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The oral microbiome and adverse pregnancy outcomes

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Abstract: Significant evidence supports an association between periodontal pathogenic bacteria and preterm birth and preeclampsia. The virulence properties assigned to specific oral pathogenic bacteria, for example, *Fusobacterium nucleatum*, *Porphyromonas gingivalis*, *Filifactor alocis*, *Campylobacter rectus*, and others, render them as potential collaborators in adverse outcomes of pregnancy. Several pathways have been suggested for this association: 1) hematogenous spread (bacteremia) of periodontal pathogens; 2) hematogenous spread of multiple mediators of inflammation that are generated by the host and/or fetal immune response to pathogenic bacteria; and 3) the possibility of oral microbial pathogen transmission, with subsequent colonization, in the vaginal microbiome resulting from sexual practices. As periodontal disease is, for the most part, preventable, the medical and dental public health communities can address intervention strategies to control oral inflammatory disease, lessen the systemic inflammatory burden, and ultimately reduce the potential for adverse pregnancy outcomes. This article reviews the oral, vaginal, and placental microbiomes, considers their potential impact on preterm labor, and the future research needed to confirm or refute this relationship.

Keywords: periodontal disease, preterm labor, oral microbiome, vaginal microbiome, bacteria, pregnancy, infant, premature birth, low birth weight

Introduction

Julius Richard Petri introduced the Petri dish to microbiology in 1887,¹ making the culturing of single or multiple microbes on a nutrient medium in a Petri dish to be a 130-year-old technology. However, bacteria seldom occur in nature as a pure culture of a single species, but rather exist and participate in a community of microbes, that is, the microbiome.² In the case of a human host, the microbiome occupies several specific anatomic niches, for example, hair, skin, gastrointestinal tract, urogenital tract, vagina, nasal, and paranasal sinuses, and the oral cavity.²⁻⁴ Under the best of conditions, each of these microbiome niches represents a species-balanced community which is important to the establishment and maintenance of human health.^{3,5}

Current evidence suggests an association between a dysbiotic oral microbiome, manifest as periodontal disease, and a variety of systemic diseases. For example, moderate and severe periodontitis have been associated with development and progression of atherosclerosis,⁶⁻⁸ cardiovascular disease,⁹⁻¹¹ stroke,¹²⁻¹⁴ complications of diabetes,¹⁵⁻¹⁷ Alzheimer's disease,¹⁸⁻²⁰ and adverse pregnancy outcomes.²¹⁻²⁷ The common denominator for this mixture of disease associations appears to be the host inflammatory response and specific microbial pathogens.²⁸⁻³⁰ Because inflammatory periodontal disease is, for the most part, preventable,³¹ intervention strategies that result in better oral/systemic health should be considered for reasons of public health. More specifically,

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such strategies should be aimed at populations susceptible to atherosclerosis-related diseases (ie, cardiovascular, stroke, diabetes, and possibly Alzheimer's disease) and women of child-bearing age.

Significant evidence is available to consider that the majority of preterm births due to infection result from an ascendancy of bacterial pathogens from the vaginal microbiome to infect the clinically sterile intrauterine cavity consisting of the placenta, amniotic fluid, and fetus.^{31–34} This does not preclude the possibility of a hematogenous spread (bacteremia) of pathogenic microbes and inflammatory mediators originating from other sources, including untreated periodontal disease, and their contributions to an adverse pregnancy outcome, such as preeclampsia, preterm birth and low birth weight, fetal growth restriction, and fetal loss.^{30,35,36}

The oral microbiome

As a result of multiple ecologic determinants, the human oral cavity presents a prodigious and multifarious microbiota.^{37–41} In a state of health, the oral microbiota maintain a symbiotic relationship with their host. However, an imbalance or maladaptation within the oral microbial community (dysbiosis) commonly results in development of a dental disease.^{42,43} In this regard, dental caries, gingivitis, and chronic or aggressive forms of periodontitis are the most common expressions of oral disease.^{39,44–46}

