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Clinical Applications of the Microbiome in Obstetrics

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ABSTRACT

Human microbiome refers to the genetic material of approximately 10^{13} microorganisms present in the human body. These microbiomes interact significantly with the physiological, metabolic, and immune systems, particularly during pregnancy. Microbiome dysbiosis in pregnant women and their fetuses is associated with obstetric complications and poor neonatal outcomes. Oral and gut microbiomes can influence the placenta, uterus, and fetus via hematogenous translocation. Through ascending translocation, vaginal microbiota can directly affect the uterine environment. Current research focuses on the presence of the placental microbiome, which is characterized by low biomass. However, more well-controlled studies are required to specifically address the contamination issues. Use of antibiotics during pregnancy and the mode of delivery, specifically cesarean section, have been linked to the establishment of the neonatal gut microbiome. Probiotic supplementation may be beneficial during pregnancy, particularly for women receiving antibiotic treatment.

Key Words: Microbiota; Obstetrics; Complication; Placenta; Probiotics

INTRODUCTION

Microbiome, which is distributed throughout the gastrointestinal, reproductive, respiratory, oral, and integumentary systems, plays crucial roles in genetic diversity, immune interactions, responses to pharmaceuticals, and metabolic regulation. Consequently, it is often referred to as the "second" or "forgotten" organ[1,2]. The microbiome community can be influenced and modified by alterations in the physiological state of the host. During pregnancy, women experience various physiological changes that affect their microbiome composition. Analysis of the neonatal meconium at birth indicates the presence of a microbiome in the fetal gastrointestinal tract during the prenatal period. Examination of maternal feces, placenta, amniotic fluid, and neonatal meconium revealed shared microbial characteristics, implying maternal–fetal transmission[3,4]. Furthermore, the composition of the

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vaginal microbiome differs between non-pregnant and pregnant women, and dysbiosis of the microbiome is correlated with obstetric complications[5,6]. Pregnancy alters the microbiomes of the maternal oral cavity, gastrointestinal tract, and reproductive system, which play a key role in determining the pregnancy outcomes and composition of the neonatal microbiome. Therefore, this comprehensive review aimed to scrutinize the use and potential benefits of the microbiome in obstetrics.

MATERNAL MICROBIOME AND PREGNANCY OUTCOMES

1. Oral microbiome

Changes in hormonal, metabolic, and immunological statuses during pregnancy influence the oral microbiome composition. Increase in the abundance of pathogenic microbiota, such as *Prevotella*, *Streptococcus*, and *Veillonella*, increases the susceptibility to gingivitis[7]. Additionally, periodontal disease during pregnancy is associated with obstetrical complications, such as preterm birth (relative risk [RR], 1.6; 95% confidence interval [CI], 1.3 to 2.0), low birth weight (RR, 1.7; 95% CI, 1.3 to 2.1), and preeclampsia (RR, 2.2; 95% CI, 1.4 to 3.4)[8]. Increase in the abundance of Porphyromonas gingivalis in the oral microbiome is associated with a high risk of threatened preterm labor (odds ratio [OR], 1.8; 95% CI, 1.0 to 3.5) and preterm birth (OR, 2.5; 95% CI, 1.1 to 6.3), whereas an increase in the abundance of Prevotella intermedia has been linked to preeclampsia[9,10]. Furthermore, a study analyzing oral microbiomes in pregnant women with gestational diabetes mellitus (GDM) reported a positive correlation between *Neisseria* and *Leptotrichia* abundance and blood glucose levels[11]. The association between periodontal disease and adverse pregnancy outcomes may be due to the hematogenous transmission of pathogens and transfer of inflammatory mediators generated by immune responses to these microbiomes[12].

2. Gastrointestinal microbiome

During pregnancy, significant changes occur in the gastrointestinal functions that support fetal growth. These changes involve hormonal, immune, and metabolic adaptations, which may alter the composition and activity of the gut microbiome compared to those in non-pregnant women[13]. During the first and third trimesters of pregnancy, *Proteobacteria* and *Actinobacteria* proportions increase, whereas species richness of the gut micro-

biome decreases. These compositional changes in the third trimester are believed to be caused by hormonal fluctuations and alterations in the immune system at the intestinal mucosal surface[14]. Progesterone levels increase as pregnancy progresses and are associated with an increase in *Bifidobacterium* spp. abundance. The specific composition of the gut microbiome plays a crucial role in the breakdown of breast milk-derived host indigestible human milk oligosaccharides, which are essential for infant development[15]. Thus, the gut microbiome undergoes remodeling during pregnancy to adapt to the physiological and anatomical changes, aiding in the establishment of the gut microbiome at the newborn and infant stages. Furthermore, *Bifidobacterium* promotes the neurocognitive development of preterm infants[16].

