Influence of Maternal Microbiome in Preterm Birth

Subjects: Obstetrics & Gynaecology

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Preterm birth (PTB) is a global health issue and one of the most challenging problems affecting 12.9 million births worldwide. PTB is a multi-etiological disease and remains incompletely understood.

preterm birth microbiota

1. Vaginal Microbiome and Preterm Birth

During pregnancy, feto-maternal tolerance regulates the maternal immune response between anti-inflammatory and proinflammatory states. If this balance is disrupted by ascending microorganisms, the maternal immune system changes and leads to preterm labor [1]. It has been observed that the complexity and diversity of the vaginal microbiome increases with PTB, whereas the vaginal microbiome is less complex and less diverse in normal pregnancy. As mentioned before, the complement system plays an important role in normal pregnancy, therefore, complement activation leads to the chemotactic recruitment of immune cells including macrophage and dendritic cells involving PTB [2]. PTB is also related to proinflammatory cytokine profiles such as IL-1β, IL-6, macrophage inflammatory protein (MIP)-1β, and eotaxin [3]. Park et al. [4] investigated the roles of cytokines in the cervicovaginal fluid as predictive markers of PTB. MIP-1α, MIP-1β, IL-6, IL-7, and IL-17α in the cervicovaginal fluid were associated with PTB and IL-6, and IL-17α had a higher sensitivity than the fetal fibronectin test.

Previous studies showed that *Lactobacillus iners* was associated with an increased risk of PTB despite the differences depending on ethnicity, whereas *Lactobacillus crispatus* showed a protective effect against PTB in all ethnicities [5][6]. In addition, the dominant population of *Lactobacillus iners* around 16 gestational weeks was closely related to the increased risk of shortening of the cervix and PTB before 34 gestational weeks [7]. As well as *Lactobacillus* spp., bacterial vaginosis-associated bacteria including *Gardnerella vaginalis, Atopobium vaginae, and Veillonellaceae bacterium* were associated with an increased risk of PTB before 34 gestational weeks [3]. Son et al. [8] investigated the comparisons of obstetrical outcomes according to the vaginal microbiota grouped by trimester. Abnormal vaginal microbiota, especially the presence of *Klebsiella pneumonia,* in the 2nd trimester was associated with a significant increase in PTB before 28 weeks.

Results of recent studies between the vaginal microbiome and PTB are presented in **Table 1**. Molecular-based new technologies have been applied to take advantage of the new information about the role of the vaginal microbiota in spontaneous labor and PTB. However, the current evidence is still limited, and clinical data have poor quality and results are controversial. Recently, most of the studies have demonstrated an association between the

composition of the vaginal microbiota and PTB (**Table 1**). The more recently published studies provide evidence of an association between a dysbiotic microbiota and PTB, especially the role of *L. iners* in vaginal eubiosis and dysbiosis.

Table 1. Recent studies between Vaginal Microbiome and Preterm Birth.

	Condition Studied	Summary
2019 Fettweis et al. [3]	45 preterm and 90 term birth controls	Preterm-delivered women had significantly lower vaginal levels of *Lactobacillus crispatus* and higher levels of *Sneathia amnii*, and *Prevotella* species.
2018 Freitas et al. [9]	46 preterm and 170 term birth controls	The preterm-delivered women had increased richness and diversity and higher *Mycoplasma* or *Ureaplasma* prevalence.
2017 Callahan et al. [10]	Low risk for PTB: predominantly Caucasian (*n* = 39) high-risk for PTB: predominantly African American (*n* = 96)	*Lactobacillus crispatus* was related to low risk of PTB, while *Lactobacillus iners* and *Gardnerella vaginalis* had association with PTB.
2017 Stafford et al. [11]	No preterm labor group (*n* = 121), preterm labor group (*n* = 41)	The microbiome of women who experienced PTB showed 2-fold lower community state type (CST) I-dominated microbiota at 20–22 weeks. CST V was 2-fold higher in the preterm-delivered women compared to term-delivered women.
2017 Stout et al. [12]	Nested case-control study, 24 cases and 53 controls	The vaginal microbiome demonstrated decreased vaginal richness and Shannon diversity in preterm delivery. [15]
2016 Nelson et al. [13]	Nulliparous African American women, 13 preterm and 27 term birth controls	Decreased bacterial diversity with lower abundance of *Coriobacteriaceae*, *Sneathia*, *Prevotella*, and *Aerococcus* were found in preterm delivery. [16]
2014 Romero et al. [14]	Nested case-control study, 18 cases and 72 controls	As pregnancy progressed, four *Lactobacillus* spp. were increased and anaerobic microbiomes were decreased. [17][18]

