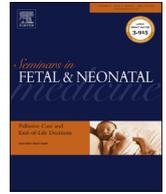




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## Review

## Maternal microbiome – A pathway to preterm birth



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## S U M M A R Y

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Despite great medical advances in preventing maternal and infant mortality in the past century, one issue remains unresolved: why do so many women give birth prematurely? A major new field of human microbiome studies has begun to shed light on the impact of microbes (of both the commensal and pathogen varieties) on pregnancy outcomes. Recent advances in next-generation sequencing and metagenomic analysis have revealed that maternal microbiomes at a variety of niches including the oral, vaginal, gut, cervical, and even the placenta itself govern pregnancy outcomes. In this review, we describe how alterations in the microbial biomasses impact preterm birth and we discuss the major research questions concerning the cause and/or interdependent relationships between microbiome, infection, and preterm delivery.

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## 1. Introduction

In spite of tremendous research efforts, the puzzle of preterm birth (PTB) is far from being solved. PTB affects 1 in 10 pregnancies, resulting in ~15 million preterm deliveries worldwide [1]. Infants born preterm are at high risk of neonatal mortality and face multiple short- and long-term major health morbidities, which potentially impede childhood development and increase health care expenditures [1]. PTB continues to challenge clinical practice: only a few strategies are available to detect women at risk of delivering preterm, and current interventions to prevent preterm delivery are largely ineffective [2]. This is partly because of the heterogeneous etiology of PTB. Apart from provider-initiated PTB, two-thirds of PTB occur after spontaneous onset of preterm labor due to various pathological processes including preterm premature rupture of membranes (PPROM), intrauterine infection/inflammation, cervical insufficiency, uterine anomalies and pathologic

uterine distention (polyhydramnios, multiple gestation), decidual senescence [3,4]. In addition, the interplay of environmental risk factors (stress, smoking, heavy work) [5] and the interrelated biological pathways of parturition [6] create challenges in understanding the mechanisms underlying PTB, hindering the opportunities to translate the research findings into effective interventions.

## 2. Microbial etiologies for preterm birth

A widely proposed hypothesis links infection and inflammation with spontaneous PTB, including associations with subclinical intrauterine infection, intra-amniotic, and extrauterine maternal infections, such as kidney infection and periodontal disease [7–11]. The micro-organisms most widely associated with PTB have been postulated to originate from one of two places: (i) the reproductive or genitourinary tract, ascending upward through the cervix; or (ii) they may reach the uterus through a haematogenous route [7,8,12]. Substantial data from more than three decades ago provide evidence for a causal role of lower genital tract infection in the etiology of a portion of PTB cases [4,7]. The conventional paradigm suggests

