of the maternal gut microbiome suggests alterations in thalamocortical axonogenesis related to reduced limb sensation. Therefore, this hypothesis posits that a decrease in maternal gut bacteria alters proper brain development and behaviors in offspring [18].

1.7. Benefits on the vertical transfer over the cesarean section

Vaginal seeding is the practice of transferring vaginal fluids to a newborn's mouth, nose, or skin using a swab or gauze. The purpose is to provide beneficial maternal bacteria to infants, especially those born by cesarean. This method is believed to help with gut colonization, possibly reducing the infant's chances of developing asthma, allergies, and immune-related conditions later [19]. According to recent research babies born by vaginal delivery tend to get more protective microbiome and different immune development that is protective against multiple diseases. The results to improve microbiome was performing a "vaginal seeding" aims to make the microbiomes of the skin and intestine of newborn babies by cesarean section resemble those of babies born vaginally [7].

The Fecal transplantation, also known as fecal microbiota transplantation (FMT), stool transplant, bacteriotherapy, or intestinal microbiota transplant, is a procedure that involves collecting stool from a healthy donor and transferring it into a patient's digestive system [20].

The main reason of the clinical trial was done this way is to test if vaginal seeding decreases the risk of obesity in children, but the main limitation is the number of children needed and the length of follow-up time required, so the conclusion was made its first in an animal model [7].

2. Conclusion

The diversity of maternal microorganisms is key in the development of the embryo and the newborn, determining also the health in adulthood and the predisposition to acquire diseases. Factors such as smoking, age, diet, probiotic consumption and antibiotic use, as well as oral and vaginal cavity hygiene, influence the composition of the maternal microbiome.

The development of allergic diseases and asthma is mainly associated with maternal exposure to stress, consumption of unpasteurized cow's milk and the farm environment. On the other hand, antibiotic consumption mediates increased susceptibility to the development of sepsis in the fetus. Also, deficiency of diversity in the maternal microbiome is associated with impaired development of thalamocortical axonogenesis, with consequent lack of sensitivity and behavioral problems.

Although research has not yet been able to determine with certainty the mechanism of interaction between the maternal microbiome and the development of disease, the discovery of 16S rRNA sequencing has determined that amniotic fluid, umbilical cord blood and fetal membranes contain bacteria, which explains the alterations in the offspring.

In addition, while significant progress has been made in understanding the role of the maternal microbiome in fetal and newborn development, there remain gaps in fully elucidating the mechanisms involved. The discovery of bacteria in traditionally considered sterile environments opens new avenues for research. These findings underscore the need for further studies to clarify the complex interactions between maternal microorganisms and long-term health outcomes in offspring. Advancing our knowledge in this area could open a way for new preventative strategies and therapeutic interventions aimed at optimizing maternal and child health.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

References

- [1] Dunlop, A. L., Mulle, J. G., Ferranti, E. P., Edwards, S., Dunn, A. B., & Corwin, E. J. Maternal Microbiome and Pregnancy Outcomes That Impact Infant Health [Internet]. Atlanta: The National Association of Neonatal Nurses; 2015 [cited 2024 Nov 07]. Available from: https://journals.lww.com/advancesinneonatalcare/abstract/2015/12000/maternal_microbiome_and_pregnancy_outcomes_that.4.aspx
- [2] Peroni, D. G., Nuzzi, G., Trambusti, I., Di Cicco, M. E., & Comberiati, P. Microbiome Composition and Its Impact on the Development of Allergic Diseases [Internet]. Switzerland: Frontiers; 2020 [cited 2024 Nov 07]. Available from: <https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2020.00700/full>
- [3] Sinha, T., Brushett, S., Prins, J., & Zhernakova, A. The maternal gut microbiome during pregnancy and its role in maternal and infant health [Internet]. Netherlands: Elsevier; 2023 [cited 2024 Nov 07]. Available from: <https://pubmed.ncbi.nlm.nih.gov/37068462/>
- [4] Del Rosario, Del Carmen. Bacterial identification by 16S rRNA sequencing: rationale, methodology and applications in clinical microbiology. Edition (Volume 22, Issue 4). Netherlands: Elsevier; 2024.
- [5] Tian M, Li Q, Zheng T, Yang S, Chen F, Guan W, Zhang S. Maternal microbe-specific modulation of the offspring microbiome and development during pregnancy and lactation. [Internet]. Bethesda, Maryland: National Library Of Medicine; 2023 [cited 2024 Nov 07]. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC10187089/>