Chronic periodontitis is a highly prevalent, dysbiosis-initiated, inflammatory condition that results in destruction of the supporting tissues of the teeth. This destructive process, a host response to pathogenic bacteria and their toxins such as cytolytic enzymes and lipopolysaccharides, is mediated by a proinflammatory cellular response involving neutrophils, lymphocytes, macrophages, and osteoclasts.^{45–50} The host response also generates a variety of inflammatory mediators, such as interleukin (IL)-1 β , tumor necrosis factor- α , IL-6, prostaglandin E₂, matrix metalloproteinase-8 and -9, which, in turn, can have a downstream effect on other organ systems by contributing to the body's overall inflammatory burden.^{51–56}

Through reverse transcription-polymerase chain reaction, microarray, and pyrosequencing technology, the microbiome of the human oral cavity has been found to be made up of a minimum of 700+ distinct microbial species, with suggestions that this number may be as high as 1,200–1,500.^{39–41} By comparison, the microbial flora consistently associated with chronic periodontitis is reported to involve only a limited number of species.^{39,40,57} Dominating, in terms of virulence,

among the periodontitis-associated bacterial species are mainly Gram-negative anaerobic bacteria, such as *Porphyromonas gingivalis*, *Filifactor alocis*, multiple species of *Prevotella*, particularly, *Prevotella intermedia*, *Tannerella forsythia*, multiple species of *Treponema*, particularly, *Treponema denticola*, *Aggregatibacter actinomycetemcomitans*, *Fusobacterium nucleatum*, *Parvimonas micros*, *Campylobacter recta*, multiple species of *Eubacterium*, and multiple species of *Bacteroides*.^{37,39–41,57–59} Interestingly, two of these bacteria are considered “keystone” microbes, *Po. gingivalis* and *Fi. alocis*. Keystone microbes are characterized by their relatively low numbers in a biofilm community and inherent virulence factors that allow manipulation of the host innate immune system and remodeling of a normally benign microbiota into one that is dysbiotic.^{42,60–64} In addition to being keystone microbes, both *Po. gingivalis* and *Fi. alocis* are highly invasive microbes, a virulence factor that allows avoidance of the host immune response.^{65–69} Other microbes associated with periodontitis (*T. denticola*, *Pr. intermedia*, *Fu. nucleatum*, *A. actinomycetemcomitans*, *C. rectus*, and so on) are also known to exhibit tissue-invasive tendencies, particularly in severe disease.^{70–72} This combination of tissue invasiveness, when combined with multiple transient bacteremias (common in patients with periodontal disease during mastication, oral hygiene, or dental treatment) leads to a body-wide dissemination of bacteria and activation of systemic inflammation-causing organ system complications and, in the case of pregnancy, adverse outcomes.^{21,25,73–77}

Prevalence of periodontitis

Combined data from the 2009 to 2010 and the 2011 to 2012 cycles of the National Health and Nutrition Examination Survey revealed that 46% of US adults, aged ≥ 30 years, representing ~ 65 million people, exhibited some degree of periodontitis.^{78,79} Of this group, 8.9% presented with severe periodontitis, which equates to ~ 12.6 million people.⁷⁹ Increased prevalence rate of periodontitis was associated with increasing age, male gender, and current tobacco smoking. Prevalence rates based on ethnic grouping were rather revealing when considered in terms of access to care issues, that is, Hispanic (63.5%), non-Hispanic blacks (59.1%), non-Hispanic Asian Americans (50%), and non-Hispanic whites (40.8) were predominantly affected.⁷⁹

Worldwide, severe periodontitis is estimated to be present in 10%–15% of the adult population,^{80,81} with prevalence varying considerably from country to country. For example, 20% of adults between the ages of 20 and 79 years in a large West Pomerania (Germany) study were reported to exhibit

severe periodontitis.⁷¹ The same study reported a prevalence rate of 35.3% of the population presenting with moderate periodontitis.⁷¹

Studies from India report that prevalence of periodontitis with attachment loss of ≥ 3 mm (moderate to severe disease) varies from 46% to 78%.⁸² However, depending on the age group and rural vs urban populations, the prevalence of periodontal disease in India can vary from $\approx 50\%$ to a maximum of 91%.^{82–88} Periodontal disease prevalence data collected since the year 2000 and for women of reproductive age (18–45 years) are sparse. The data, not unexpectedly, show that both severity and prevalence of the disease increase with increasing age.^{83–88}

Specific to reproductive aged women, Bansal et al,⁸⁴ in their study that included 205 females, reported that 6.58% of those aged between 20 and 24 years exhibited bleeding on probing (BOP) and 50.61% of subjects aged between 25 and 34 years presented with visible amounts of dental calculus. The authors did not address severity of disease in the traditional manner, but rather assessed the need for treatment using the Community Periodontal Index of Treatment Needs (CPITN).⁸⁹ A CPITN score of 1=BOP; score of 2=presence of supra- or subgingival calculus; score of 3=periodontal probing depth of 3.5–5.5 mm; score of 4=probing depth ≥ 5.5 mm. Thus, based on the CPITN data, severity of disease in the Bansal et al⁸⁴ study is judged to be slight to moderate.