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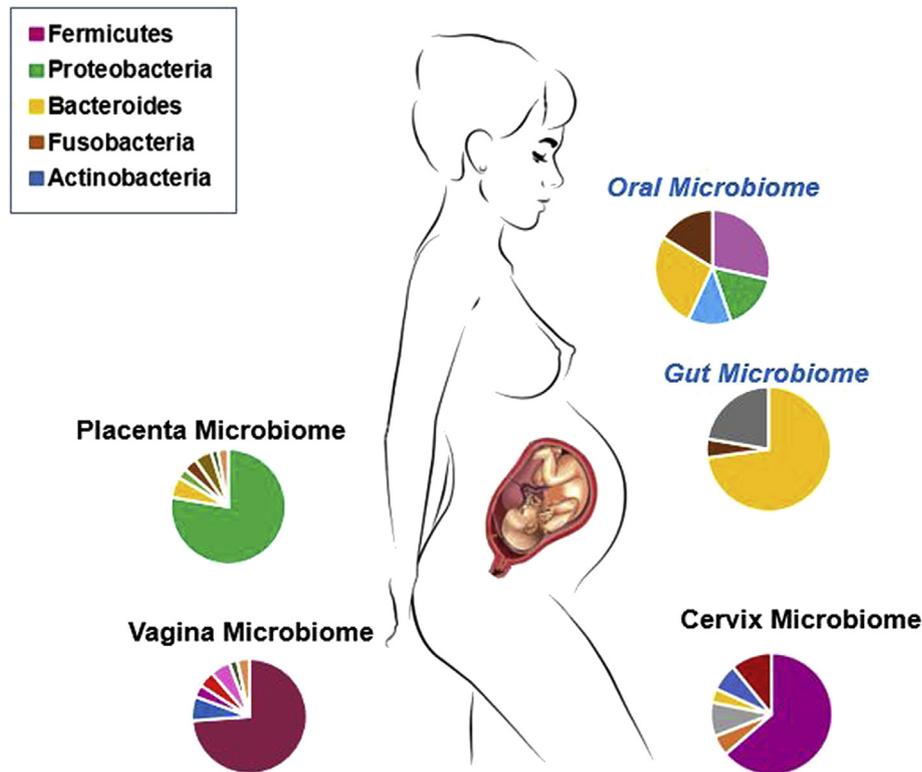
that the initiating infection, either clinical or subclinical, mono- or polymicrobial, usually ascends from vagina and cervix to the chorioamniotic space and may affect the myometrium, fetal membranes or amniotic fluid, resulting in intra-amniotic infection and immune stimulation within the otherwise sterile intrauterine environment [9]. As noted above, the infection may be haematogenous, either from periodontal disease and oral flora from periodontal niche [12,13], through fallopian tube, or seeding during manipulations such as amniocentesis. Further experimental evidence for an unequivocal association between infection and PTB included data showing that antibiotic treatment of ascending intrauterine infections may prevent PTB in experimental models of chorioamnionitis, that treatment of asymptomatic bacteriuria prevents PTB, and that systemic administration of microbial products to pregnant animals results in spontaneous preterm labor and delivery [3,14].

However, the inflammatory/infectious pathway does not fully explain the mechanism of PTB, and anti-inflammatory and antibiotic treatments have not reduced the rates of PTB. The underlying assumption of this hypothesis was that the uterus, and presumably placenta and fetal membranes, are sterile, thus any presence of bacteria is pathologic. This has been a dogma in medicine for over 100 years, implying that the presence of bacteria in the amniotic fluid is related to imminent preterm delivery and poor outcome for the fetus [15–17].

Emerging literature suggests that this long-held belief of a sterile womb may not be correct. New theories promoting a role for the bacterial content, the microbiome of reproductive organs in regulation of the timing of parturition, have been launched [18,19]. Evolving data suggest that the placenta and fetal membranes might

not be sterile even in absence of infection [9]. A wealth of bacterial species has been shown to reside within the placenta [20–24]; yet, the microbiome of the placenta is different from other organ systems. It is more similar to the oral cavity than to the vagina, which was the general belief until recently [18]. Studies in both animal models and humans showed that specific bacteria may also be detected in the meconium [25] and umbilical cord blood of healthy newborns [19]. On the other hand, presence of bacteria in amniotic fluid specimens of asymptomatic women at term suggested that, rather than the presence of bacteria, the quantity of bacteria, or perhaps changes in proportion of various bacteria species, may initiate the cascade leading to inflammation, infection, and PTB.

Due to these novel findings, the classic dogma of “sterile womb” and PTB initiated by an ascending infection from the vaginal cavity has been challenged [13,17] and the theory of resident bacterial flora in organ systems, including reproductive organs, makes headway (Fig. 1). This emerging hypothesis led to the development in 2008 of The Human Microbiome Project whose purpose is to describe the structure, function, and diversity of the human microbiome across multiple sites of the human body and to understand its role in human health and disease ([www.hmpdacc.org](http://www.hmpdacc.org)). Characterization of the human microbiome may also be critical in understanding the physiology of human parturition. Evidence suggests that the functional alterations resulting from the hormonal and physical changes during pregnancy are accompanied by consequent changes in “normal” microbiota signature of reproductive organs [7]. Distortion of the fine balance in the composition of the bacterial communities from within reproductive organs may play an important role in triggering and sustaining early uterine contractions.



