The Potential Role of Maternal Periodontitis on Preterm Birth and Adverse Neonatal Neurologic Outcomes

Gregory Charles Valentine¹, Sandra E Juul²

ABSTRACT

Periodontitis is an often overlooked but important risk factor for both preterm birth and adverse neonatal outcomes. With preterm birth being the leading cause of mortality for all children under the age of 5, any potentially modifiable risk factor associated with preterm birth must be fully evaluated. Periodontal disease is due to bacterial infection of the gingivae with resulting localized and systemic inflammation that can have profound effects in both nonpregnant and pregnant individuals. In pregnancy, several studies have demonstrated an association between periodontitis and preterm birth. Furthermore, extensive evidence demonstrates that fetal exposure to systemic inflammation during gestation predisposes to brain injury and neurodevelopmental delay. Thus, periodontitis and the resulting inflammatory cascade not only affect the pregnant individual but also have significant lifelong consequences on the development and well-being of future offspring. In this review, we will first discuss the epidemiology, prevalence, and pathophysiology of periodontitis. We will then explore the medical literature evaluating the association between periodontitis and preterm birth prior to delving into the potential for neurodevelopmental delay and brain injury among offspring. Finally, we will conclude by discussing future directions and unanswered questions related to periodontitis and its relationship with preterm birth and adverse neonatal outcomes.

Keywords: Inflammation, Neurologic impairment, Periodontitis, Preterm birth.

Newborn (2022): 10.5005/jp-journals-11002-0008

INTRODUCTION

Periodontitis is an often overlooked but important risk factor for both preterm birth and adverse neonatal outcomes. With preterm birth being the leading cause of mortality for all children under the age of 5, any potentially modifiable risk factor associated with preterm birth must be fully evaluated.¹⁻³

Periodontal disease is due to bacterial infection of the gingivae with resulting localized and systemic inflammation that can have profound effects in both nonpregnant and pregnant individuals. In pregnancy, several studies have demonstrated an association between periodontitis and preterm birth.⁴⁻⁹ Furthermore, extensive evidence demonstrates that fetal exposure to systemic inflammation during gestation predisposes to brain injury and neurodevelopmental delay.¹⁰⁻¹³ Thus, periodontitis and the resulting inflammatory cascade not only affect the pregnant individual but also have significant lifelong consequences on the development and well-being of future offspring.

In this review, we will first discuss the epidemiology, prevalence, and pathophysiology of periodontitis. We will then explore the medical literature evaluating the association between periodontitis and preterm birth prior to delving into the potential for neurodevelopmental delay and brain injury among offspring. Finally, we will conclude by discussing future directions and unanswered questions related to periodontitis and its relationship with preterm birth and adverse neonatal outcomes.

PERIODONTITIS

Epidemiology

Periodontitis is a noncommunicable disease of significant concern as it has a prevalence of 45–50% worldwide and is the sixth most common human disease.¹⁴ Some studies even report periodontitis occurring in nearly 90% of certain populations.¹⁵,¹⁶ Resource-limited settings have a substantially higher burden of periodontal disease and dental caries. For example, among nearly 400 pregnant or recently postpartum women in Malawi, the prevalence of dental disease (including dental caries and periodontal disease) was 76.7%.¹⁷ Similar results have been found elsewhere with rates of gingivitis occurring in 47, 86, and 89% of pregnant women in Brazil, Thailand, and Ghana, respectively.¹⁸⁻²⁰

Having a periodontal disease is associated with overall poorer health. Known risk factors for periodontitis include smoking, low socioeconomic status, low educational level, obesity, stress, diabetes, and increasing age.²¹,²² Periodontal disease is known to be independently associated with other noncommunicable

¹Department of Pediatrics, Division of Neonatology, University of Washington, Seattle, Washington; Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine at Baylor College of Medicine, Houston, Texas, United States of America
²Department of Pediatrics, Division of Neonatology, Center on Human Development and Disability, University of Washington, Seattle, Washington, United States of America