- [6] Ruiz-Triviño J, Álvarez D, Cadavid J ÁP, Alvarez AM. From gut to placenta: understanding how the maternal microbiome models life-long conditions. [Internet]. Switzerland: Frontiers; 2023 [cited 2024, Nov 07]. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC10754986/>
- [7] Levy B, Anindita R, Valera D, Glim M, Szatmary A, Martingano J A, Baxevanis A, Abraham A, LoVette A, Cámaras B. Moms' microbes may influence babies' future health. [Internet]. National Institutes of Health: NIH; 2024 [cited 2024, Nov 07]. Available from: https://irp.nih.gov/blog/post/2024/10/moms-microbes-may-influence-babies-future-health?utm_source=linkedin&utm_medium=social&utm_campaign=blog&utm_id=NIH_IRP
- [8] Dotterud CK, Storrø O, Johnsen R, Oien T. Probiotics in pregnant women to prevent allergic disease: a randomized, double-blind trial. Edition (Volume 163, Issue 3). Hoboken, New Jersey: *British Journal of Dermatology*; 2010.
- [9] Kubala, J., MS, & RD. Should you take probiotics during pregnancy?. [internet]. San Francisco: Healthline; 2021 [cited 2024, Nov 07]. Available from: <https://www.healthline.com/nutrition/probiotics-during-pregnancy>
- [10] Gomez-Arango LF, Barrett HL, McIntyre HD, Callaway LK, Morrison M, Nitert MD. Contributions of the maternal oral and gut microbiome to placental microbial colonization in overweight and obese pregnant women. [Internet]. London: Nature; 2017 [cited 2024, Nov 07]. Available from: <https://pubmed.ncbi.nlm.nih.gov/28588199/>
- [11] CDC. Talking to Pregnant Women about Oral Health. [internet]. [cited 2024, Nov. 07]. Available from: <https://www.cdc.gov/oral-health/hcp/conversation-tips/talking-to-pregnant-women-about-oral-health.html>.
- [12] Gao, Y., Nanan, R., Macia, L., Tan, J., Sominsky, L., Quinn, T. P., O'Hely, M., Ponsonby, A.-L., Tang, M. L. K., Collier, F., Strickland, D. H., Dhar, P., Brix, S., Phipps, S., Sly, P. D., Ranganathan, S., Stokholm, J., Kristiansen, K., Gray, L. E. K., & Vuillermin, P. The maternal gut microbiome during pregnancy and offspring allergy and asthma. (Volume 148, Issue 3). Milwaukee, Wisconsin: *The Journal of Allergy and Clinical Immunology*, 2021.
- [13] McLoughlin R, Mills K. Influence of gastrointestinal commensal bacteria on the immune responses that mediate allergy and asthma [Internet]. Milwaukee, Wisconsin: *Journal of Allergy and Clinical Immunology*; 2011 [Cited 2024, Nov 07]. Available from: [https://www.jacionline.org/article/S0091-6749\(11\)00274-0/full](https://www.jacionline.org/article/S0091-6749(11)00274-0/full)
- [14] Joshua Odendaal, Naomi Black, Phillip R Bennett, Jan Brosens, Siobhan Quenby, David A MacIntyre. The endometrial microbiota and early pregnancy loss. *Human Reproduction*; 2024 Edition (Volume 39, Issue 4). United Kingdom: Oxford Academic; 2024.
- [15] Annalisa Inversetti, Enrica Zambella, Alice Guarano, Marinella Dell'Avanzo, Nicoletta Di Simone. Endometrial Microbiota and Immune Tolerance in Pregnancy [Internet] MDPI: *International Journal of Molecular Sciences*; © 2023 [cited 2024 Nov 11]. Available from: <https://doi.org/10.3390/ijms24032995>
- [16] Zhou P, Zhou Y, Liu B, Jin Z, Zhuang X, Dai W, Yang Z, Feng X, Zhou Q, Liu Y, Xu X, Zhang L. Perinatal Antibiotic Exposure Affects the Transmission between Maternal and Neonatal Microbiota and Is Associated with Early-Onset Sepsis. Edition (Volume 5, Issue 1). Washington D.C: American Society for microbiology; 2020.
- [17] Babu, S. T., Niu, X., Raetz, M., Savani, R. C., Hooper, L. V., & Mirpuri, J. (2018). Maternal high-fat diet results in microbiota-dependent expansion of ILC3s in mice offspring. [Internet]. Ann Arbor, Michigan: *JCI Insight*; 2018 [cited 2024, Nov 07]. Available from: <https://doi.org/10.1172/jci.insight.99223text>
- [18] Helen E. Vuong, Geoffrey N. Pronovost, Drake W. Williams, Elena J. L. Coley, Emily L. Siegler, Austin Qiu, Maria Kazantsev, Chantel J. Wilson, Tomiko Rendon & Elaine Y. Hsiao. The maternal microbiome modulates fetal neurodevelopment in mice. [Internet]. London: Nature; 2020 [cited 2024, Nov 07]. Available from: <https://doi.org/10.1038/s41586-020-2745-3>
- [19] Kurt R. Wharton, MD, and Meredith L. Birsner, MD. Vaginal Seeding. Edition (Volume 130, Issue 5). Washington D.C: The American College of Obstetricians and Gynecologists ACOG; 2017.
- [20] The Johns Hopkins University. Fecal transplant. [Internet]. Maryland: Johns Hopkins Medicine; 2024 [cited 2024, Nov 07]. Available from: <https://www.hopkinsmedicine.org/health/treatment-tests-and-therapies/fecal-transplant>.