8-8-2017

The oral microbiome and adverse pregnancy outcomes.

Charles M. Cobb
University of Missouri-Kansas City

Patricia J. Kelly
University of Missouri-Kansas City

Karen B. Williams
University of Missouri-Kansas City

Shilpa Babbar
Saint Louis University

Mubashir Angolkar
Jawaharlal Nehru Medical College

See next page for additional authors

Authors
Charles M. Cobb, Patricia J. Kelly, Karen B. Williams, Shilpa Babbar, Mubashir Angolkar, and Richard J. Derman

International Journal of Women's Health

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

The oral microbiome and adverse pregnancy outcomes

This article was published in the following Dove Press journal:
International Journal of Women's Health
8 August 2017
Number of times this article has been viewed

Charles M Cobb[1]
Patricia J Kelly[2]
Karen B Williams[3]
Shilpa Babbar[4]
Mubashir Angolkar[5]
Richard J Derman[6]

[1]Department of Periodontics, School of Dentistry, [2]Department of Public Health Nursing, School of Nursing and Health Studies, [3]Department of Biomedical & Health Informatics, School of Medicine, University of Missouri-Kansas City, Kansas City, MO, [4]Department of Obstetrics, Gynecology & Women's Health, Division of Maternal & Fetal Medicine, School of Medicine, Saint Louis University, St Louis, MO, USA; [5]Department of Public Health, Jawaharlal Nehru Medical College (JNMC), KLE University, Karnataka, India; [6]Department of Obstetrics & Gynecology, Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, PA, USA

Correspondence: Patricia J Kelly
University of Missouri, School of Nursing and Health Studies, 2464 Charlotte St, Kansas City, MO 85716, USA
Tel +1 913 522 7364
Fax +1 816 235 1701
Email kellypj@umkc.edu

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,

submit your manuscript | www.dovepress.com
Dovepress
http://dx.doi.org/10.2147/IJWH.S142730

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)-1β, 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 ≈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 al[84] study is judged to be slight to moderate.

Batra et al[85] 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 al[87] and Rao et al[88] both assessed rural Indian populations from Punjab and Mustabad, Krishna District, respectively. One study used the CPITN[87] and the other the Community Periodontal Index[88] indices for screening of patients and approximation of disease severity. Females represented ≈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 al[90] 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 al[86] 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 al[97] 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 al[98] and Prince et al[99] 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 al[100] 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 al[99] reported that during pregnancy, there is an overall increase of bacteria from the taxa of *Lactobacillus*, *Clostridiales*, *Bacterodies*, and *Actinomycetales*. However, none of these taxa were noted as having any negative effects on pregnancy. Prince et al[99] 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 al[105] diagnosed a microbial infection or severe inflammation (defined as amniotic fluid levels of IL-6 ≥11.3 ng/mL) in 63 of 305 (≈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. *Parviomonas*) 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 al[102] 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 ~40% of preterm births are vaginal and intrauterine infection related and ~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 al[32] 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 confounders[30]; 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.

References

1. Google celebrates Julius Richard Petri, inventor of the Petri dish. Available from: https://www.theguardian.com/science/grrlscientist/2013/may/31/google-julius-richard-petri-inventor-petri-dish. Accessed November 24, 2016.
2. Zhou Y, Mihindukulasuriva KA, Gao H, et al. Exploration of bacterial community classes in major human habitats. *Genome Biol*. 2014;15(5):R66.
3. Cho I, Blaser MJ. The human microbiome: at the interface of health and disease. *Nat Rev Genet*. 2012;13(4):260–270.
4. Ding T, Schloss PD. Dynamics and associations of microbial community types across the human body. *Nature*. 2014;509(7500):357–360.
5. Lourenço TGB, Heller D, Silva-Boghossian CM, et al. Microbial signature profiles of periodontally healthy and diseased patients. *J Clin Periodontol*. 2014;41(11):1027–1036.