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had intermediate or low *Lactobacillus* spp. dominance and high diversity [18]. In another prospective cohort study, the authors reported that reduced *Lactobacillus* spp. abundance and high diversity were shown in about 25% of pregnant women prior to PPROM, but only 3% of women delivered the baby at term without the rupture of membranes [19]. PPROM was associated with changes in the microbiome during pregnancy and a shift toward higher diversity, predominantly occurring during the second trimester, although a vaginal microbiota dominated with any bacterial species rather than *Lactobacillus* was related to subsequent PPROM throughout all of the pregnancy period including during the first trimester [17]. This study also found that the first trimester miscarriage associated with a *Lactobacillus* spp-depleted vaginal microbiome and women who had the risk of miscarriage in the first trimester had a 2-fold increased risk of PTB and 3-fold increased risk of PPROM [20]. This study showed the potential relationship between miscarriage and PPROM and the first trimester microbiome.

2. Endometrial Microbiome in Preterm Birth

The endometrium is the important site where the blastocyst is implanted during pregnancy and is a crucial place, not only for supporting fetal growth by supplying oxygen and nutrients but also for preventing infections to protect the embryo and fetus [21]. During the implantation period, the endometrium undergoes significant morphologic and functional change, which is followed by decidualization, and many immune cells' compositions are altered. The endometrium is not a sterile tissue, and microorganisms at the endometrium interact with the endometrial epithelium and modify immune cell expression and cytokines. This change can affect endometrial receptivity and may impair adequate implantation [22].

As well as implantation, modification of the endometrial immune system during pregnancy has been related to adverse pregnancy outcomes including miscarriage, preeclampsia (PE), FGR, and PTB [23]. A previous study reported a relationship between reduced levels of *Lactobacillus* species in the endometrial microbiota and adverse pregnancy outcome [24]. Interestingly, the endometrial bacterial population was different from the bacterial composition of the vagina but was similar with that of the cervix regarding bacterial load and composition. To date, the role of endometrial microbiota in pregnancy outcomes is not fully understood and much remains to be investigated.

3. Oral-Placental Microbiome in Preterm Birth

The tolerogenic maternal immune response is the most important factor for a healthy pregnancy. Interruption of this state leads to maternal anti-fetal rejection, placental damage, and obstetric complications such as FGR and PTB. The cause of this allograft rejection is either a cellular (T cell) or humoral (antibody) immune response, and severe rejection leads to fetal death akin to graft failure in organ transplantation. The fetal systemic inflammatory is similar to allograft rejection despite the absence of pathogens [25].

The possibility that the microbiome is present in the placental site was suggested [26]. The presence of fetal genital tract microbes colonization in the placenta or amniotic membranes has been thought to result in subclinical infection and a concomitant initiation of labor [27]. It is well known that ascending microbes from the vagina such as *Ureaplasma*, *Mycoplasma*, and GBS species have been related to placental colonization, chorioamnionitis, and PTB. Moreover, oral cavity microbes including *Streptococcus* and *Fusobacterium* spp. are known to contribute to the placental microbiome through hematogenous transfer [28]. Harboring bacteria were found in the placentas from term pregnant women who delivered by sterile cesarean section without infection sign and the amniotic fluid from women who had intact membranes [29]. A previous study reported that the placental microbiome from the vaginal and oral microbiomes was identified at the time of delivery using 16S ribosomal RNA gene sequencing analysis. An increased *Fusobacterium nucleatum*, *Gemella asaccharolytica*, and *Ureaplasma* spp. was found in the fetal membranes, and this is associated with shorter gestation and PTB [30]. A placental microbiome that is similar to the oral cavity, the tonsils and tongue, including *Firmicutes*, *Tenericutes*, and *Fusobacteria*, was found in placentas that were previously undetectable in the microbiome using 16S rRNA sequencing [27].

Even though common oral pathogens were identified in the placenta of women with periodontal disease, which is related to increased risk of PTB, it is not clear if the management of periodontal disease during pregnancy

decreased PTB [31]. There is insufficient information to determine whether periodontal management can prevent preterm birth. Many studies have been performed to reveal the relationship between the existence of an oral-placental microbiome and adverse pregnancy outcomes, but this research area is still controversial.

