Oral microbiome shifts during pregnancy and adverse pregnancy outcomes: Hormonal and Immunologic changes at play

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1 | BACKGROUND

Current evidence suggests that oral microbial dysbiosis is a primary etiological factor in oral diseases, such as dental caries and chronic periodontitis.1,2 Oral microbial dysbiosis is also associated with the pathogenesis of systemic diseases, such as cardiovascular disease,3 diabetes mellitus,4 and adverse pregnancy outcomes.

Previously, studies relying on traditional culture-based and PCR-based methods identified a limited number of gram-negative anaerobia bacteria as keystone periodontal pathogens, in particular, Porphyromonas gingivalis, Tannerella forsythia, Treponema denticola, Aggregatibacter actinomycetemcomitans, Fusobacterium nucleatum, and Prevotella intermedia.5,6 They have been used as diagnostic markers of periodontitis.6 Evidence shows that these periodontal pathogens have been associated with adverse pregnancy outcomes.7-9 However, the oral cavity is comprised of a prodigious microbiome, including hundreds of “not-yet-cultivable” bacterial species whose functions remain unknown.10

With the recent development of metagenomic sequencing technologies, a growing body of studies have revealed a greater degree of complexity in the oral microbiome than was previously appreciated.11,12 Thus, the contributions of the oral microbiome and an oral microbial dysbiosis to maternal metabolism, immunity, and infants’ health have brought new considerations.

To develop better prediction and intervention approaches for adverse pregnancy outcomes, it is critical to understand the oral microbiome changes during pregnancy and their association with adverse pregnancy outcomes. This review will summarize recent data describing: (a) normal changes in the oral microbiome that occur during pregnancy; (b) pathogenic changes in the oral microbiome believed to occur in association with adverse pregnancy outcomes; and (c) the association between the placental microbiome and the oral microbiome.

2 | CHANGES IN THE ORAL MICROBIOME THAT OCCUR DURING PREGNANCY

The oral cavity, the entrance of the digestive and respiratory system, contains a total of 770 microbial species, consisting of 687 species from version 14.51 of the Human Oral Microbiome Database and 83 species that have been added based on publicly available data on the microbiota of the aerodigestive tract outside of the mouth.10,13 The diversity and composition of the oral microbiome can be affected by numerous environmental factors, including pH, anaerobic conditions, nutrition, and hormone levels.14-16 In 2010, Carrillo-de-Albornoz et al17 reported that the presence of both subgingival Po. gingivalis and Pr. intermedia was increased during...
### TABLE 1  Summary of oral microbes implicated in human placental fetal unit infections

| Study               | Oral microbes detected                | Placental fetal unit | Pregnancy outcomes                  | Detection method(s)          | Results                                                                                                                                 |
|---------------------|---------------------------------------|----------------------|-------------------------------------|------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|
| Radochova et al.57  | *Streptococcus intermedius*, *F. nucleatum* | amniotic fluid       | preterm prelabor rupture of membranes | PCR                          | Periapathogenic bacteria (2 × *Streptococcus intermedius* and 1 × *F. nucleatum*) were found in the amniotic fluid of 4% (3/78) of women |
| Ercan et al.51      | *Campylobacter rectus*, *Ta. forsythia*, *Po. gingivalis*, *F. nucleatum* | amniotic fluid       | preterm birth and low birth weight  | PCR                          | *Campylobacter rectus*, *Ta. forsythia*, *Po. gingivalis*, and *F. nucleatum* were detected in the amniotic fluid and subgingival plaque samples of three patients who gave birth to preterm low birth and low birth weight neonates |
| Han et al.54        | *F. nucleatum*, *Leptotrichia (Sneathia) spp.*, *Bergeyella* sp., *Peptostreptococcus* sp., *Bacteroides* sp., *Clostridiales* spp. | amniotic fluid       | preterm birth                       | Culture PCR                  | Uncultivated, or difficult-to-cultivate species may play a key role in the initiation of preterm birth |
| León et al.56       | *Po. gingivalis*                       | amniotic fluid       | Threatened premature labor          | PCR                          | *Po. gingivalis* was present in both the subgingival samples and the respective amniotic fluid sample |
| Wang et al.59       | 18 species detected including *Escherichia coli*, *Streptococcus agalactiae*, *F. nucleatum*, *Sneathia sanguinegens* | cord blood           | preterm birth                       | PCR                          | The majority (72%) of cord blood species were also detected in the matching amniotic fluid, with *E. coli* and *F. nucleatum* as the most prevalent. |
| Gonzales-Marin et al.53 | *Po. gingivalis*, *F. nucleatum* | neonatal gastric aspirates | complicated pregnancies            | PCR                          | Neonatal strains were more likely to originate from the mother’s oral cavity than to be vaginal strains |
| Gonzales-Marin et al.52 | *F. nucleatum*                       | neonatal gastric aspirates | preterm birth                       | PCR                          | *F. nucleatum* of oral origin could be involved with pregnancy complications |
| Ruth McCuaig et al.65 | *Po. gingivalis*, *F. nucleatum*, *A. actinomycetemcomitans* | Placenta             | preterm birth                       | PCR                          | Fusobacterium spp. are not detected more in placentas from preterm birth and may potentially be lower |
| RM Doyle et al.50    | *Mycoplasma hominis*, *Aerococcus christensenii*, *Gardnerella vaginalis*, *F. nucleatum* | placental membranes  | preterm birth                       | 16S rDNA pyrosequencing (V1-V2 and V5-V7) | 6 genera (Fusobacterium, Streptococcus, Mycoplasma, Aerococcus, Gardnerella, and Ureaplasma) and 1 family (Enterobacteriaceae) were either present in greater relative abundances in preterm samples or absent in term deliveries |
| Katz et al.55       | *Po. gingivalis*                       | Placenta             | Chorioamnionitis                    | Immunocytochemistry          | The antigens of *Po. gingivalis* were detected in the placental syncytiotrophoblasts, chorionic trophoblasts, decidual cells, and amniotic epithelial cells, as well as the vascular cells |