**Fig. 1.** Microbiomes during pregnancy. The conventional paradigm is that the placenta is a sterile organ and that adverse pregnancy outcomes are associated with microbes that originate from the reproductive tract (vaginal) and ascend through the cervix to colonize the placenta. However, evidence also suggests that other microbial communities including oral and gut may impact pregnancy health by routing hematogenously to the placenta. (Adapted with permission from Belizário JE, Napolitano M. Human microbiomes and their roles in dysbiosis, common diseases, and novel therapeutic approaches. *Front Microbiol* 2015;6:1050. <http://dx.doi.org/10.3389/fmicb.2015.01050>.)

### 3. The role of maternal microbiomes from non-reproductive organs in PTB

#### 3.1. Oral microbiome

Several studies report intrauterine infections caused by microbial species that are not routinely present in the urogenital tract [7,26,27]. In 1996, in a prospective cohort study of 1020 pregnant women assessing the effect of oral health on pregnancy outcomes, Offenbacher *et al.* observed an increased risk of PTB in healthy women with moderate-to-severe periodontal disease, launching the hypothesis that periodontal disease is a risk factor for PTB [28]. Since then, a reciprocal relationship between PTB and periodontal disease has been established. Three distinct lines of evidence including epidemiologic (case-controlled studies, prospective studies), biologic, and interventional studies explored the link between oral flora and PTB. However, the results from these studies are conflicting, with some researchers finding an association between periodontal disease and PTB, while others did not. Therefore, definite conclusions regarding this relationship have not been reached. Epidemiologic evidence including cohort and case–control studies found varying degrees of association between periodontal status and PTB alone, low birth weight alone, or PTB associated with low birth weight [29]. In an effort to better understand the mechanisms behind the periodontal disease–PTB association, several microbiologic studies examined amniotic fluid, maternal and cord serum, and gingival crevicular fluid. Although the biological mechanisms were not well defined, several mechanistic hypotheses were proposed linking periodontal disease to early uterine contractions. Infection from periodontal disease results in elevation of local and systemic prostaglandins (e.g. PGE<sub>2</sub>) and cytokines (e.g. interleukin (IL)-1, IL-6, tumor necrosis factor- $\alpha$ ) that are able to initiate uterine contractions and promote premature labor. In addition, the periodontal disease may act as a reservoir of bacterial by-products such as lipopolysaccharide, which also contributes to increasing the levels of pro-inflammatory cytokines and prostaglandins. Bacterial spreading ensures possible hematogenous dissemination of commensal oral flora, including periodontal pathogens, through the circulation, to the maternal–fetal unit where they produce an inflammatory response with neutrophil activation and release of pro-inflammatory cytokines [24].

A recent systematic review and meta-analysis of published case–controls studies including 10,418 patients found an increased estimated odds for PTB in women with periodontal disease during pregnancy (odds ratio (OR) 1.78, confidence interval (CI) 1.58–2.01). The authors concluded that presence of important confounders whose effects could not be addressed precluded the validation of the meta-analysis outcomes [30]. Other cohort and case–control studies did not find associations between periodontal disease and PTB [31]. The fact that treating periodontal disease does not always mitigate the risk of PTB also challenges an association between periodontal disease and PTB.

The difference in opinions between studies may be explained by the difference in definitions used for periodontal disease, reflecting different pathologic entities and disease severities [29]. Further investigations suggested that pregnancy response to periodontal disease may be modulated by the immune and genetic characteristics of the fetus and the mother, the inflammation of the maternal–fetal unit being amplified by a particular maternal phenotype. Thus, the role of oral microbiome in PTB remains unclear; additional studies should explore the various aspects of a relationship more complex than initially hypothesized. Several questions remain to be answered: (i) What, if any, is the role of oral microbiome in absence of periodontal diseases in human parturition? (ii) What proportion of oral flora is transmitted to the uterus and what

is the purpose of this transmission? (iii) When do these flora become pathogens? Periodontal disease is a preventable risk factor. Since treatment of periodontal disease does not always prevent PTB, (iv) what other factors intervene to modulate the biologic responses? (v) Are some women with periodontal disease at higher risk than others; if so, why? (vi) Would promotion of early detection and treatment of periodontal disease before and during pregnancy prove beneficial for prevention of PTB in women at risk?