GDM is the most common pregnancy complication that can progress to obesity, type 2 diabetes, and metabolic syndrome. GDM is associated with a decrease in the abundances of *Bifidobacterium* and *Faecalibacterium* species and an increase in the abundances of *Bacteroides, Lachnospiraceae, Enterobacteriaceae, Ruminococcaceae, Collinsella,* and *Eggerthella* species[17]. A recent study aimed to achieve the early diagnosis of GDM by analyzing the clinical records, cytokine profiles, and characteristics of the gut microbiota. This study reported a negative correlation between *Prevotella copri* abundance and the occurrence of GDM. Based on this finding, a machine learning model was used to effectively predict GDM in the first trimester of pregnancy (area under the receiver operating characteristic curve, 0.83)[18]. Therefore, gut microbiota can serve as a useful biomarker for predicting GDM. Gestational hypertension is the leading cause of maternal mortality. Analysis of the gut microbiota of pregnant women with preeclampsia revealed dysbiosis and reduction in bacterial diversity. In particular, the abundance of opportunistic pathogens, such as Fusobacterium and *Veillonella,* increased, whereas that of beneficial species, such as *Faecalibacterium* and Akkermansia, decreased. The abundance of these pathogenic microbiota increases in the placenta of preeclamptic women, indicating the potential translocation of gut microbiota to the placenta. Consequently, the increase in placental inflammation mediated by microbiota suggests its involvement in the pathogenesis of preeclampsia[19]. Bacterial infections and the resulting inflammatory responses are significant causes of preterm labor and premature rupture of membranes[20]. Gut microbiota has been identified in the amniotic fluid and vaginal samples, suggesting that increased gut permeability allows the translocation of microbiota through

the bloodstream to the vagina. This translocation leads to changes in the vaginal microbiota, such as an increase in the abundances of *Prevotella, Peptoniphilus, Dialister* spp., and *Streptococcus.* proportions. These changes eventually induce inflammation in the placenta and membranes, leading to preterm labor[21,22].

3. Vaginal microbiome

In healthy women of reproductive age, the vaginal microbiome is predominantly composed of *Lactobacillus* spp., including *Lactobacillus iners, Lactobacillus crispatus, Lactobacillus gasseri,* and *Lactobacillus jensenii*. These lactobacilli maintain an acidic vaginal pH (3.8 to 4.4) and produce lactic acid, bacteriocins, and hydrogen peroxide, thereby providing a protective barrier against genital infections[23].

Furthermore, dysbiosis, characterized by a reduction in *Lactobacillus* species abundance, is associated with implantation failure in women undergoing assisted reproductive techniques[24]. During pregnancy, the vaginal microbiome undergoes changes characterized by decreased species diversity and richness, with a dominance of *Lactobacillus* spp. This shift towards a *Lactobacillus*-dominant composition during pregnancy enables the vaginal microbiome to maintain a relatively stable and balanced state compared to that in non-pregnant women[5,25].

A recent meta-analysis indicated that women with a vaginal microbiome composition characterized by low levels of *Lactobacilli* with higher proportion of *L. jensenii* related a higher risk of preterm birth compared to those with a dominant presence of *L. crispatus* (OR, 1.69; 95% CI, 1.15 to 2.49)[26]. Additionally, *L. iners* was the predominant species in Korean women who experienced miscarriages, accounting for 76.0% of their vaginal microbiome composition[27]. In cases of preterm premature rupture of membranes, an increase in the diversity of the vaginal microbiome was observed along with dysbiosis, characterized by an increase in the abundance of pathogenic bacterial species, including *L. iners, Gardnerella vaginalis, Prevotella bivia, Ochrobactrum, Prevotella timonensis,* and *Ureaplasma parvum* spp.[28].

In a recent study examining the microbiome during labor in cases of preterm premature rupture of membranes, some taxa, including *Escherichia, Shigella,* and *Facklamia,* were associated with an increased risk of early onset neonatal sepsis. Additionally, administration of ampicillin and macrolide antibiotics is associated with a reduction in the abundance of *Lactobacillus* spp., which play a preventive role and increase the microbial diversity, indicating that antibiotics may disrupt the vaginal microbiome

balance[29]. Therefore, dysbiosis of the vaginal microbiome is associated with various pregnancy complications, such as miscarriage, preterm birth, and preterm premature rupture of membranes, indicating a link between the vaginal microbiome and inflammatory state of pregnant women.