Batra et al⁸⁵ reported that 45.5% of females, in a rural population, aged 20–29 years and 83.9% of those aged 30–39 years had CPITN scores of ≥ 2 or greater. Such a range of scores would indicate periodontal disease severity ranging from slight to severe.

Other studies addressing disease prevalence in women of reproductive age are equally imprecise. For example, studies by Grewal et al⁸⁷ and Rao et al⁸⁸ both assessed rural Indian populations from Punjab and Mustabad, Krishna District, respectively. One study used the CPITN⁸⁷ and the other the Community Periodontal Index⁸⁸ indices for screening of patients and approximation of disease severity. Females represented $\approx 55\%$ of the population in both studies. In general, both studies reported that females, regardless of age group, had a greater prevalence of periodontal disease than did males, roughly 55% vs 44%.

A study by Murthy et al⁹⁰ assessed the association of periodontal disease to preterm birth and low birth weight. The study evaluated 240 primigravida Indian women equally divided between those with and without periodontitis. All participants exhibited BOP, 48% exhibited dental calculus accumulation, and those with periodontitis had pocketing of

3.5–4.5 mm (slight to moderate disease). The study reported that periodontitis and anemia were independent risk factors for low birth weight, in spite of the slight to moderate severity of periodontal disease.

The CPITN index has been used by the majority of epidemiology studies to express severity of disease and treatment needs in Indian populations. However, as noted by Chandra et al⁸⁶ and Shewale et al,⁹¹ the CPITN is known to grossly underestimate the levels of moderate and severe disease. Given the presentation of data using CPITN from various studies and the issue of underestimation of disease severity, one can still reasonably conclude that periodontal disease in Indian women of reproductive age (18–45 years) ranges from 10% to 35%, increasing in both prevalence and severity with increasing age.

The vaginal microbiome

The Human Microbiome Project (2012)⁹² reported that the vaginal microbiome exhibits an uncomplicated microbial diversity, compared to that of the gastrointestinal tract or the oral cavity. In healthy subjects, there appears to be minimal variation in the diversity of the vaginal microbiota.⁹³ Species of *Lactobacillus* typically dominate the vaginal microbiota, comprising greater than 70% of the microflora.⁹⁴ As in other bacterial communities, the dominance of one or more species, in this case *Lactobacilli*, generally prevents colonization by undesirable extrinsic species and, thereby, may provide a protective function.^{93–96} Yet, Hyman et al⁹⁷ report that changes in the proportions of *Lactobacillus* in the vaginal microbiome and the presence of noxious bacteria were not correlated to preterm birth. The authors noted that race/ethnicity and sampling location likely impact determination of the vaginal microbiome. This latter statement was supported by Green et al⁹⁸ and Prince et al⁹⁹ in their respective reviews in which it was noted that the vaginal microbiome can fluctuate during various states of health, during hormonal fluctuations (ie, menstrual cycle and menopause), and between women of various ethnicities. A recent study by Hickey et al¹⁰⁰ further supports the impact of hormonal change on the vaginal microbiota, reporting that puberty and initiation of cyclic menstruation have profound effects. Last, Prince et al⁹⁹ reported that during pregnancy, there is an overall increase of bacteria from the taxa of *Lactobacillus*, *Clostridiales*, *Bacteroides*, and *Actinomycetales*. However, none of these taxa were noted as having any negative effects on pregnancy. Prince et al⁹⁹ did note that most of the studies looking at the vaginal microbiome are cross-sectional, which allows for the characterization of a pregnancy and gestational age-common

microbiome, but lacks the capacity for description of dynamic changes that may occur in individuals over time.