4. Microbiomes. The Prevention of the PTB

There is evidence to show the relationship between maternal microbiome profiles and increased risk of PTB, therefore, a large number of studies have investigated the effectiveness of antibiotics for the treatment and prevention of PTB. The maternal microbiome including the vaginal, oral-placenta, and gut microbiomes can play important roles in causing preterm birth (**Figure 1**).

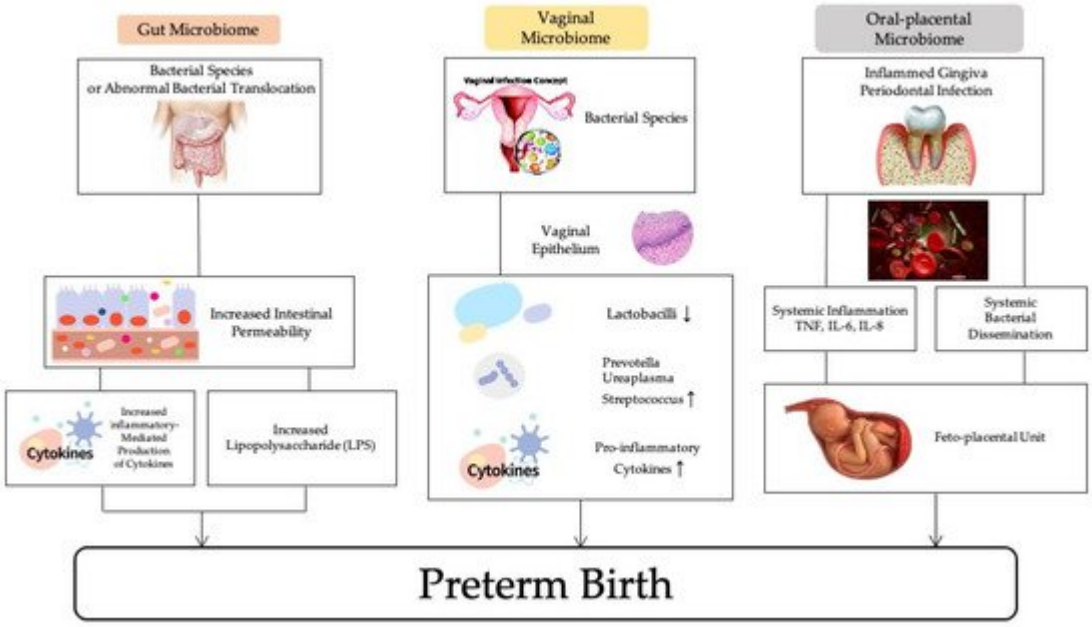

Figure 1. The association of maternal microbiomes and preterm birth.

The target of treatment for pregnant women was usually BV and the results were inconsistent [32][33]. The double blinded PREMEVA trial was conducted to evaluate the effect of oral clindamycin in early pregnancy to prevent late miscarriage (16–21 weeks of gestation) or spontaneous early PTB (22–32 weeks of gestation). There was no difference between the treatment and the placebo group [34]. However, another study showed that screening and treating BV in pregnant women with previous history of PTB is still effective in preventing PTB [32]. The use of certain antibiotics such as metronidazole may cause bacterial lysis and the release of endotoxins [35], and these are strong stimulators of inflammation and may enhance the inflammatory phenotype [36]. In addition, some antibiotics may be effective against *Lactobacillus* but not against microorganisms associated with BV, which was commonly found in antibiotic resistance genes [37].

Antibiotic treatment to ameliorate PTB could fail for women with abnormal vaginal microbes, positive fetal fibronectin, or previous PTB history, and it has raised interest in the positive regulation of vaginal microbiomes using probiotics or live bio-therapeutic products. Several studies have been conducted to reveal the effectiveness

of probiotics to prevent PTB. Probiotics may be taken orally or, less commonly, vaginally. One study found that oral probiotic use in pregnancy did not decrease the risk of PTB [38], but an observational study revealed that probiotic milk intake in early pregnancy, not mid to late pregnancy, was related to reduce the risk of PTB [39]. Recent randomized controlled studies have reported that oral probiotics do not affect the vaginal microbiome during pregnancy [40][41].

Increased concentration of folic acid has been found in the placenta of PTB women without excess gestational weight gain [42]. One study showed that folic acid consumption started after the first and second trimester is related to an increase in the risk of PTB [43], but another study found folic acid supplementation slightly reduces the risk of PTB [44].

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