Corresponding Author: Gregory Charles Valentine, Department of Pediatrics, Division of Neonatology, University of Washington, Seattle, Washington; Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine at Baylor College of Medicine, Houston, Texas, United States of America
Source of support: Nil
Conflict of interest: None
diseases which have lifelong ramifications including diabetes mellitus, cardiovascular disease, chronic kidney disease, and chronic obstructive pulmonary disease.\textsuperscript{23–26} Moreover, in individuals with multiple morbidities, having periodontitis is associated with decreased survival.\textsuperscript{27,28} Thus, periodontitis is associated with overall poor health status and is a potential modifiable risk factor that can be targeted to potentially prevent further health decline or death.

**Periodontitis Pathophysiology**

Periodontitis is a multifactorial origin that begins with bacterial colonization of the gingival tissues. Initially, dental plaque develops, which consists of bacteria surrounding themselves within a protective biofilm that is resistant to antimicrobial agents.\textsuperscript{27,28} The dental plaque is polymicrobial with Gram-positive, facultative bacteria such as *Streptococcus* and *Actinomyces* considered primary colonizers in an initially higher oxygen setting and Gram-negative, anaerobic bacteria such as *Fusobacterium* colonizing in more oxygen-depleted later stages.\textsuperscript{29–31} In fact, the shift between aerobic to anaerobic conditions is a hallmark of the progression from gingivitis to periodontitis.\textsuperscript{31,32}

Colonization with periodontopathic bacteria leads to a host response that is the main culprit behind the tissue destruction and local inflammatory reaction associated with periodontitis. The bacteria stimulate the innate immune response, which leads to inflammation and neutrophil migration.\textsuperscript{33} Pro-inflammatory cytokines and other inflammatory mediators, such as prostaglandins, tumor necrosis factor-alpha (TNF-alpha), and interleukin 1-beta (IL-1 beta), are secreted.\textsuperscript{33} Subsequently, cytokines stimulate the adaptive immune response, which leads to differentiation of T and B cells along with activation of the receptor activator of nuclear factor-kB (RANK).\textsuperscript{34} While T and B cells lead to targeted tissue destruction, activation of RANK leads to osteoclast activation with resulting bone resorption and tooth loss.\textsuperscript{34}

Gingivitis, or inflammation of the gingivae, is the initial sign of inflammation and tissue destruction and is a reversible process. Histopathologically, gingivitis does not involve any loss of bone or periodontal tissue support structures.\textsuperscript{35,36} Bleeding, red, and/or swollen gums can occur and are clinical signs and symptoms of the acute inflammatory injury associated with gingivitis. In this earlier phase of periodontal disease, dental hygiene is paramount to prevent the progression of gingivitis into periodontitis.\textsuperscript{35} If not reversed, the continued inflammatory injury and resulting tissue destruction of these events lead to periodontitis with the destruction of collagen fibers, loosening of teeth, bone resorption, and eventual loss of teeth.\textsuperscript{37}

**Pregnancy and Risk of Periodontitis**

Pregnant women are at higher risk for periodontal disease.\textsuperscript{15,16,38} It has been well-documented since the 1960s that there exists an association between gingival inflammation and pregnancy.\textsuperscript{39–41} In women who had preexisting periodontal disease, pregnancy led to increased periodontal probing depths and worsening of bleeding gums which resolved after delivery.\textsuperscript{42} While the exact mechanism for how or why increased gingival inflammation occurs during pregnancy is not known, there are key studies elucidating a likely role of circulating hormones such as estrogen and progesterone. These hormones are commonly elevated in pregnancy due to production by the corpus luteum and subsequent placenta.\textsuperscript{43,44} Both estrogen and progesterone receptors are located in the periodontium including the periodontal ligament, the structure that connects teeth to the underlying alveolar bone which becomes eroded during periodontitis, further supporting the role of these hormones on oral health.\textsuperscript{45,46}