6. Macedo Paizan ML, Vilela-Martin JF. Is there an association between periodontitis and hypertension? *Curr Cardiol Rev*. 2014;10(4):355–361.
7. Szulc M, Kustrzycki W, Janczak D, et al. Presence of periodontopathic bacteria DNA in atheromatous plaques from coronary and carotid arteries. *BioMed Res Int*. 2015;2015: Article ID 825397.
8. Chistiakov DA, Orekhov AN, Bobryshev YV. Links between atherosclerotic and periodontal disease. *Exp Mol Pathol*. 2016;100(1):220–235.
9. Gurav AN. The implication of periodontitis in vascular endothelial dysfunction. *Eur J Clin Invest*. 2014;44(10):1000–1009.
10. Hansen GM, Egeberg A, Holmstrkup P, et al. Relation of periodontitis to risk of cardiovascular and all-cause mortality (from a Danish nationwide cohort study). *Am J Cardiol*. 2016;118(4):489–493.
11. Orlandi M, Suvan J, Petrie A, et al. Association between periodontal disease and its treatment, flow-mediated dilatation and carotid intima-media thickness: a systematic review and meta-analysis. *Atheroscler*. 2014;236(1):39–46.
12. Lafon A, Pereira B, Dufour T, et al. Periodontal disease and stroke: a meta-analysis of cohort studies. *Eur J Neurol*. 2014;21(9):1155–1161, e66–e67.
13. Lafon A, Tala S, Ahossi V, et al. Association between periodontal disease and non-fatal ischemic stroke: a case-control study. *Acta Odont Scand*. 2014;72(8):687–693.
14. Lee YL, Hu HY, Huang N, et al. Dental prophylaxis and periodontal treatment are protective factors to ischemic stroke. *Stroke*. 2013;44(4): 1026–1030.
15. Borgnakke WS, Ylöstalo PV, Taylor GW, et al. Effect of periodontal disease on diabetes: systematic review of epidemiologic observational evidence. *J Clin Periodontol*. 2013;40(Suppl 14):S135–S152.
16. Taylor JJ, Preshaw PM, Lalla E. A review of the evidence for pathogenic mechanisms that may link periodontitis and diabetes. *J Clin Periodontol*. 2013;40(Suppl 14):S113–S134.
17. Preshaw PM, Alba AL, Herrera D, et al. Periodontitis and diabetes: a two-way relationship. *Diabetologia*. 2012;55(1):21–31.
18. Noble JM, Scarmeas N, Celenti RS, et al. Serum IgG antibody levels to periodontal microbiota are associated with incident Alzheimer disease. *PLoS One*. 2014;9(12):e114959.
19. Gaur S, Agnihotri R. Alzheimer's disease and chronic periodontitis: is there an association? *Geriatrics Gerontol Inter*. 2015;15(4):391–404.
20. Martande SS, Pradeep AR, Singh SP, et al. Periodontal health condition in patients with Alzheimer's disease. *Am J Alzheimer's Dis Other Dement*. 2014;29(6):498–502.
21. Cassini MA, Pilloni A, Condo SG, et al. Periodontal bacteria in the genital tract: are they related to adverse pregnancy outcome? *Int J Immunopathol Pharmacol*. 2013;26(4):931–939.
22. Coppenhagen-Glazer S, Sol A, Abed J, et al. Fap2 of Fusobacterium nucleatum is a galactose-inhibitable adhesin involved in coaggregation, cell adhesion, and preterm birth. *Infect Immun*. 2015;83(3): 1104–1113.
23. Pozo E, Mesa F, Ikram MH, et al. Preterm birth and/or low birth weight are associated with periodontal disease and increased placental immunohistochemical expression of inflammatory markers. *Hist Histopathol*. 2016;31(2):231–237.
24. Sgolastra F, Petrucci A, Severino M, et al. Relationship between periodontitis and pre-eclampsia: a meta-analysis. *PLoS One*. 2013;8(8): e71387.
25. Takeuchi N, Ekuni D, Irie K, et al. Relationship between periodontal inflammation and fetal growth in pregnant women: a cross-sectional study. *Arch Gyencol Obstet*. 2013;287(5):951–957.
26. Khadem N, Rahmani ME, Sanaei A, et al. Association between preterm and low-birth weight with periodontal disease: a case-control study. *Iran J Reprod Med*. 2012;10(6):561–566.
27. Gomes-Filho IS, Pereira EC, Cruz SS, et al. Relationship among mother's glycemic level, periodontitis, and birth weight. *J Periodontol*. 2016;87(3):238–247.
