DOI: 10.1111/prd.12386

REVIEW ARTICLE

Periodontology 2000 WILEY

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

Changchang Ye[1,2] | **Yvonne Kapila**[1]

[1]Division of Periodontology, Department of Orofacial Sciences, School of Dentistry, University of California San Francisco, San Francisco, California

[2]State Key Laboratory of Oral Diseases & National Clinical Research Center for Oral Diseases, West China Hospital of Stomatology, Sichuan University, Chengdu, China

Correspondence
Yvonne Kapila, Division of Periodontology, Department of Orofacial Sciences, School of Dentistry, University of California San Francisco, San Francisco, CA 94143, USA.
Email: Yvonne.Kapila@ucsf.edu

Funding information
Larry Berkelhammer funds to Yvonne L. Kapila

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*.[1,5] 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 al[17] 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[57]	*Streptococcus intermedius*, *F. nucleatum*	amniotic fluid	preterm prelabor rupture of membranes	PCR	Periopathogenic 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* spp. *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 spices were 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[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[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)

TABLE 1 (Continued)

Study	Oral microbes detected	Placental fetal unit	Pregnancy outcomes	Detection method(s)	Results
Swati et al[58]	*Po. gingivalis*, *F. nucleatum*, *Tr. denticola*, *Pr. intermedia* *A. actinomycetemcomitans*	Placenta	Hypertension	PCR	Periodontal pathogens were found to be high in the group with hypertension than the controls
Mostajeran[60]	*A. actinomycetemcomitans*, *Pr. intermedia*, *Po. gingivalis*, *Tr. denticula*, *Ta. forsythensis*	Placenta	Preeclampsia	PCR	There was no significant difference between the preeclampsia group and control group regarding the relative frequency of women with different types of periopathogenic bacterial infection of the placenta
Ye et al[8]	*Po. gingivalis*, *F. nucleatum*, *Tr. denticola*. *Ta. forsythia*, *Pr. intermedia*, *A. actinomycetemcomitans*	Placenta	Threatened premature labor, Preterm low birth weight	PCR	All 6 bacteria may access the placenta. The increased presence of *F. nucleatum* in placenta was related to threatened premature labor. There was no difference in bacterial load between the preterm low birth weight group and the healthy delivery group

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,[18] 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.[19] Lin et al[20] 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*, *Streptocoocus*, and *Rothia* were less abundant.[21,22] 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.[18,23] During pregnancy, periodontal tissues show an enhanced inflammatory response to the oral microbiome. Tilakaratne et al[23] 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.[24] 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.[18,25,26] On the other hand, the level of *Rothia dentocariosa* in saliva was negatively related with gingival inflammation during pregnancy.[26]

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).[7] Together, adverse pregnancy outcomes affect more than 20% of newborns worldwide annually.[27] However, half of the causes remain unknown.

Maternal periodontitis may be a potential risk factor for adverse pregnancy outcomes.[28] Periodontal keystone pathogens are believed to play a significant role in the mechanism by which

periodontitis affects birth results. Clinical evidence, including our previous studies, indicate that higher amounts of *Po. gingivalis* in subgingival plaque increase the risk of preterm birth.[29,30] Further, *Pr. intermedia* and *A. actinomycetemcomitans* were more prevalent in subgingival samples of women with preeclampsia.[31,32]

Moreover, oral microbial dysbiosis is also associated with gestational diabetes mellitus. Wang et al[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.[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 placental tissues, and induces preterm birth and low birth weight.[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.[39,40] However, several studies that applied sequencing-based methods failed to detect a placental microbiome.[41-43] Although the existence of a placental microbiome in healthy mothers remains controversial, there may be potential pathogens present.[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.[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.[46,47] Animal models revealed that ascending infections led to preterm births and stillbirths.[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[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.[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.[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[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.

REFERENCES

1. Hajishengallis G, Lamont RJ. Beyond the red complex and into more complexity: the polymicrobial synergy and dysbiosis (PSD) model of periodontal disease etiology. *Mol Oral Microbiol*. 2012;27:409-419.