#### 3.2. Gut microbiome

Much of the perinatal literature on the gut microbiota and PTB focuses on infant intestinal flora. Little information is available on maternal intestinal microbiome and preterm delivery. Although strong evidence suggests that vaginal microbiota changes during pregnancy, only recently has it been shown that gut microbiome differs between early and late pregnancy. Weight gain in pregnancy and leptin levels associate with differences in microbial community structure in pregnancy dependent upon gestational age [32] in pregnant mice, suggesting that altered nutrition is a permissive factor in modifying the metabolism and microbiome during pregnancy. Advanced molecular techniques were able to identify an association between PTB and intestinal microbiota. Using terminal restriction fragment length polymorphisms (T-RFLP), Shiozaki *et al.* evaluated the intestinal and vaginal microbiome of women who delivered preterm compared to those who delivered at term and were able to demonstrate that the intestinal/oral cavity, rather than the vaginal compartment, housed the microbiota that when altered would result in preterm delivery [33]. Studies in mice provided further evidence for the association between gut microbiota and pregnancy health. Employing a 16S-based rRNA genes microarray analysis of the maternal caecal content, Connor *et al.* showed that gut microbiota influences maternal health and adaptation to pregnancy through effects on immune function and nutrient metabolism [34]. It is not clear, however, if there are longitudinal alterations of the microflora colonizing the gut throughout pregnancy or if there are causal pathways activated by gut microbiota leading to labor activation. The above studies provide evidence to promote further inquiry in the potential roles of the gut microbiome in human parturition.

### 4. The role of reproductive organs' microbiome in PTB

#### 4.1. Vaginal microbiome

The lower genital tract harbors a microflora of *Lactobacillus* species, which was first described in the late nineteenth century by the German gynecologist Albert Döderlein. Culture-dependent and culture-independent approaches surveyed further the vaginal microbial communities' composition and structure, revealing that *Lactobacillus* are the dominant vaginal genus in the majority of women. It is believed that bacterial colonization of the vaginal niche by lactobacilli confers resistance, acting as a barrier through a variety of mechanisms against colonization by other bacteria, ascending from the genital tract or from systemic infectious diseases [35,36]. The vaginal microbiota is unique in that it undergoes major compositional changes throughout women's lifespan, from birth, to puberty, reproductive age, and menopause. Very little is known, however, about the environmental and local factors modulating the changes in the composition of the vaginal microbiota through these stages. Several lines of evidence point towards a major role for the microbiome in the maintenance of pregnancy [37–39]. Using comparative metagenomics in a cross-sectional approach, Aagard *et al.* showed that vaginal microbiome differs in pregnancy, with variation of taxa across vaginal subsite and

gestational age [40] supporting previous studies that compared the vaginal microbiome of pregnant and non-pregnant women [41]. A more recent longitudinal high-throughput pyrosequencing of 16S rRNA gene of the vaginal bacterial communities of pregnant women characterized the normal vaginal microbiota throughout normal pregnancy, at every 4 weeks until 24 weeks and every 2 weeks until birth, showing that vaginal microbiome becomes more stable and less diverse as pregnancy progresses [42]. Thus, it was proposed that the enhanced stability of the vaginal microflora in pregnancy confers greater resilience and has a protective role against ascending infection of the genital tract [42]. As such, failure of the lactobacilli-driven defense with bacterial overgrowth and change in the proportion of normal flora are linked to PTB [7,39], amniotic fluid infection, and chorioamnionitis. Recent findings from Hayman et al. concur, showing a decrease in the diversity of the vaginal flora with PTB and that uncultured vaginal bacteria play an important role in PTB [39]. Presence of a *Lactobacillus*-poor and *Gardnerella*- or *Ureaplasma*-abundant vaginal community appear to exhibit both dose–response and temporal relationships with PTB, being perhaps predictive of PTB [43]. Other studies found no difference in the relative abundance of bacterial taxa between women who deliver preterm and those who deliver at term [38]. The presence of vaginal flora detected by polymerase chain reaction in negative culture of amniotic fluid from women with PPRM suggests a larger role of bacteria in relation to PTB than was previously appreciated [39,44]. More research is needed to demonstrate the association between increase or decrease in the relative abundance of specific bacteria in the vaginal flora and PTB.