28. Teles R, Wang C-Y. Mechanisms involved in the association between periodontal diseases and cardiovascular disease. *Oral Dis*. 2011; 17(5):450–461.
29. Iwai T. Periodontal bacteremia and various vascular diseases. *J Periodont Res*. 2009;44(6):689–694.
30. Papapanou PN. Systemic effects of periodontitis: lessons learned from research on atherosclerotic vascular disease and adverse pregnancy outcomes. *Int Dent J*. 2015;65(6):283–291.
31. Reynolds MA. Modifiable risk factors in periodontitis: at the intersection of aging and disease. *Periodontol 2000*. 2014;64(1):7–19.
32. Mendez GL, Kaakoush NO, Quinlivan JA. Bacterial aetiological agents of intra amniotic infections and preterm birth in pregnant women. *Front Cell Infect Microbiol*. 2013;3:58.
33. Romero R, Mazor M. Infection and preterm labor. *Clin Obstet Gynecol*. 1988;31(3):553–584.
34. DiGiulio DB. Diversity of microbes in amniotic fluid. *Semin Fetal Neonatal Med*. 2012;17(1):2–11.
35. Han YW, Ikegami A, Bissada NF, et al. Transmission of an uncultivated Bergeyella strain from the oral cavity to amniotic fluid in a case of preterm birth. *J Clin Microbiol*. 2006;44(4):1475–1483.
36. Rai B, Kaur J, Kharb S [webpage on the Internet]. Pregnancy gingivitis and periodontitis and its systemic effect. *Internet J Dent Sci*. 2008;6(2). Available from: http://ispub.com/IJDS/6/2/5532. Accessed January 29, 2017.
37. Dewhirst FE, Chen T, Izard J, et al. The human oral microbiome. *J Bacteriol*. 2010;92(19):5002–5017.
38. He J, Li Y, Cao Y, et al. The oral microbiome diversity and its relation to human diseases. *Folia Microbiol*. 2015;60(1):69–80.
39. Hong B-Y, Araujo MVF, Strausbaugh LD, et al. Microbiome profiles in periodontitis in relation to host disease characteristics. *PLoS One*. 2015;10(5):e0127077.
40. Park O-J, Yi H, Jeon JH, et al. Pyrosequencing analysis of subgingival microbiota in distinct periodontal conditions. *J Dent Res*. 2015;94(7): 921–927.
41. Paster BJ, Boches SK, Galvin JL, et al. Bacterial diversity in human subgingival plaque. *J Bacteriol*. 2001;183(12):3770–3783.
42. 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(6):409–419.
43. Jiao Y, Hasegawa M, Inohara N. The role of oral pathobionts in dysbiosis during periodontitis development. *J Dent Res*. 2014;93(6):539–546.
44. Belstrom D, Fiehn N-E, Nielsen CH, et al. Differences in bacterial saliva profile between periodontitis patients and a control cohort. *J Clin Periodontol*. 2014;41(2):104–112.
45. Darveau RP. Periodontitis: a polymicrobial disruption of host homeostasis. *Nat Rev Microbiol*. 2010;8(7):481–490.
46. Hajishengallis G. The inflammophilic character of the periodontitis-associated microbiota. *Mol Oral Microbiol*. 2014;29(6):248–257.
47. Socransky SS, Haffajee AD. Evidence of bacterial etiology: a historical perspective. *Periodontol 2000*. 1994;5:7–25.
48. Khan SA, Kong EF, Meiller TF, et al. Periodontal diseases: bug induced, host promoted. *PLoS Pathog*. 2015;11(7):e1004952.
49. Hienz SA, Paliwal S, Ivanovski S. Mechanisms of bone resorption in periodontitis. *J Immunol Res*. 2015;2015:615486.
50. Petersen C, Round JL. Defining dysbiosis and its influence on host immunity and disease. *Cell Microbiol*. 2014;16(7):1024–1033.
51. Marques-Rocha JL, Samblas M, Milagro FI, et al. Noncoding RNAs, cytokines, and inflammation-related diseases. *FASEB J*. 2015;29(9): 3595–3611.
52. Palm F, Lahdentausta L, Sorsa T, et al. Biomarkers of periodontitis and inflammation in ischemic stroke: a case-control study. *Innate Immun*. 2014;20(5):511–518.
53. Sawada S, Chosa N, Ishisaki A, et al. Enhancement of gingival inflammation induced by synergism of IL-1beta and IL-6. *Biomed Res*. 2013;34(1): 31–40.
54. Schenkein HA, Loos BG. Inflammatory mechanisms linking periodontal diseases to cardiovascular diseases. *J Periodontol*. 2013;84(Suppl 4): S51–S69.
55. Silva N, Abusleme L, Bravo D, et al. Host response mechanisms in periodontal diseases. *J Applied Oral Sci*. 2015;23(3):329–355.