2. Jiao Y, Hasegawa M, Inohara N. The role of oral pathobionts in dysbiosis during periodontitis development. *J Dent Res*. 2014;93:539-546.
3. Kholy KE, Genco RJ, Van Dyke TE. Oral infections and cardiovascular disease. *Trends Endocrinol Metab*. 2015;26:315-321.
4. Ohlrich EJ, Cullinan MP, Leichter JW. Diabetes, periodontitis, and the subgingival microbiota. *J Oral Microbiol*. 2010;2:5818.
5. Socransky SS, Haffajee AD, Cugini MA, Smith C, Kent RL Jr. Microbial complexes in subgingival plaque. *J Clin Periodontol*. 1998;25:134-144.
6. Salminen A, Kopra KA, Hyvarinen K, et al. Quantitative PCR analysis of salivary pathogen burden in periodontitis. *Front Cell Infect Microbiol*. 2015;5:69.
7. Han YW, Wang X. Mobile microbiome: oral bacteria in extra-oral infections and inflammation. *J Dent Res*. 2013;92:485-491.
8. Ye C, Katagiri S, Miyasaka N, et al. The periodontopathic bacteria in placenta, saliva and subgingival plaque of threatened preterm labor and preterm low birth weight cases: a longitudinal study in Japanese pregnant women. *Clin Oral Investig*. 2020;24:4261-4270.
9. Cobb CM, Kelly PJ, Williams KB, Babbar S, Angolkar M, Derman RJ. The oral microbiome and adverse pregnancy outcomes. *Int J Womens Health*. 2017;9:551-559.
10. Dewhirst FE, Chen T, Izard J, et al. The human oral microbiome. *J Bacteriol*. 2010;192:5002-5017.
11. Park OJ, Yi H, Jeon JH, et al. Pyrosequencing analysis of subgingival microbiota in distinct periodontal conditions. *J Dent Res*. 2015;94:921-927.
12. Hong BY, Furtado Araujo MV, Strausbaugh LD, Terzi E, Ioannidou E, Diaz PI. Microbiome profiles in periodontitis in relation to host and disease characteristics. *PLoS One*. 2015;10:e0127077.
13. Chen T, Yu WH, Izard J, Baranova OV, Lakshmanan A, Dewhirst FE. The human oral microbiome database: a web accessible resource for investigating oral microbe taxonomic and genomic information. *Database (Oxford)*. 2010;2010:baq013.
14. Mascarenhas P, Gapski R, Al-Shammari K, Wang HL. Influence of sex hormones on the periodontium. *J Clin Periodontol*. 2003;30:671-681.
15. Ursell LK, Clemente JC, Rideout JR, Gevers D, Caporaso JG, Knight R. The interpersonal and intrapersonal diversity of human-associated microbiota in key body sites. *J Allergy Clin Immunol*. 2012;129:1204-1208.
16. Jensen J, Liljemark W, Bloomquist C. The effect of female sex hormones on subgingival plaque. *J Periodontol*. 1981;52:599-602.
17. Carrillo-de-Albornoz A, Figuero E, Herrera D, Bascones-Martinez A. Gingival changes during pregnancy: II. Influence of hormonal variations on the subgingival biofilm. *J Clin Periodontol*. 2010;37:230-240.
18. Balan P, Chong YS, Umashankar S, et al. Keystone species in pregnancy gingivitis: a snapshot of oral microbiome during pregnancy and postpartum period. *Front Microbiol*. 2018;9:2360.
19. Wu M, Chen SW, Jiang SY. Relationship between gingival inflammation and pregnancy. *Mediators Inflamm*. 2015;2015:623427.
20. Lin W, Jiang W, Hu X, et al. Ecological shifts of supragingival microbiota in association with pregnancy. *Front Cell Infect Microbiol*. 2018;8:24.
21. Aas JA, Paster BJ, Stokes LN, Olsen I, Dewhirst FE. Defining the normal bacterial flora of the oral cavity. *J Clin Microbiol*. 2005;43:5721-5732.
22. Elisabeth M, Bik CDL, Armitage GC, Loomer P. Bacterial diversity in the oral cavity of ten healthy individuals. *ISME J*. 2010;4:962-974.
23. Tilakaratne A, Soory M, Ranasinghe AW, Corea SM, Ekanayake SL, de Silva M. Periodontal disease status during pregnancy and 3 months post-partum, in a rural population of Sri-Lankan women. *J Clin Periodontol*. 2000;27:787-792.
24. Mealey BL, Moritz AJ. Hormonal influences: effects of diabetes mellitus and endogenous female sex steroid hormones on the periodontium. *Periodontol 2000*. 2003;32:59-81.