The placental microbiome

While the placenta has long been considered to be sterile in normal gestation,⁹⁹ several authors^{93,101–104} have now reported that the placenta in healthy pregnancies has its own resident microbiome. Indeed, it appears that the presence of bacterial infiltration of the placenta, without histologic evidence of infection, is not an unusual observation.^{101,103,104} Combs et al^{105,106} have shown that there is no association of preterm birth with a relatively benign intra-amniotic invasion of bacteria, that is, in the absence of inflammation. In contrast, preterm birth rates were higher in the presence of a combination of bacterial invasion and concomitant inflammatory response, indicated by elevated amniotic fluid levels of IL-6. Interestingly, in their initial study, Combs et al¹⁰⁵ diagnosed a microbial infection or severe inflammation (defined as amniotic fluid levels of IL-6 ≥ 11.3 ng/mL) in 63 of 305 ($\approx 20\%$) women with preterm labor. Of those identified with microbial infection ($n=27$), the offending microbe in roughly 50% of the patients was of a genus and species commonly found in the oral cavity, for example, *Fu. nucleatum*, *Bergeyella* sp., *Clostridium* sp., *Actinomyces* sp., *Peptostreptococcus* (a.k.a. *Parvimonas*) sp., and *Candida albicans*.

Given this observation, one might argue that the mere presence of bacteria in the placenta is not the important determinant of preterm birth. Rather the specific types of bacterial populations present would seem to play a bigger role. For example, the presence of “keystone” microbes, such as *Po. gingivalis* and/or *Fi. alocis*, both having the ability to interact with previously benign microbes, converting them into active pathogens, may play a sinister role in microbial dysbiosis that leads to an adverse pregnancy outcome. Given this line of thought, it is interesting to note that Aagaard et al¹⁰² reported that the bacterial taxonomic profile of the placenta microbiome was more similar to that of the oral cavity than to skin, nasal, vaginal, or the gastrointestinal floras of nonpregnant control patients.

The placental microbiome was found to contain, among others, bacteria belonging to the following phyla: Firmicutes, Tenericutes, Proteobacteria, Bacteroidetes, and Fusobacteria.¹⁰² The majority of bacterial species in these phyla are Gram-negative, anaerobic, and common to the human oral cavity. As suggested by Stout et al,¹⁰¹ the similarities of the two microbiomes (vaginal and oral) may indicate a hematogenous spread of the associated microbes. A hematogenous spread of oral microbes, in turn, presents

the possibility of their participation in the pathogenic mechanisms of preterm birth or other adverse pregnancy outcomes, such as preeclampsia or fetal death.^{24,107–112}

Bacteria and adverse pregnancy outcomes

Infection-related preterm birth is reported as the leading cause of infant mortality and morbidity.¹¹⁰ Evidence indicates that $\sim 40\%$ of preterm births are vaginal and intrauterine infection related and $\sim 50\%$ are associated with intra-amniotic infections.^{97,113,114} Given this background, an understanding of the origin of the offending bacteria and routes of invasion of the placenta and amniotic cavity becomes requisite. A review by Mendez et al³² concluded that the most common intra-amniotic bacterial taxa were species associated with the vagina, although other species were commonly associated with the oral cavity, gastrointestinal and respiratory tracts. The authors concluded that the collective data indicate a primary role for the ascending route of infection during pregnancy and a possible secondary role for the hematogenous route of invasion.

In spite of the evidence and the biologic plausibility supporting a hematogenous dissemination of oral microbes and a role in adverse pregnancy outcomes,^{115–118} a paradox remains. Results of intervention studies in which periodontal disease was treated in the second trimester of pregnancy have generated conflicting results.^{30,119–127} Reasons for this lack of effect may involve several design and methodology issues, such as 1) variations in the comprehensive nature of the periodontal examination, that is, partial vs full-mouth examination, which result in an imprecise determination of disease severity; 2) variations in the consistency in timing of the periodontal examination with respect to gestational age; 3) lack of masking of examiners; 4) lack of multivariable analyses that considered confounders³⁰; 5) variations in treatment protocols; 6) treatment failed to adequately reduce periodontal inflammation; and 7) treatment rendered in the second trimester may be too late to elicit a beneficial effect on pregnancy outcomes. The obvious intervention study remains to be done, that is, definitive treatment of inflammatory periodontal disease prior to conception, followed by periodontal maintenance every 3 months during pregnancy.