56. Yucel-Lindberg T, Bage T. Inflammatory mediators in the pathogenesis of periodontitis. *Expert Rev Mol Med*. 2013;15:e7.
57. Socransky SS, Haffajee AD. Periodontal microbial ecology. *Periodontol 2000*. 2005;38:135–187.
58. Aas KA, Paster BJ, Stokes IN, et al. Defining the normal bacteria flora of the oral cavity. *J Clin Microbiol*. 2005;42(11):5721–5732.
59. Oliveira RRDS, Fermiano D, Feres M, et al. Levels of candidate periodontal pathogens in subgingival biofilm. *J Dent Res*. 2016;95(6): 711–718.
60. Hajishengallis G, Darveau RP, Curtis MA. The keystone-pathogen hypothesis. *Nat Rev Microbiol*. 2012;10(10):717–725.
61. Darveau RP, Hajishengallis G, Curtis MA. Porphyromonas gingivalis as a potential community activist for disease. *J Dent Res*. 2012;91(9): 816–820.
62. Hajishengallis G. Immunomicrobial pathogenesis of periodontitis: keystones, pathobionts, and host response. *Trends Immunol*. 2014; 35(1):3–11.
63. Hajishengallis G. Periodontitis: from microbial immune subversion to systemic inflammation. *Nat Rev Immunol*. 2015;15(1):30–44.
64. Zenobia C, Hajishengallis G. Porphyromonas gingivalis virulence factors involved in subversion of leukocytes and microbial dysbiosis. *Virulence*. 2015;6(3):236–243.
65. Aruni AW, Roy F, Fletcher HM. Filifactor alocis has virulence attributes that can enhance its persistence under oxidative stress conditions and mediate invasion of epithelial cells by Porphyromonas gingivalis. *Infect Immun*. 2011;79(10):3872–3886.
66. Aruni AW, Zhang K, Dou Y, et al. Proteome analysis of coinfection of epithelial cells with Filifactor alocis and Porphyromonas gingivalis shows modulation of pathogen and host regulatory pathways. *Infect Immun*. 2014;82(8):3261–3274.
67. Aruni AW, Mishra A, Dou Y, et al. Filifactor alocis – a new emerging periodontal pathogen. *Microbes Infect*. 2015;17(7):517–530.
68. Chen H, Liu Y, Zhang M, et al. A Filifactor alocis-centered co-occurrence group associates with periodontitis across different oral habitats. *Sci Rep*. 2015;5: Article No. 9053.
69. Wang Q, Jotwani R, Le J, et al. Filifactor alocis infection and inflammatory responses in the mouse subcutaneous chamber model. *Infect Immun*. 2014;82(3):1205–1212.
70. Tribble GD, Lamont RJ. Bacterial invasion of epithelial cells and spreading in periodontal tissue. *Periodontol 2000*. 2010;52(1): 68–83.
71. Li Y, Guo H, Wang X, et al. Coinfection with Fusobacterium nucleatum can enhance the attachment and invasion of Porphyromonas gingivalis or Aggregatibacter actinomycetemcomitans to human gingival epithelial cells. *Arch Oral Biol*. 2015;60(9):1387–1393.
72. Mendes L, Azevedo NF, Felino A, et al. Relationship between invasion of the periodontium by periodontal pathogens and periodontal disease: a systematic review. *Virulence*. 2015;6(3):208–215.
73. Hill GB. Preterm birth: associations with genital and possibly oral microflora. *Ann Periodontol*. 1998;3(1):222–232.
74. Mobeen N, Jehan I, Banday N, et al. Periodontal disease and adverse birth outcomes: a study from Pakistan. *Am J Obstet Gynecol*. 2008; 198(5):514.e1–514.e8.
75. Chakki BA, Ealla KR, Hunsingi P, et al. Influence of maternal periodontal disease as a risk factor for low birth weight infants in Indian population. *J Contemp Dent Pract*. 2012;13(5):676–680.
76. Fardini Y, Chung P, Dumm R, et al. Transmission of diverse oral bacteria to murine placenta: evidence for the oral microbiome as a potential source of intrauterine infection. *Infect Immun*. 2010;78(4): 1789–1796.
77. Paropkari AD, Leblebicioglu B, Christian LM, et al. Smoking, pregnancy and the subgingival microbiome. *Sci Rep*. 2016;6:30388.
78. Eke PI, Dye BA, Wei L, et al. Prevalence of periodontitis in adults in the United States: 2009–2010. *J Dent Res*. 2012;91(10):914–920.
79. Eke PI, Dye BA, Wei L, et al. Update on prevalence of periodontitis in adults in the United States: NHANES 2009 to 2012. *J Periodontol*. 2015; 86(5):611–622.