One proposed mechanism for pregnancy-associated gingivitis and periodontitis is alteration of the oral, and specifically periodontal, microbiota. One study found increased levels of *Bacteroides intermedius* in the second trimester of pregnancy which decreased postpartum, which is believed to be due to the increased levels of estrogen and progesterone acting as growth factors for this bacteria.\textsuperscript{52,57} *Porphyromonas gingivalis* and *Prevotella intermedia*, both periodontopathic bacteria leading to gingival inflammation, are also known to be associated with increased maternal hormone levels during pregnancy.\textsuperscript{49} Another study demonstrated that pregnant women had higher levels of the periodontogenic bacteria *Campylobacter rectus* in unstimulated salivary samples compared to their nonpregnant counterparts.\textsuperscript{49} These studies and others suggest a potential role of increased maternal hormone levels and alterations in the oral and periodontal microbiota including elevated levels of periodontopathic bacteria that increase the risk of periodontitis. Further studies are necessary to confirm these findings.

Alterations of the immune function of the gravid are another potential mechanism leading to an increased risk of gingival inflammation. During pregnancy, a state of relative immunosuppression occurs to prevent rejection of fetal tissues.\textsuperscript{50} Resulting alterations in neutrophils and other innate and adaptive immune cells leads to an increased propensity for inflammation.\textsuperscript{51–54} Specifically, neutrophil chemotaxis and adherence are diminished during pregnancy.\textsuperscript{54} Moreover, pro-inflammatory cytokine production and secretion are increased during pregnancy; *in vivo* models demonstrate increased production of IL-6, IL-8, IL-1, TNF-alpha, and prostaglandin E2.\textsuperscript{55–59} However, some *in vivo* human studies have not found clear differences in these pro-inflammatory cytokines comparing pregnant individuals to nonpregnant controls.\textsuperscript{60,61} Thus, in pregnancy, there appears to be a predisposition toward impairment in neutrophil function with possible alterations in levels of pro-inflammatory cytokine levels.

Overall, there is evidence linking the increased levels of maternal estrogen and progesterone that occur during pregnancy with both worsening of preexisting gingival inflammation and further predisposition to new formation of gingivitis or periodontitis through likely alterations in the periodontal microbiota and the subsequent heightened, and potentially dysregulated, maternal inflammatory response. Thus, pregnant women represent a vulnerable population that are at higher inherent risk for the development of periodontitis with potential ramifications of the disease not only on the gravid but also the developing fetus(es).

**Periodontitis and Risk of Preterm Birth**

Periodontitis during pregnancy is associated with poor maternal and perinatal outcomes including gestational diabetes, preeclampsia, fetal growth restriction, low birth weight (LBW), preterm delivery, and perinatal mortality.\textsuperscript{62–66} Here, we will specifically evaluate the literature surrounding periodontitis and its association with one of these outcomes—preterm birth.

**Periodontitis and Preterm Birth: A Review of the Medical Literature**

In 1996, Offenbacher et al. first published a case–control study of 124 pregnant or postpartum women evaluating rates of preterm low-birth-weight (PLBW) deliveries (defined as birth weight <2500 g
and one of the following: gestational age <37 weeks, preterm labor, or premature rupture of membranes). After multivariate logistic regression models were applied, periodontitis was significantly associated with PLBW delivery. Similar findings were later reported in other studies. For example, Jeffcoat et al. reported that pregnant women with generalized periodontal disease at 21–24 weeks of gestation had an increased risk for preterm delivery (adjusted odds ratio (AOR) 4.45, 95% confidence interval (CI) 2.16–9.18). However, studies have not consistently demonstrated this strong association with even one study from the United Kingdom (UK), suggesting potential prevention of preterm birth in women with periodontitis.

While some studies, like the UK study, have contradictory findings, a significant body of evidence supports an association between periodontitis during pregnancy and preterm birth, PLBW, or LBW neonates. A meta-analysis published in 2016 evaluated published case–control studies evaluating pregnancy outcomes related to maternal periodontitis during pregnancy and reported a risk ratio of 1.61 (p < 0.001) for preterm birth using data from 16 studies. Furthermore, the risk ratio for having a neonate <2500 g at birth was 1.65 (p < 0.001) and for PLBW was 3.44 (p < 0.001). Another systematic review reported 62 studies suggesting periodontitis as a potential risk factor for preterm birth or LBW neonates. Thus, a large body of evidence supports maternal periodontitis as a likely modifiable risk factor for having preterm, PLBW, or LBW neonates.