Although one in four cases of PTB is associated with proven intra-amniotic infection, it still not clear whether these patients may be identified by the changes in the composition and stability of the vaginal microbiome [38]. Even if the vaginal bacteria from the same species are identified, they may have a different genomic make-up that may convey different metabolic or biochemical pathways, with different functions in women who deliver preterm or at term. This may at least partly explain why treating apparently pathologic vaginal flora has not resulted in a decrease in PTB [45,46]. In fact, the opposite has been noted [47]. Thus, the mechanisms through which bacterial community stability promotes health in the vaginal niche and how it contributes to parturition, either term or preterm, remain to be determined.

#### 4.2. Cervical microbiome

The existence of a cervical microbiome independent of the vaginal microbiome is an evolving concept. There is very little in the literature describing cervical microbiota, but studies related to human papilloma virus allude to its presence [48,49]. Recent evidence entertains the notion of microflora commensal within the cervix. A longitudinal study showed that microbiome of the cervix is very similar to that of vagina, predominantly of lactobacilli and *Gardnerella*, but has a wide variety of viral and bacterial organisms [49]. Although this evidence is compatible with the notion of bacterial colonization of the cervix, there are no published studies to associate the cervical microbiome with the cascade of biochemical and physiological events leading to onset of labor, either term or preterm. However, a major role for the uterine cervix in PTB is widely recognized.

The uterine cervix provides both a gateway and a barrier between “sterile” uterine compartment and non-sterile and sometimes hostile external microbial environment. The thick mucus plug from the cervical canal is known not only to physically protect the uterine cavity from the vaginal flora but also to have antimicrobial and cytotoxic activity [50]. In addition, cervical insufficiency, a well-recognized condition contributing to PTB, was

traditionally thought to be caused by a physical sphincter dysfunction and treated surgically. These have been longstanding paradigms in the maintenance of normal human pregnancy [51]. The new advances in the understanding of preterm parturition point to a role of yet under-recognized microbiome in human genital tract that may mediate biochemical and biophysical interactions between microbiome and cervical dysfunction. Cervical insufficiency may stem from microbial activation of pro-inflammatory agents that mobilize hyaluronidases, matrix metalloproteinases, and other molecular agents that promote collagenolysis in cervical stroma, which may predate clinical manifestations. Short cervix has been associated with intra-amniotic inflammation and activation of pro-inflammatory cytokines and chemokines, such as monocyte chemoattractant protein-1 (MCP-1) and interleukin-6 [52]. It is not yet known, however, whether such inflammatory processes are mediated by a residential, commensal, microbiome within cervical stroma or due to contamination with flora of another origin [53]. One hypothesis is that cervical microbiome is of oral cavity origin.

Several questions need to be addressed by future investigations in order to shed light in our understanding of the role of cervical microbiome in cervical activation and labor initiation: (i) Is there another mechanism responsible for cervical ripening? (ii) Is it, at least theoretically, possible that microbial activation, not invasion, contributes to premature cervical softening and ripening? (iii) If so, is the cervix just a transit for passage of bacteria to the uterus, or does it have its own microbiome that regulates its own environment autonomously? (iv) Does what happens locally within the cervix have global impact to the uterus and beyond? Metagenomics and meta-transcriptomic longitudinal approaches of the microbial composition of the cervix in pregnancy and throughout women's lifespan may add valuable information to our understanding of the role of the cervix in human parturition – term or preterm.