80. Petersen PE, Ogawa H. The global burden of periodontal disease: towards integration with chronic disease prevention and control. *Periodontol 2000*. 2012;60(1):15–29.
81. Zahn Y, Holtfreter B, Meisel P, et al. Prediction of periodontal disease: modeling and validation in different general German populations. *J Clin Periodontol*. 2014;41(3):224–232.
82. Shaju JP, Zade RM, Das M. Prevalence of periodontitis in the Indian population: a literature review. *J Indian Soc Periodontol*. 2011;15(1): 29–34.
83. Agarwal V, Khatri M, Singh G, et al. Prevalence of periodontal disease in India. *J Oral Health Community Dent*. 2010;4(Suppl):7–16.
84. Bansal M, Mittal N, Sigh TB. Assessment of the prevalence of periodontal diseases and treatment needs: a hospital-based study. *J Indian Soc Periodontol*. 2015;19(2):211–215.
85. Batra M, Tangade P, Gupta D. Assessment of periodontal health among the rural population of Moradabad, India. *J Indian Assoc Public Health Dent*. 2014;12(1):28–32.
86. Chandra A, Yadav OP, Sarula S, et al. Epidemiology of periodontal disease in Indian population since last decade. *J Int Soc Prev Community Dent*. 2016;6(2):91–96.
87. Grewal Y, Datta R, Singh K, et al. Prevalence of periodontal disease in the rural population of Punjab, India. *J Pharm Biomed Sci*. 2014; 4(5):532–535.
88. Rao MVR, Katari PK, Vegi L, et al. Prevalence of periodontal disease among rural population of Mustabad, Krishna district. *J Int Soc Prev Community Dent*. 2016;6(Suppl 1):S59–S63.
89. Ainamo J, Barmes D, Beagrie, et al. Development of the World Health Organization (WHO) community periodontal index of treatment needs (CPITN). *Int Dent J*. 1982;32(3):281–291.
90. Murthy S, Mubashir A, Kodkany BS, et al. Pregnancy periodontitis and low birth weight: a cohort study in rural Begaum, India. *Global J Med Public Health*. 2012;1(4):42–48.
91. Shewale AH, Gattani DR, Bhata N, et al. Prevalence of periodontal disease in the general population of India: a systematic review. *J Clin Diagnostic Res*. 2016;10(6):ZE04–ZE09.
92. Human Microbiome Project Consortium. Structure, function and diversity of the healthy human microbiome. *Nature*. 2012;486(7402):207–214.
93. Fox C, Eichelberger K. Maternal microbiome and pregnancy outcomes. *Fertil Steril*. 2015;104(6):1358–1363.
94. Miller EA, Beasley DE, Dunn RR, et al. Lactobacilli dominance and vaginal pH: why is the human vaginal microbiome unique? *Front Microbiol*. 2016;7: Article 1936.
95. Hickey RJ, Zhou X, Pierson JD, et al. Understanding vaginal microbiome complexity from an ecological perspective. *Transl Res*. 2012; 160(4):267–282.
96. Kamada N, Ghen GY, Inohara N, Núñez G. Control of pathogens and pathobionts by the gut microbiota. *Nat Immunol*. 2013;14(7):685–690.
97. Hyman RW, Fukushima M, Jiang H, et al. Diversity of the vaginal microbiome correlates with preterm birth. *Reprod Sci*. 2014;21(1): 32–40.
98. Green KA, Zarek SM, Catherino WH. Gynecologic health and disease in relation to the microbiome of the female reproductive tract. *Fertil Steril*. 2015;104(6):1351–1357.
99. Prince AL, Chu DM, Seferovic MD, et al. The perinatal microbiome and pregnancy: moving beyond the vaginal microbiome. *Cold Spring Harb Perspect Med*. 2015;5(6):a023051.
100. Hickey RJ, Zhou X, Settles ML, et al. Vaginal microbiota of adolescent girls prior to the onset of menarche resemble those of reproductive-age women. *mBiol*. 2015;6(2):e00097–e00015.
101. Stout MJ, Conlon B, Landeau M, et al. Identification of intracellular bacteria in the basal plate of the human placenta in term and preterm gestations. *Am J Obstet Gynecol*. 2013;208(3):226.e1–226.e7.
102. Aagaard K, Ma J, Antony KM, et al. The placenta harbors a unique microbiome. *Sci Trans Med*. 2014;6(237):237ra65.
103. Fortner KB, Grotegut CA, Ransom CE, et al. Bacteria localization and chorion thinning among preterm premature rupture of membranes. *PLoS One*. 2014;9(1):e83338.