While evidence supports the association between maternal periodontitis during pregnancy and preterm, LBW, or PLBW neonates, studies have subsequently assessed whether interventions during pregnancy to treat periodontitis can prevent these adverse outcomes. Two randomized controlled trials evaluated the impact of treating periodontitis with dental scaling and root planing on the prevention of preterm birth. Interestingly, neither trial demonstrated prevention of preterm birth, LBW, or fetal growth restriction with dental scaling and root planing of the mother in the second trimester. Other findings have similarly not found improvements in birth outcomes related to periodontal treatment during gestation. These results suggest that traditional methodologies for treating maternal periodontal disease during the second trimester of pregnancy do not likely have significant effects in the prevention of adverse offspring outcomes.

Biologic Plausibility and Potential Pathophysiological Explanation(s) for Association with Preterm Birth

While periodontitis appears to be associated with preterm birth, what are the possible pathophysiologic explanations? First, one must understand the current theories and hypotheses surrounding how preterm birth occurs prior to delving into how periodontitis may causally connect. While the mechanistic pathway for the development of preterm labor is not fully elucidated, one leading theory is the preterm parturition syndrome. This theory proposes that birth, irrespective of if occurring at term or preterm, has a common terminal pathway leading to parturition that includes uterine myometrial contractions, membrane activation with eventual rupture, and cervical ripening. However, in preterm labor, there are multiple insults of varying strength that may lead to premature activation of this terminal pathway. These triggers can range from infection, inflammation, cervical disorders, hormonal disorders, allergic phenomena, uterine overdistension, uteroplacental insufficiency, gene–environment interaction, and stress. Periodontitis likely leads to multiple insults leading to premature activation of the common terminal pathway including inflammation, infection, and potential alterations in the placental microbiota.

Preterm birth is well known to be associated with extrauterine maternal infections, such as malaria, pneumonia, and pneumonia, during pregnancy. Furthermore, intrauterine infections are well known to be associated with preterm birth. In fact, intrauterine infection is considered the only firm causal link with preterm birth with a known mechanistic pathophysiologic understanding. For example, when systemic administration of microbial products is provided to a pregnant animal or intrauterine infection develops, preterm labor and resulting birth occur. Ultimately, the association with preterm birth is the strongest with intrauterine infection but also linked with extrauterine infections. Thus, the infectious process of periodontitis has strong potential for leading to premature birth.

Part of the innate immune system includes pattern recognition receptors such as toll-like receptors (TLRs). Interestingly, TLRs are found in the maternal genital tract including on the vagina, cervix, endometrium, and fallopian tubes. Ligation of TLRs leads to activation of downstream signaling cascade through nuclear factor-kB (NF-kB) and eventual production and secretion of cytokines and chemokines creating a pro-inflammatory milieu. In one mouse model of preterm birth, when TLR-4 contains a mutation that prevents proper signaling, these mice are less likely to deliver preterm when exposed to intrauterine inoculations of LPS compared to wild-type mice, supporting the mechanistic role of TLRs in signaling and activation of preterm birth. Moreover, certain TLRs such as TLR-2 are known to promote apoptosis of trophoblastic cells, specialized cells that form the placenta and ensure proper uteroplacental vascular supply. As a consequence, when TLR-2 is stimulated by a pathogen, promotion of trophoblast apoptosis can occur leading to the potential development of intrauterine growth restriction of the fetus, preeclampsia in the mother, and/or miscarriage, all findings that have been associated with maternal periodontitis during pregnancy. Thus, it is plausible that periodontitis activates the innate immune system and signaling cascade, which then likely plays an active role in the activation of preterm labor.