4. Placental microbiome

Placenta, traditionally considered a sterile tissue, has been found to harbor a microbiome through advancements in culture techniques and metagenomic analyses[4,30,31]. The presence of similar microbiomes in the placenta, amniotic fluid, and meconium supports the feto–maternal interface hypothesis, suggesting potential colonization of the oral or gut microbiota in the placenta and fetus[4]. Aagaard et al.[31] reported that the placental microbiome consists of commensal microorganisms from phyla, such as *Firmicutes, Tenericutes, Proteobacteria, Bacteroidetes,* and *Fusobacteria*. It is characterized by low bacterial density or enrichment with metabolically active microbial communities. In healthy pregnant women, the placental microbiome exhibits greater similarity to the oral microbiome[31].

However, a study that analyzed the bacterial 16S ribosomal gene using multiple variable (V) region genomic DNA sequencing and divided the placenta into three parts, namely the basal plate, placental villous tissue, and fetal membrane, found different microbial profiles. *Ralstonia insidiosa* and *Mesorhizobium* spp. were predominantly detected in the basal plate and placental villous tissue, whereas *L. crispatus, L. iners,* and *Ureaplasma nucleatum* spp. were most abundant in the fetal membrane. Notably, the presence of these microbial taxa in the fetal membrane suggests a potential origin of the vaginal microbiota[32].

A recent meta-analysis indicated that *Lactobacillus,* commonly found in the typical vaginal microbiota, has raised concerns regarding its potential for contamination in placental microbiome analysis during vaginal delivery. Additionally, cases of preterm birth and premature rupture of membranes in pregnant women demonstrate an increase in the abundance of pathogenic microbiota, such as *Ureaplasma, Fusobacterium, Mycoplasma, Streptococcus,* and *Enterococcus*[33]. This suggests that infection may influence the placental microbiota composition. Additionally, when analyzing placental microbiota with low biomass, it is crucial to effectively manage the potential confounding effects of other microbiota to ensure accurate results.

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5. Breast milk microbiome

Traditionally, breast milk has been considered as a sterile fluid. However, these perceptions have shifted owing to the detection of microbiomes, such as Lactobacillus, *Lactococcus,* and *Bifidobacterium.*

Breast milk microbiome is influenced by the mother's diet, health, body mass index, medication intake, and delivery methods of the mother. Therefore, the established breast milk microbiome influences the diversity of the neonatal gut and oral and respiratory tract microbiomes, maintains intestinal immune homeostasis, and contributes to preventing microbiome dysbiosis. Nonetheless, further research is warranted to determine the influence of breast milk on gut microbiome colonization in neonates and infants[34,35].

6. Microbiome and preterm birth

In summary, the maternal microbiota associated with pregnancy includes the oral cavity, gut, vagina, and placental microbiota. Pathogenic oral and gut microbiomes can potentially induce compositional shifts and dysbiosis in the amniotic fluid, placental, and vaginal microbiomes via hematogenous translocation (hematogenous pathway). Moreover, dysbiosis of the vaginal microbiome can directly affect the uterus via ascending translocation. Through these two pathways, inflammation can occur in the placenta and amniotic fluid, ultimately leading to the initiation of preterm labor and potentially culminating in preterm birth.

SPECIFIC CONSIDERATIONS FOR THE MICROBIOME

1. Antibiotics and cesarean section

Intrapartum antibiotic prophylaxis is administered as a preventive measure during the premature rupture of membranes prior to labor, a cesarean section, and when group B *Streptococcus* screening yields positive results before delivery. Based on the administration or non-administration of prophylactic antibiotics, analysis of the infant meconium microbiome revealed a decrease in microbial richness and increase in the diversity of the antibiotic-receiving group over a 3-month period. Additionally, the abundance of *Bacteroidetes* decreased, whereas that of Firmicutes (specifically *Clostridium* and *Enterococcus* genera) exhibited an increased in a previous study[36]. These findings suggest an association between antibiotic use and microbial dysbiosis in pregnant women and their newborns.