104. Steel JH, Malatos S, Kennea N, et al. Bacteria and inflammatory cells in fetal membranes do not always cause preterm labor. *Pediatr Res*. 2005;57(3):404–411.
105. Combs CA, Gravett M, Garite TJ, et al. Amniotic fluid infection, inflammation, and colonization in preterm labor with intact membranes. *Am J Obstet Gynecol*. 2014;210(2):125.e1–125.e15.
106. Combs CA, Garite TJ, Lapidus JA, et al. Detection of microbial invasion of the amniotic cavity by analysis of cervicovaginal proteins in women with preterm labor and intact membranes. *Am J Obstet Gynecol*. 2015;212(4):482.e1–482.e12.
107. Straka M. Pregnancy and periodontal tissues. *Neuro Endocrinol Lett*. 2011;32(1):34–38.
108. 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(Pt 1):133–144.
109. Ide M, Papapanou PN. Epidemiology of association between maternal periodontal disease and adverse pregnancy outcomes: systematic review. *J Periodontol*. 2013;84(Suppl 4):S181–S194.
110. Kumar A, Basra M, Begum N, et al. Association of maternal periodontal health with adverse pregnancy outcome. *J Obstet Gynaecol Res*. 2013;39(1):40–45.
111. Ha JE, Jun JK, Ko HJ, et al. Association between periodontitis and preeclampsia in never-smokers: a prospective study. *J Clin Periodontol*. 2014;41(9):869–874.
112. Han YW. Fusobacterium nucleatum: a commensal-turned pathogen. *Curr Opin Microbiol*. 2015;23(2):141–147.
113. Burd I, Balakrishnan B, Kannan S. Models of fetal brain injury, intrauterine inflammation and preterm birth. *Am J Reprod Immunol*. 2012;67(4):287–294.
114. Ganu RS, Ma J, Aagaard KM. The role of microbial communities in parturition: is there evidence of association with preterm birth and perinatal morbidity and mortality. *Am J Perinatol*. 2013;30(8):613–624.
115. Parihar AS, Katoch V, Rajguru SN, et al. Periodontal disease: a possible risk factor for adverse pregnancy outcome. *J Int Oral Health*. 2015;7(7):137–142.
116. Pretorius C, Jagatt A, Lamont RF. The relationship between periodontal disease, bacterial vaginosis, and preterm birth. *J Perinat Med*. 2007;35(2):93–99.
117. Leitich H, Bodner-Adler B, Brunbauer M, et al. Bacterial vaginosis as a risk factor for preterm delivery: a meta-analysis. *Am J Obstet Gynecol*. 2003;189(1):139–147.
118. Igari K, KudoT, Toyofuku T, et al. Association between periodontitis and the development of systemic diseases. *Oral Biol Dent*. 2014;2:4.
119. Jeffcoat MK, Geurs NC, Reddy MS, et al. Periodontal infection and preterm birth: results of a prospective study. *J Am Dent Assoc*. 2001;132(7):875–880.
120. Moore S, Ide M, Coward PY, et al. A prospective study to investigate the relationship between periodontal disease and adverse pregnancy outcome. *Br Dent J*. 2004;197(5):251–258.
121. Michalowicz BS, Hodges JS, DiAngelis AJ, et al. Treatment of periodontal disease and the risk of preterm birth. *N Engl J Med*. 2006; 355(18):1885–1894.
122. Offenbacher S, Boggess KA, Murtha AP, et al. Progressive periodontal disease and risk of very preterm delivery. *Obstet Gynecol*. 2006;107(1):29–36.
123. Marcones GA, Parry S, Nelson DB, et al. Treatment of localized periodontal disease in pregnancy does not reduce the occurrence of preterm birth: results from the Periodontal Infections and Prematurity Study (PIPS). *Am J Obstet Gynecol*. 2010;202(2):147.e1–147.e8.
124. Jeffcoat M, Parry S, Sammel M, et al. Periodontal infection and preterm birth: successful periodontal therapy reduces the risk of preterm birth. *BJOG*. 2011;118(2):250–256.
125. Pirie M, Linden G, Irwin C. Intrapregnancy non-surgical periodontal treatment and pregnancy outcome: a randomized controlled trial. *J Periodontol*. 2013;84(10):1391–1400.