One might argue that the hematogenous spread of oral microbial pathogens (bacteremia) is prevented by systemic “biologic filters” such as the reticuloendothelial systems of the liver and spleen and the maternal–fetal barrier. However, multiple avenues exist for how bacteria of oral origin can participate in placental and intrauterine infections. Take for example, *Fu. nucleatum*, a highly prevalent oral

microbial species that is associated with both periodontal disease^{128,129} and adverse pregnancy complications.^{130,131} Several investigators^{132,133} have shown that *Fu. nucleatum* can be induced to express adhesin FadA, a protein that interacts with E-cadherin which is a major mediator of cell-to-cell attachment of epithelial and endothelial cells. *Fu. nucleatum* adheres to and invades host cells and facilitates invasion by otherwise noninvasive bacteria.^{134–136} Indeed, host cell attachment and invasion by *Fu. nucleatum* has been shown to play a critical role in intrauterine infection.^{133,136}

A second consideration is the potential role for *Po. gingivalis*, mentioned earlier along with *Fi. alocis*, as a “keystone” microbe. *Po. gingivalis* has been detected in the amniotic fluid of pregnant females at risk for premature delivery^{137,138} and in the placentas of patients with preeclampsia.¹³⁹ Immunohistochemistry techniques have shown that the microbe has a demonstrated presence in placental tissues, for example, syncytiotrophoblasts, chorionic trophoblasts, decidual cells, amniotic epithelial cells, and endothelial cells, obtained from subjects diagnosed with chorioamnionitis. Last, animal studies have demonstrated the ability of *Po. gingivalis* to achieve transplacental passage, resulting in chorioamnionitis and placentitis.^{140,141}

A third conceivable pathway for establishment of oral microbial pathogens in the vaginal, microbiome which, in a pregnancy may contribute to the placental microbiome, can be explained by direct transmission through sexual practices. This latter pathway does not seem to have been addressed in the research literature.

Regardless of the origin, infections leading to adverse pregnancy outcomes that involve bacteria common to the oral cavity raise at least two relevant questions from a public health viewpoint:

1. Will preconception treatment of periodontal disease, that is, reduction of inflammation, bacterial loads, and inflammatory mediators, in a reproductive age female, reduce the incidence of adverse pregnancy outcomes?
2. Given the possibility of transmission of oral pathogenic microbes during sexual activities, will preconception treatment of periodontal disease in both partners reduce the incidence of adverse pregnancy outcomes?

Given the cost of dental care in the US and some other developed countries, the maldistribution of dental practitioners in urban vs rural localities, and the lack of dental care in many underdeveloped countries, a profound disparity exists in access to dental care and in periodontal health in poor and/or rural populations.^{142–150} Assuming that research initiatives will eventually answer the two questions listed

above, the medical and dental public health communities still need to develop strategies to address access to care.

Conclusion

Significant evidence supports an association between the dissemination of pathogenic bacteria associated with moderate and severe periodontitis and extraoral infections and inflammation. The virulence properties assigned to specific oral pathogenic bacteria, for example, *Fu. nucleatum*, *Po. gingivalis*, *Fi. alocis*, *C. rectus*, and others, render them as potential collaborators in adverse outcomes of pregnancy.^{21,151–154} The biologic plausibility of the association between periodontal disease, the inherent bacteria and systemic impact of inflammatory mediators, and adverse pregnancy outcomes likely involves several pathways: 1) a hematogenous spread (bacteremia) of periodontal pathogens;¹⁵¹ 2) a hematogenous spread of multiple mediators of inflammation that are generated by the host and/or fetal immune response to pathogenic bacteria;^{116,155} and 3) a possible oral microbial pathogen transmission, with subsequent colonization, in the vaginal microbiome resulting from sexual practices. The medical and dental public health communities should address intervention strategies aimed at controlling oral inflammatory disease, which will lessen the systemic inflammatory burden and suppress the potential for adverse pregnancy outcomes.

Author contributions

CMC, PJK, and KBW procured and read all articles and the team wrote the manuscript. SB and MA were reviewers and offered multiple suggestions that were incorporated into the manuscript. RJD is the team director and conceived several hypotheses around which the manuscript is structured. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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