(Continues)
pregnancy, which was positively correlated with maternal hormone levels. Recent evidence has revealed that although the microbial diversity remains stable during the course of pregnancy, the composition of the oral microbiome undergoes a pathogenic shift during pregnancy that reverts back to baseline or a “healthy microbiome” during the postpartum period; the shift is believed to be mediated by female sex hormones, such as progesterone and estrogen. Lin et al reported that the genera *Neisseria*, *Porphyromonas*, and *Treponema* were overrepresented in the pregnant group, whereas *Streptococcus* and *Veillonella* were less represented compared with the non-pregnant group. By contrast, other studies reported that the genera most abundant during pregnancy were *Fusobacteria* and *Spirochaetes*, whereas *Haemophilus*, *Neisseria*, *Streptococcus*, and *Rothia* were less abundant. The compositional shift during pregnancy potentially places individuals at risk of infection by harmful oral microbiota that may trigger disease.

Moreover, maternal periodontal status was reported to deteriorate during gestation. Thus, preexisting gingivitis or periodontitis can significantly worsen during pregnancy. Longitudinal studies have shown that periodontal parameters, including plaque index, gingival index, pocket probing depth, and gingival bleeding, deteriorate during gestation. During pregnancy, periodontal tissues show an enhanced inflammatory response to the oral microbiome. Tilakaratne et al reported that pregnant women had a significantly higher gingival index and pocket probing depth with similar plaque index compared with non-pregnant women. These changes are consistent with the high prevalence of pregnancy gingivitis, which is reported to be the most common oral manifestation during pregnancy, with a prevalence of 30%-100% worldwide. Prospective studies reported that the levels of *Po. gingivalis*, *Tr. denticola*, *Pr. intermedia*, *Ta. forsythia*, *Campylobacter rectus*, *A. actinomycetemcomitans*, and *Fretibacterium* sp. human oral taxon 360 in the oral microbiome were positively correlated with gingival inflammation during pregnancy. On the other hand, the level of *Rothia dentocariosa* in saliva was negatively related with gingival inflammation during pregnancy.

### TABLE 1

| Study          | Oral microbes                     | Results                                                                 | Detection methods |
|----------------|----------------------------------|------------------------------------------------------------------------|-------------------|
| Swati et al    | *Po. gingivalis*, *F. nucleatum*, *Tr. denticola*, *Pr. intermedia*, *A. actinomycetemcomitans* | Periodontal pathogens were found to be high in the group with hypertension than the controls | PCR               |
| Mostajeran     | *A. actinomycetemcomitans*, *Pr. intermedia*, *Ta. forsythia* | There was no significant difference between the prematurity group and control group regarding the relative frequency of women with different types of periopathogenic bacterial infection of the placenta | PCR               |
| Ye et al       | *Po. gingivalis*, *F. nucleatum*, *Tr. denticola*, *Pr. intermedia*, *A. actinomycetemcomitans*, *Fretibacterium* sp. human oral taxon 360 | All 6 bacteria may access the placenta. The increased presence of F. nucleatum in placenta was related to the altered prematurity load. There was no difference in bacterial load between the preterm low birth weight group and the healthy delivery group | PCR               |

### 3 PATHOGENIC ORAL MICROBES BELIEVED TO BE ASSOCIATED WITH ADVERSE PREGNANCY OUTCOMES

Adverse pregnancy outcomes is a broad term that includes preterm birth (delivery < 37 weeks gestation), low birth weight (< 2500g regardless of gestational age), small for gestational age (birth weight < 10th percentile of gestational age), stillbirth (pregnancy loss > 20 weeks), and preeclampsia (late gestational hypertension). Together, adverse pregnancy outcomes affect more than 20% of newborns worldwide annually. However, half of the causes remain unknown.