126. Jeffcoat MK, Jeffcoat RL, Gladowski PA, et al. Impact of periodontal therapy on general health: evidence from insurance data for five systemic conditions. *Am J Prev Med*. 2014;47(2):166–174.
127. Penova-Veselinovic B, Keelan JA, Wang CA, et al. Changes in inflammatory mediators in gingival crevicular fluid following periodontal disease treatment in pregnancy: relationship to adverse pregnancy outcome. *J Reproduct Immunol*. 2015;112(11):1–10.
128. Li Y, Guo H, Wang X, et al. Coinfection with *Fusobacterium nucleatum* can enhance the attachment and invasion of *Porphyromonas gingivalis* or *Aggregatibacter actinomycetemcomitans* to human gingival epithelial cells. *Arch Oral Biol*. 2015;60(9): 1387–1393.
129. Topcuoglu N, Kulekci G. 16S rRNA based microarray analysis of ten periodontal bacteria in patients with different forms of periodontitis. *Anaerobe*. 2015;35(Pt A):35–40.
130. Han YW, Fardini Y, Chen C, et al. Term stillbirth caused by oral *Fusobacterium nucleatum*. *Obstet Gynecol*. 2010;115(2 Pt 2):442–445.
131. Han YW, Shen T, Chung P, et al. Uncultivated bacteria as etiologic agents of intra-amniotic inflammation leading to preterm birth. *J Clin Microbiol*. 2009;47(1):38–47.
132. Ikegami A, Chung P, Han YE. Complementation of the fadA mutation in *Fusobacterium nucleatum* demonstrates that the surface-exposed adhesin promotes cellular invasion and placental colonization. *Infect Immun*. 2009;77(7):3075–3079.
133. Fardini Y, Wang X, Témoin S, et al. *Fusobacterium nucleatum* adhesin FadA binds vascular endothelial cadherin and alters endothelial integrity. *Mol Microbiol*. 2011;82(6):1468–1480.
134. Edwards AM, Grossman TJ, Rudney JD. *Fusobacterium nucleatum* transports noninvasive *Streptococcus cristatus* into human epithelial cells. *Infect Immun*. 2006;74(1):654–662.
135. Han YW, Redline RW, Li M, et al. *Fusobacterium nucleatum* induces premature and term stillbirths in pregnant mice: implication of oral bacteria in preterm birth. *Infect Immun*. 2004;72(4):2272–2279.
136. Han YW, Shi W, Huang GT, et al. Interactions between periodontal bacteria and human oral epithelial cells: *Fusobacterium nucleatum* adheres to and invades epithelial cells. *Infect Immun*. 2000; 68(6):3140–3146.
137. 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(7): 1764–1770.
138. Barak S, Oettinger-Barak O, Machtei EE, et al. Evidence of periodontopathic microorganisms in placentas of women with preeclampsia. *J Periodontol*. 2007;78(4):670–676.
139. Katz J, Chegini N, Shiverick KT, et al. Localization of *P. gingivalis* in preterm delivery placenta. *J Dent Res*. 2009;88(6):575–578.
140. Boggess KA, Madianos PN, Preisser JS, et al. Chronic maternal and fetal *Porphyromonas gingivalis* exposure during pregnancy in rabbits. *Am J Obstet Gynecol*. 2005;192(2):554–557.
141. Belanger M, Reyes L, von Deneen K, et al. Colonization of maternal and fetal tissues by *Porphyromonas gingivalis* is strain-dependent in a rodent animal model. *Am J Obstet Gynecol*. 2008;199(10): 86.e1–86.e7.
142. Sanmartin C, Hennessy D, Lu Y, et al. Trends in out-of-pocket health care expenditures in Canada, by household income, 1997–2009. *Health Rep*. 2014;25(4):13–17.
143. Allareddy V, Rampa S, Lee MK, et al. Hospital-based emergency department visits involving dental conditions: profile and predictors of poor outcomes and resource utilization. *J Am Dent Assoc*. 2014; 145(4):331–337.
144. Listl S, Galloway J, Mossey PA, et al. Global economic impact of dental diseases. *J Dent Res*. 2015;94(10):1355–1361.
145. Obeidat SR, Alsa'di AG, Taani DS. Factors influencing dental care access in Jordanian adults. *BMC Oral Health*. 2014;14:127.
146. Guessous I, Theler JM, Durosier I, et al. Forgoing dental care for economic reasons in Switzerland: a six-year cross-sectional study. *BMC Oral Health*. 2014;14:121.