25. Yokoyama M, Hinode D, Yoshioka M, et al. Relationship between Campylobacter rectus and periodontal status during pregnancy. *Oral Microbiol Immunol*. 2008;23:55-59.
26. Ye C, Xia Z, Tang J, et al. Unculturable and culturable periodontal-related bacteria are associated with periodontal inflammation during pregnancy and with preterm low birth weight delivery. *Sci Rep*. 2020;10:15807.
27. WHO. *Born Too Soon. The Global Action Report on Preterm Birth*. Geneva, Switzerland: World Health Organization, 2012.
28. Offenbacher S, Katz V, Fertik G, et al. Periodontal infection as a possible risk factor for preterm low birth weight. *J Periodontol*. 1996;67:1103-1113.
29. Ryu JI, Oh K, Yang H, et al. Health behaviors, periodontal conditions, and periodontal pathogens in spontaneous preterm birth: a case-control study in Korea. *J Periodontol*. 2010;81:855-863.
30. Ye C, Katagiri S, Miyasaka N, et al. The anti-phospholipid antibody-dependent and independent effects of periodontopathic bacteria on threatened preterm labor and preterm birth. *Arch Gynecol Obstet*. 2013;288:65-72.
31. Ha JE, Oh KJ, Yang HJ, et al. Oral health behaviors, periodontal disease, and pathogens in preeclampsia: a case-control study in Korea. *J Periodontol*. 2011;82:1685-1692.
32. Hirano E, Sugita N, Kikuchi A, et al. The association of Aggregatibacter actinomycetemcomitans with preeclampsia in a subset of Japanese pregnant women. *J Clin Periodontol*. 2012;39:229-238.
33. Wang J, Zheng J, Shi W, et al. Dysbiosis of maternal and neonatal microbiota associated with gestational diabetes mellitus. *Gut*. 2018;67:1614-1625.
34. Stadelmann P, Alessandri R, Eick S, Salvi GE, Surbek D, Sculean A. The potential association between gingival crevicular fluid inflammatory mediators and adverse pregnancy outcomes: a systematic review. *Clin Oral Investig*. 2013;17:1453-1463.
35. Ryu A, Park KH, Oh KJ, Lee SY, Jeong EH, Park JW. Predictive value of combined cervicovaginal cytokines and gestational age at sampling for intra-amniotic infection in preterm premature rupture of membranes. *Acta Obstet Gynecol Scand*. 2013;92:517-524.
36. Mohr S, Amylidi-Mohr SK, Stadelmann P, et al. Systemic inflammation in pregnant women with periodontitis and preterm prelabor rupture of membranes: a prospective case-control study. *Front Immunol*. 2019;10:2624.
37. Liang S, Ren H, Guo H, et al. Periodontal infection with Porphyromonas gingivalis induces preterm birth and lower birth weight in rats. *Mol Oral Microbiol*. 2018;33:312-321.
38. Ao M, Miyauchi M, Furusho H, et al. Dental infection of Porphyromonas gingivalis induces preterm birth in mice. *PLoS One*. 2015;10:e0137249.
39. Aagaard K, Ma J, Antony KM, Ganu R, Petrosino J, Versalovic J. The placenta harbors a unique microbiome. *Sci Transl Med*. 2014;6:237ra265.
40. Antony KM, Ma J, Mitchell KB, Racusin DA, Versalovic J, Aagaard K. The preterm placental microbiome varies in association with excess maternal gestational weight gain. *Am J Obstet Gynecol*. 2015;212:653.e1–653.e16.
41. Leiby JS, McCormick K, Sherrill-Mix S, et al. Lack of detection of a human placenta microbiome in samples from preterm and term deliveries. *Microbiome*. 2018;6:196.
42. Leon LJ, Doyle R, Diez-Benavente E, et al. Enrichment of clinically relevant organisms in spontaneous preterm-delivered placentas and reagent contamination across all clinical groups in a large pregnancy cohort in the United Kingdom. *Appl Environ Microbiol*. 2018;84:e00483–18.
43. Lauder AP, Roche AM, Sherrill-Mix S, et al. Comparison of placenta samples with contamination controls does not provide evidence for a distinct placenta microbiota. *Microbiome*. 2016;4:29.