#### 4.3. Placental microbiome

The conventional paradigm of placenta as a sterile organ [54] has been challenged by a number of new findings. It is now clear, that the placenta can no longer be considered strictly sterile [9,10]. Instead, it harbors a unique microbiome; the presence of which may actually be normal and not associated with adverse pregnancy outcomes [9]. Two recent studies support the existence of a ‘placental microbiome’ even in healthy pregnancies that deliver at term. Using culture-independent whole-genome shotgun sequencing of genomic DNA isolated from human placentas, Aagaard et al. identified a low-abundance, but metabolically rich, microbiome in both term and preterm placentas [18]. This microbiome included commensal bacterial species such as *E. coli* (the most abundant species), *Prevotella tanneriae*, *Bacteriodes* spp., and *Fusobacterium* spp. [18]. Following up on this study, a microbiome analysis of placental membranes from very preterm and term deliveries using 16S rDNA pyrosequencing identified bacterial colonization somewhat different from that reported by Aagaard and colleagues. These differences were attributed mostly to the differences in methodology of 16S bases analysis [55]. Stout et al. showed that intracellular bacteria are present in a third of all human placentas and in more than half of early preterm (<28 weeks of gestation) placentas [56]. These studies together confirm that consistently identifiable bacteria are present in the majority of placental membranes from both term and preterm deliveries, irrespective of mode of delivery. There is a greater spread and diversity of bacterial species in placental tissues of women with preterm labor and these bacteria can be present without any apparent complications. However, it is not known whether the bacterial load and diversity have any implications in induction of

PTB [55]. It is not clear how early in the development bacterial colonization begins, nor has the concept of “normal colonization” been defined. Furthermore, the implications of the three-part harmony between the mother, fetus, and the placental microbiome for normal parturition and for infection-associated PTB are unclear. For instance, does the placental microbiome exist because maternal transmission of bacteria constitutes a critical feature for healthy fetal development or immune education? The new evidence points out to the exciting concept of a microbiome–human symbiosis that starts early in gestation and which may impact the rest of one’s life.

## 5. Conclusion

The number of studies suggesting equivocal association of PTB with infection has to be reconciled with the emerging knowledge of alterations in microbial diversity in various maternal niches that also impact PTBs. Randomized trials of therapeutic strategies for infection have failed to prevent PTB [57–59]. This may be because the effort is targeted towards commensal bacteria. Furthermore, none of the bacterial species (identified in association with a normal term microbiome or with PTB) has been shown definitively to cause PTB. Moreover, the single greatest risk factor for spontaneous PTB is a maternal history of prior PTB, especially multiple and/or early PTB [60], suggesting that low-level infection or susceptibility to infection left over from the first pregnancy may promote PTB in subsequent pregnancies. Thus, the link between infection and PTB appears to be more complicated than once thought. It is imperative to elucidate what is ‘normal’ in terms of microbial presence and what is pathologic in understanding the dynamics of their co-existence in maternal health and disease.

Although the study of maternal transmission of microbes in mammals is in its infancy due to the longstanding “sterile womb” hypothesis, we are at the exciting and promising start of understanding these relationships in the placenta and during pregnancy and in adverse pregnancy outcomes. A greater understanding of the relationship of microbial colonization in pregnancy and the potential association with PTB should lead to novel ways to decrease the burden of spontaneous PTB.

### Practice points

- Classic dogma of the “sterile womb” has been challenged.
- Presence of a placental, vaginal, cervical, oral and gut microbiome has been demonstrated.
- Maternal microbiome from reproductive and non-reproductive niches play a role in regulation of the timing of parturition.
- Alterations in microbial diversity in various maternal niches impact preterm delivery.

### Research directions

- Define the concept of “normal colonization”.
- Description of maternal microbiome niches.
- Physiologic and pathologic alterations of maternal, fetal, and placental microbiome in normal parturition and in infection-associated preterm delivery.
- How timing and mode of delivery may shape the microbiome of the neonate.

## Conflict of interests

None declared.

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