While infection itself is associated with the preterm parturition syndrome, maternal systemic and localized inflammation plays another potential mechanistic role in the early activation of the common terminal pathway. Specifically, pro-inflammatory cytokines, such as IL-1 and TNF-alpha, likely play a central role in the initiation of parturition. A body of evidence demonstrates that IL-1 causes uterine myometrial contractions. Systemic administration of IL-1 in animal models ultimately leads to preterm labor and birth. Another pro-inflammatory cytokine TNF-alpha promotes the production and release of matrix metalloproteases that instigate membrane rupture and cervical ripening. Blockade of both IL-1 and TNF-alpha through knockout and receptor antagonist murine models demonstrates decreased rates of preterm labor and resulting preterm birth, strongly supporting the role of these two cytokines as significant mechanistic contributors to the development of preterm parturition. Evidence supports other pro-inflammatory cytokines (IL-6, IL-16, IL-8, and IL-18) in the pathogenesis of preterm parturition, many of
which have been found to be elevated in periodontitis.\textsuperscript{128–135} While pro-inflammatory cytokines are associated with preterm birth, the diminished production of anti-inflammatory cytokines (IL-10) likely also plays a pivotal role. Anti-inflammatory cytokines are known to decrease in the placenta at term, further promoting a pro-inflammatory state near the time of labor.\textsuperscript{136} Additional evidence in animal models of infection demonstrates that when IL-10 is provided, less uterine myometrial contractility occurs along with less preterm birth.\textsuperscript{137–139}

Another potential mechanism for how periodontitis may lead to preterm birth is through alterations in the oral and placental microbiotas. The traditional and long-taught notion that the “womb,” including the placenta, amniotic cavity, and fetal tissues, is sterile is now uncertain.\textsuperscript{140} Aagaard et al. demonstrated a unique, low-biomass placental microbiome that harbors unique microbes commonly found in the human oral cavity (i.e., Prevotella tannaeae, nonpathogenic Neisseria species, Bergeyella, and Fusobacterium), urinary tract (i.e., Escherichia coli), and vagina (i.e., Lactobacillus species, Ureaplasma species, and Streptococcus agalactiae).\textsuperscript{8,140} These findings suggest that while ascending spread from the vagina may occur, hematogenous spread and seeding from the oral cavity likely play another key role. In fact, the placental microbiome demonstrates greatest similarity to the oral microbiome.\textsuperscript{140} Animal models in which food contaminated with periodontogenic pathogens such as Porphyromonas gingivalis is provided to pregnant animals demonstrate decreased fecundity and higher rates of inflammation within the placenta.\textsuperscript{7} Findings in humans further support the hematogenous spread from the oral cavity to the placenta. For instance, when bacteria are detected in the amniotic fluid of women who have preterm birth, the bacteria are more commonly associated with the oral cavity rather than other regions such as the vagina.\textsuperscript{141,142} Thus, dysbiosis of the placental microbiome due to hematogenous seeding of pathobionts from the oral cavity to the placenta may be an underlying etiology for the development of preterm birth that is associated with periodontitis.\textsuperscript{67,143–145}

Overall, periodontitis has several potential methods for the activation of the terminal pathway leading to preterm parturition including extraperine infection, potential hematogenous seeding leading to intrauterine infection, dysbiosis of placental microbiome, and establishment of a pro-inflammatory state all associated with increased uterine activity, cervical ripening, and ultimately preterm birth. Further research is necessary to determine causal pathways by exploring these potential pathways leading to preterm birth in association with periodontitis.

**Periodontitis, Inflammation, and Potential Adverse Neurologic Complications in Offspring**

While periodontitis is likely associated with an increased rate of prematurity, the subsequent maternal inflammation related to periodontitis can also have detrimental effects on offspring neurodevelopment. First, prematurity is associated with increased rates of neurodevelopmental delay compared to birth at term.\textsuperscript{146–157} As periodontitis is associated with prematurity, this association is one reason for potential adverse long-term outcomes. Furthermore, fetal exposure to the resulting maternal inflammation, both local and systemic, due to periodontitis has the strong potential to injure a vulnerable, developing brain.