44. de Goffau MC, Lager S, Sovio U, et al. Human placenta has no microbiome but can contain potential pathogens. *Nature*. 2019;572:329-334.
45. Miller EA, Beasley DE, Dunn RR, Archie EA. Lactobacilli dominance and vaginal pH: Why is the human vaginal microbiome unique? *Front Microbiol*. 2016;7:1936.
46. Leitich H, Kiss H. Asymptomatic bacterial vaginosis and intermediate flora as risk factors for adverse pregnancy outcome. *Best Pract Res Clin Obstet Gynaecol*. 2007;21:375-390.
47. Lannon SMR, Adams Waldorf KM, Fiedler T, et al. Parallel detection of lactobacillus and bacterial vaginosis-associated bacterial DNA in the chorioamnion and vagina of pregnant women at term. *J Matern Fetal Neonatal Med*. 2019;32:2702-2710.
48. Vornhagen J, Quach P, Boldenow E, et al. Bacterial hyaluronidase promotes ascending GBS infection and preterm birth. *MBio*. 2016;7:e00781–16.
49. Swindle MM, Craft CF, Marriott BM, Strandberg JD, Luzarraga M. Ascending intrauterine infections in rhesus monkeys. *J Am Vet Med Assoc*. 1982;181:1367-1370.
50. Doyle RM, Alber DG, Jones HE, et al. Term and preterm labour are associated with distinct microbial community structures in placental membranes which are independent of mode of delivery. *Placenta*. 2014;35:1099-1101.
51. Ercan E, Eratalay K, Deren O, et al. Evaluation of periodontal pathogens in amniotic fluid and the role of periodontal disease in pre-term birth and low birth weight. *Acta Odontol Scand*. 2013;71:553-559.
52. Gonzales-Marin C, Spratt DA, Allaker RP. Maternal oral origin of Fusobacterium nucleatum in adverse pregnancy outcomes as determined using the 16S–23S rRNA gene intergenic transcribed spacer region. *J Med Microbiol*. 2013;62:133-144.
53. Gonzales-Marin C, Spratt DA, Millar MR, Simmonds M, Kempley ST, Allaker RP. Levels of periodontal pathogens in neonatal gastric aspirates and possible maternal sites of origin. *Mol Oral Microbiol*. 2011;26:277-290.
54. Han YW, Shen T, Chung P, Buhimschi IA, Buhimschi CS. Uncultivated bacteria as etiologic agents of intra-amniotic inflammation leading to preterm birth. *J Clin Microbiol*. 2009;47:38-47.
55. Katz J, Chegini N, Shiverick KT, Lamont RJ. Localization of P. gingivalis in preterm delivery placenta. *J Dent Res*. 2009;88:575-578.
56. Leon R, Silva N, Ovalle A, et al. Detection of Porphyromonas gingivalis in the amniotic fluid in pregnant women with a diagnosis of threatened premature labor. *J Periodontol*. 2007;78:1249-1255.
57. Radochova V, Kacerovska Musilova I, Stepan M, et al. Periodontal disease and intra-amniotic complications in women with preterm prelabor rupture of membranes. *J Matern Fetal Neonatal Med*. 2018;31:2852-2861.
58. Swati P, Ambika Devi K, Thomas B, Vahab SA, Kapaettu S, Kushtagi P. Simultaneous detection of periodontal pathogens in subgingival plaque and placenta of women with hypertension in pregnancy. *Arch Gynecol Obstet*. 2012;285:613-619.
59. Wang X, Buhimschi CS, Temoin S, Bhandari V, Han YW, Buhimschi IA. Comparative microbial analysis of paired amniotic fluid and cord blood from pregnancies complicated by preterm birth and early-onset neonatal sepsis. *PLoS One*. 2013;8:e56131.
60. Mostajeran F, Arbabi B. Is there any difference between preeclamptic and healthy pregnant women regarding the presence of periopathogenic bacteria in the placenta? *Int J Prev Med*. 2013;4:322-326.
61. Konishi H, Urabe S, Teraoka Y, et al. Porphyromonas gingivalis, a cause of preterm birth in mice, induces an inflammatory response in human amnion mesenchymal cells but not epithelial cells. *Placenta*. 2020;99:21-26.
62. Han YW, Redline RW, Li M, Yin L, Hill GB, McCormick TS. Fusobacterium nucleatum induces premature and term stillbirths in pregnant mice: implication of oral bacteria in preterm birth. *Infect Immun*. 2004;72:2272-2279.
63. 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. *Sci Rep*. 2017;7:2860.
64. Cassini MA, Pilloni A, Condo SG, Vitali LA, Pasquantonio G, Cerroni L. Periodontal bacteria in the genital tract: are they related to adverse pregnancy outcome? *Int J Immunopathol Pharmacol*. 2013;26:931-939.
65. McCuaig R, Wong D, Gardiner FW, Rawlinson W, Dahlstrom JE, Robson S. Periodontal pathogens in the placenta and membranes in term and preterm birth. *Placenta*. 2018;68:40-43.

How to cite this article: Ye C, Kapila Y. Oral microbiome shifts during pregnancy and adverse pregnancy outcomes: Hormonal and Immunologic changes at play. *Periodontol 2000*. 2021;87:276–281. https://doi.org/10.1111/prd.12386