In South Korea, cesarean section rate has significantly increased from 26.9% in 2012 to 58.7% in 2021[37]. Newborns are exposed to the microbiome as they pass through the birth canal. Therefore, infants born via cesarean section exhibit differences in microbial development compared with those born via vaginal delivery. These differences in early life microbial programming may contribute to an increased risk of pediatric obesity, asthma, and gastrointestinal disorders and may even impact the lifelong health[38-40]. To address this issue, researchers are currently examining seeding of the maternal vaginal microbiome during cesarean section. However, the practice remains controversial owing to its potential risks[41,42].

2. Probiotics

Composition, diversity, and richness of the maternal microbiome in the reproductive tract are influenced by various factors, such as dietary intake, infections, and antibiotic administration, during pregnancy. These factors play crucial roles in establishing the lifelong gut microbiome of the infant. Imbalances in the gut microbiome during early infancy can have significant implications on their immune responses, susceptibility to pathogenic bacteria, allergic reactions, including atopic diseases, and infectious conditions, such as necrotizing enterocolitis. Recent studies have focused on developing preventive and therapeutic interventions targeting microbial imbalances using probiotics[43].

Use of antibiotics during the perinatal period has significant effects on the composition, diversity, and abundance of the maternal microbiome. Prophylactic administration of antibiotics before a cesarean section is a common scenario. A systematic review analyzing the infant microbiome following cesarean section in women who received probiotics, prebiotics, or synbiotics during pregnancy and lactation revealed similarities in the microbiome of vaginally delivered infants, indicating the beneficial effects of probiotics[44]. Oral probiotics play a regulatory role in modulating the gut microbiome, specifically by modulating the secretion of proinflammatory mediators, thereby mitigating the inflammatory response and reducing the intestinal permeability. Furthermore, they contribute to the regulation of maternal metabolism, leading to decreased blood glucose levels[45].

Many studies have focused on the use of probiotics to prevent and treat GDM. A meta-analysis examining the metabolic outcomes of probiotic supplementation in pregnant women with

GDM revealed a significant reduction in the homeostatic model assessment of insulin resistance (–0.69; 95% CI, –1.24 to –0.14; *P*=0.01). However, no significant effects were observed on fasting blood glucose (mean difference, –0.13; 95% CI, –0.32 to 0.06; *P*=0.18) or low-density lipoprotein cholesterol (–0.16; 95% CI, –0.45 to 0.13; *P*=0.67)[46]. Moreover, probiotic supplementation did not significantly prevent hypertensive disorders in women with gestational diabetes[47]. However, other meta-analyses encompassing studies from 2010 to 2020 reported that probiotic administration could effectively lower metabolic markers, such as blood glucose, lipid profiles, inflammatory markers, and antioxidant markers[48].

A meta-analysis of randomized and cluster-randomized trials assessing probiotic supplementation in GDM found limited evidence for its preventive effects (mean RR, 0.80; 95% CI, 0.54 to 1.20) and even indicated an increased risk of preeclampsia (RR, 1.85; 95% CI, 1.04 to 3.29)[49]. Heterogeneity in the effects of probiotics on GDM may be attributed to the diverse types of probiotic formulations used. Further studies are required to clarify these discrepancies. Deficiency of *Lactobacillus* species can contribute to bacterial vaginosis, which increases the risk of preterm birth. Therefore, oral or vaginal probiotic administration should be considered for correcting vaginal dysbiosis, preventing vaginal infections, and reducing the risk of preterm birth[50]. However, a recent meta-analysis showed that the administration of probiotics or prebiotics does not effectively reduce preterm birth before 37 weeks (RR, 1.08; 95% CI, 0.71 to 1.63)[51]. A meta-analysis and systematic review of randomized placebo-controlled trials on the effects of probiotic supplementation during pregnancy revealed that no increase in adverse obstetric outcomes, complications, or infections, regardless of the duration of probiotic administration. Therefore, probiotic administration during pregnancy is relatively safe[52].

Use of probiotics during pregnancy may help mitigate the dysbiosis caused by antibiotics. However, further investigations are necessary to determine their efficacy in reducing the risk of gestational diabetes, preterm birth, and other pregnancy complications.

CONCLUSION

Balance of maternal microbiota during pregnancy plays a crucial role in reducing the risk of pregnancy complications and is essential for the establishment of early life microbiome in newborns. Additionally, microbiota serves as a valuable biomarker for predicting and diagnosing adverse pregnancy outcomes, and correcting dysbiosis opens up various therapeutic approaches.

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None

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