There exists a substantial body of evidence supporting the link between adverse neurologic outcomes with fetal exposure to maternal infection or its resulting inflammation.\textsuperscript{10,12,13,158–159} Animal models across a large array of species (rat, mouse, sheep, rabbit, and piglet) consistently demonstrate a strong association between maternal inflammation and adverse neonatal neurologic outcomes. Specifically, increased numbers of macrophages and microglia within the white matter along with resulting white matter injury are well-known complications of maternal inflammation on the neonatal brain.\textsuperscript{12,13,158,160–162} These findings suggest a role for inflammation leading to microglial activation, potential proliferation, and subsequent white matter damage.

Further exploring the potential pathophysiology of fetal neural injury associated with maternal infection and inflammation, studies have elucidated differential effects within specific structures within the brain. For example, in response to inflammation and cytokine signaling (i.e., IL-6), there is a proliferation of primitive neural precursors within the subventricular zone.\textsuperscript{163} Cytokine signaling is associated with microglial activation and proliferation which are associated with neuronal injury.\textsuperscript{164} However, the role of microglia in the development of neuronal injury is still unknown and not fully defined. While microglial proliferation occurs in the subventricular zone, exposure to prenatal inflammation leads to decreased neurogenesis within the hippocampal subgranular zone.\textsuperscript{159,165,166} The hippocampus is critically important in memory formation and learning. Diminished neurogenesis during fetal development within the hippocampus may be one potential etiology for future neurodevelopmental impairments.

While fetal exposure to maternal inflammation leads to changes in the developing fetal brain, the timing of exposure is also of paramount importance as the immature fetal brain undergoes critical windows of development *in utero*. Exposure to inflammation during these periods may potentiate adverse effects. It is well documented in the medical literature that certain maternal infections, such as Zika virus, toxoplasmosis, or cytomegalovirus, have increased risk of transmission or worse prognosis for offspring if infection occurs during certain time periods during gestation.\textsuperscript{167–169} Zika virus, for example, is known to preferentially lead to adverse offspring outcomes in a murine model if maternal infection occurs on embryonic day 8 as opposed to day 4 or 12.\textsuperscript{169} Thus, critical windows of inherent vulnerability to infection and related inflammation occur in the developing fetus.

In times of maternal inflammation, the human placenta upregulates conversion of tryptophan to serotonin (5-HT), an important hormone in fetal neurogenesis and future neurocognitive disorders. Normally, placental-derived 5-HT reaches the fetal brain. In times of maternal inflammation, the subsequent increase in 5-HT within the placenta leads to increased concentration within the fetal brain leading to significant potential for alterations in neurogenesis.\textsuperscript{170} 5-HT plays a critical role in neural crest stem cell survival, growth, migration, and proliferation as well as overall synaptogenesis.\textsuperscript{171–176} With 5-HT being one of the first neurotransmitters to emerge during embryogenesis, and with 5-HT neurons proliferating from gestational weeks 5–10, any dysregulation of 5-HT signaling during this crucial developmental window has the potential to cause lasting long-term, detrimental effects on neurodevelopment. 5-HT is a neuromodulator and intricately connected to future mood and anxiety disorders and even autism.\textsuperscript{177} Thus, maternal inflammation and subsequent derangements in neuromodulators
Maternal Periodontitis and Neonatal Outcomes

These polyols prevent periodontitis via multiple mechanisms that are known to prevent dental caries and periodontal disease. Alcohols within the polyol family (e.g., sorbitol, xylitol, or erythritol) and other aspects prior to larger scale-up of this affordable and optimal dosing, use in varying geographical and cultural contexts, studies are needed to determine any potential adverse effects, decreased perinatal brain injury in offspring. 

Postponed preterm birth, increased the rate of live births, and mice that were exposed to low-dose fluoride supplementation communities. In fact, in a murine model of preterm birth, pregnant cost strategy has the potential for far-reaching effects within countries, causes of preterm birth are oftentimes unknown. It preterm birth more commonly occur. In low- and middle-income settings rather than lower income settings where higher rates of periodontitis may exceed 80–90% of pregnant or recently postpartum women. Therefore, research exploring the association of periodontitis, its treatment, and any association with preterm birth would be well suited in these settings where the magnitude of effect will lead to increased power for detection. 