Maternal periodontitis may be a potential risk factor for adverse pregnancy outcomes. Periodontal keystone pathogens are believed to play a significant role in the mechanism by which
periodontitis affects birth results. Clinical evidence, including higher amounts of *Po. gingivalis* in subgingival plaque increase the risk of preterm birth.\textsuperscript{29,30} Further, *Pr. intermedia* and *A. actinomyctemcomitans* were more prevalent in subgingival samples of women with preeclampsia.\textsuperscript{31,32}

Moreover, oral microbial dysbiosis is also associated with gestational diabetes mellitus. Wang et al\textsuperscript{33} evaluated the oral, gut, and vaginal microbiome of patients with gestational diabetes mellitus and healthy pregnancy controls. The authors found that the oral microbiome had the largest changes at the phyla level compared with the gut and vaginal microbiome. In addition, the abundance of *Neisseria/Leptotrichia* in the oral microbiome of pregnant women was positively correlated with glucose levels.

One possible mechanism by which oral pathogens affect labor might be related to the maternal immuno-inflammatory response induced by periodontal pathogens. When stimulated by bacterial pathogens, host cells release pro-inflammatory cytokines as part of the immune response. Clinical studies revealed that increased levels of inflammatory mediators in gingival crevicular fluid have been found in women with adverse pregnancy outcomes, and pro-inflammatory cytokines might be able to precipitate labor.\textsuperscript{34-36}

Animal studies confirm that oral infection with *Po. gingivalis* increases maternal serum cytokine levels of tumor necrosis factor-alpha 2.5-fold, interleukin-17 2-fold, interferon gamma 2.5-fold, interleukin-6 2-fold, and interleukin-1-beta 2-fold, enhances expression of toll-like receptor 2 and Fas/Fas ligand pathway mediators in placentia tissues, and induces preterm birth and low birth weight.\textsuperscript{37-38}

4 | ASSOCIATION BETWEEN THE PLACENTAL MICROBIOME AND THE ORAL MICROBIOME

Intrauterine infection as a causal factor in adverse pregnancy outcomes in association with the oral microbiome will be discussed. Intrauterine infection plays a major role in adverse pregnancy outcomes. The placenta was previously considered to be a sterile organ in the absence of clinical infection. Recent studies report that the placenta has its own endogenous microbiome and that the nature of this colonization may differ between healthy and complicated pregnancies.\textsuperscript{39,40} However, several studies that applied sequencing-based methods failed to detect a placental microbiome.\textsuperscript{41-43} Although the existence of a placental microbiome in healthy mothers remains controversial, there may be potential pathogens present.\textsuperscript{44} Another myth is the origin of these microbes. The evidence indicates two possible origins: ascending infection from the lower genital tract and hematogenous transmission from the oral microbiome.

One route is via an ascending infection of a microbial dysbiosis of vaginal origin. The vaginal microecological environment is complex, although *Lactobacillus* typically dominates the vaginal microbiota, comprising greater than 70% of the microflora.\textsuperscript{45} Dysbiosis of the vaginal flora manifests as bacterial vaginosis and it can be a cause of intrauterine infections, stillbirth, premature delivery, and neurologic damage to the fetus.\textsuperscript{46,47} Animal models revealed that ascending infections led to preterm births and stillbirths.\textsuperscript{48,49}

A second possible route is via hematogenous transmission of a microbial dysbiosis from the oral cavity. Oral microbes have been extensively detected in placental fetal units in clinical studies, where they might be involved in the development and progression of inflammation\textsuperscript{8,50-60} (Table 1). The most prevalent periodontal pathogens in placental fetal units are *Po. gingivalis* and *F. nucleatum*. Animal studies also demonstrated that oral infection with *Po. gingivalis* or *F. nucleatum* leads to colonization in the mouse placenta, causing localized infection and increased levels of the pro-inflammatory cytokines interleukin-1, interleukin-6, interleukin-8, and tumor necrosis factor-alpha, leading to preterm and term stillbirth.\textsuperscript{37,38,61,62} Studies, which reported that the placenta has its own microbiome, also indicated that the placental microbiome has a taxonomic profile composed of nonpathogenic commensal microbiota from the *Firmicutes, Tenericutes, Proteobacteria, Bacteroidetes*, and *Fusobacteria* phyla. This profile is distinct from that of the vagina, but similar to that of the oral microbiome.\textsuperscript{39,63} These combined data support the concept of a hematogenous spread of microbes from the oral cavity to the maternal/placental fetal unit through a recurrent bacteremia.

Moreover, another possibility of oral microbial pathogen transmission to the placenta may result from sexual practices with subsequent vaginal colonization. Cassini et al\textsuperscript{64} reported that periodontal pathogens were detected in human urogenital tract microflora, and the most representative species in the genital tract of the preterm group were *Tr. denticola, Ta. forsythia*, and *Pr. intermedia*. The presence of the periodontal pathogen *Tr. denticola* in the vaginal flora, regardless of the amount, was adversely associated with preterm delivery.

5 | CONCLUSIONS

Based on the aggregate data described above, the composition of the oral microbiome shifts the risk status for adverse pregnancy outcomes during pregnancy under the influence of sex hormones. These changes in the oral microbiome composition increase the risk of both gingival inflammation and adverse pregnancy outcomes, information that sheds light on considerations for potential protective factors and therapeutic approaches. Moreover, oral microbiome data have shown potential to predict adverse pregnancy outcomes, although further research is needed to confirm their predictive potential.

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