147. Thompson B, Cooney P, Lawrence H, et al. Cost as a barrier to accessing dental care: findings from a Canadian population-based study. *J Pub Health Dent*. 2014;74(3):210–218.
148. Fisher C, Sood K. What is driving the growth in medical tourism? *HMQ*. 2014;31(3):246–262.
149. Osborn R, Squires D, Doty MM, et al. In new survey of eleven countries, US adults still struggle with access to and affordability of health care. *Health Affairs*. 2016;35(12):2327–2336.
150. Lugo I, Arteaga S, Sanchez V. Oral health status, perceptions, and access to dental care in the Hispanic population. *Gen Dent*. 2014;62(4):24–30.
151. Han YW, Wang X. Mobile microbiome: oral bacteria in extra-oral infections and inflammation. *J Dent Res*. 2013;92(6):485–491.
152. Boggess KA, Moss K, Madianos P, et al. Fetal immune response to oral pathogens and risk of preterm birth. *Am J Obstet Gynecol*. 2005; 193 (3 Pt 2):1121–1126.
153. Gogeneni H, Buduneli N, Ceyhan-Öztürk B, et al. Increased infection with key periodontal pathogens during gestational diabetes mellitus. *J Clin Periodontol*. 2015;42(6):506–512.
154. Prince AL, Antony KM, Ma J, et al. The microbiome and development: a mother's perspective. *Semin Reprod Med*. 2014;32(1): 14–22.
155. Prince AL, Antony KIM, Chu DM, et al. The microbiome, parturition, and timing of birth: more questions than answers. *J Reprod Immunol*. 2014;104–105:12–19.