Furthermore, while randomized controlled trials have explored the effects of dental planing and root scaling on pregnant women with periodontitis during pregnancy compared to after pregnancy and did not find an effect on prevention of preterm birth, other prevention or treatment strategies targeting periodontitis need to similarly be vigorously explored. One possibility is the evaluation of fluoridated water sources. Studies have reported that exposure to fluoridated water sources provides protection against periodontal disease in adults. This low-cost strategy has the potential for far-reaching effects within communities. In fact, in a murine model of preterm birth, pregnant mice that were exposed to low-dose fluoride supplementation postponed preterm birth, increased the rate of live births, and decreased perinatal brain injury in offspring. However, further studies are needed to determine any potential adverse effects, optimal dosing, use in varying geographical and cultural contexts, and other aspects prior to larger scale-up of this affordable and accessible option. 

Another potential strategy is the evaluation of certain sugar alcohols within the polyol family (e.g., sorbitol, xylitol, or erythritol) that are known to prevent dental caries and periodontal disease. These polyols prevent periodontitis via multiple mechanisms that include disruption of periodontopathic bacterial energy production processes, reduction of adhesion of microorganisms to the teeth, and diminishing gingival inflammation via inhibiting LPS-induced inflammatory cytokine expression and signaling (TNF-alpha, IL-1 beta, and NF-kB). These sugar alcohols have the potential for preventing maternal periodontitis and further studies are needed on the effects on the maternal–neonatal dyad and associated outcomes.

**Conclusion**

Preterm birth is the leading cause of neonatal mortality, morbidity, and poor neurodevelopmental outcomes worldwide. Efforts seeking innovative methods to prevent preterm birth are critically important to attempt to prevent the 15 million preterm deliveries occurring every year globally. Substantial evidence links maternal periodontitis during pregnancy with adverse pregnancy outcomes including preterm birth, PLBW, and LBW offspring. With up to 90% of pregnant women suffering from poor oral hygiene in some resource-limited settings, periodontitis is likely an overlooked, important contributor to preterm birth. While no randomized controlled trials have reported the prevention of these adverse outcomes, these intervention studies have largely been limited to dental scaling and root planing. Further randomized controlled trials are needed evaluating other strategies to both treat and prevent periodontitis on offspring outcomes, preferentially in settings where periodontitis is highly prevalent. Moreover, fetal exposure to inflammation secondary to periodontitis and/or alterations in the developing neonatal microbiota are potentially modifiable risk factors for adverse neurodevelopmental outcomes in offspring. Therefore, these further studies should evaluate the impact not only on prevention of preterm, PLBW, or LBW neonates, but also on adverse long-term neurologic and neurodevelopmental outcomes of offspring.

**ORCID**

Gregory Charles Valentine https://orcid.org/0000-0002-3055-2987

**Abbreviations**

- 5-HT: Serotonin
- IL: Interleukin
- LBW: Low birth weight
- PLBW: Premature low birth weight
- PTB: Preterm birth
- RANK: Receptor activator of nuclear factor-kB
- TLR: Toll-like receptor
- TNF-alpha: Tumor necrosis factor-alpha

**References**

Maternal Periodontitis and Neonatal Outcomes


Maternal Periodontitis and Neonatal Outcomes


Maternal Periodontitis and Neonatal Outcomes


130. Cox SM. Interleukin-1 beta, -1 alpha, and -6 and prostaglandins in vaginal/cervical fluids of pregnant women before and during labor. J Clin Endocrinol Metab 1993. DOI: 10.1210/jc.77.3.805.


164. Lively S, Schlchter LC. Microglia responses to pro-inflammatory stimuli (LPS, IFNγ+TNFα) and reprogramming by resolving cytokines (IL-4, IL-10). Front Cell Neurosci 2018;12:215. DOI: 10.3389/fncel.2018.00215.


