REVIEW ARTICLE

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

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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.

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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 caries was recently estimated to be 69.3% and composite 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

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diseases which have lifelong ramifications including diabetes mellitus, cardiovascular disease, chronic kidney disease, and chronic obstructive pulmonary disease.[23–26] Moreover, in individuals with multiple morbidities, having periodontitis is associated with decreased survival.[25] 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 has 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.[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.[29–31] In fact, the shift between aerobic to anaerobic conditions is a hallmark of the progression from gingivitis to periodontitis.[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.[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.[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).[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.[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.[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.[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.[37]

Pregnancy and Risk of Periodontitis

Pregnant women are at higher risk for periodontal disease.[15,16,38] It has been well-documented since the 1960s that there exists an association between gingival inflammation and pregnancy.[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.[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.[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.[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.[42,47] *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.[48] Another study demonstrated that pregnant women had higher levels of the periodontogenic bacteria *Campylobacter rectus* in unstimulated salivary samples compared to their nonpregnant counterparts.[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 gravida 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.[50] Resulting alterations in neutrophils and other innate and adaptive immune cells leads to an increased propensity for inflammation.[51–54] Specifically, neutrophil chemotaxis and adherence are diminished during pregnancy.[54] Moreover, pro-inflammatory cytokine production and secretion are increased during pregnancy; *in vitro* models demonstrate increased production of IL-6, IL-8, IL-1, TNF-alpha, and prostaglandin E2.[55–59] However, some *in vivo* human studies have not found clear differences in these pro-inflammatory cytokines comparing pregnant individuals to nonpregnant controls.[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 gravida 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.[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.[67] Similar findings were later reported in other studies.[68,69] 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].[68,69] 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.[70]

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.[71–76] 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.[71] 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).[71] Another systematic review reported 62 studies suggesting periodontitis as a potential risk factor for preterm birth or LBW neonates.[76] 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.[77,78] Other findings have similarly not found improvements in birth outcomes related to periodontal treatment during gestation.[79] 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.[80] 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.[80] 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 pyelonephritis, during pregnancy.[81–92] 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.[93–97] For example, when systemic administration of microbial products is provided to a pregnant animal or intrauterine infection develops, preterm labor and resulting birth occur.[95,98–107] Further supporting the role of maternal infection on the development of preterm birth, when antibiotics are administered for the treatment of intrauterine infections or asymptomatic bacteriuria, prevention of preterm birth can occur.[108–110] 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.[111] 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.[107,112] 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.[113–116] 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.[117] Another pro-inflammatory cytokine TNF-alpha promotes the production and release of matrix metalloproteases that instigate membrane rupture and cervical ripening.[118–124] 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.[125–127] Evidence supports other pro-inflammatory cytokines (IL-6, IL-16, and IL-18) in the pathogenesis of preterm parturition, many of

which have been found to be elevated in periodontitis.[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.[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.[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.[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 tannerae*, nonpathogenic *Neisseria* species, *Bergeyella*, and *Fusobacterium*), urinary tract (i.e., *Escherichia coli*), and vagina (i.e., *Lactobacillus* species, *Ureaplasma* species, and *Streptococcus agalactiae*).[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.[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.[9] 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.[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 labor that is associated with periodontitis.[67,143–145]

Overall, periodontitis has several potential methods for the activation of the terminal pathway leading to preterm parturition including extrauterine 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.[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.[10–13,158,159] 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.[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.[163] Cytokine signaling is associated with microglial activation and proliferation which are associated with neuronal injury.[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.[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.[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.[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.[170]

5-HT plays a critical role in neural crest stem cell survival, growth, migration, and proliferation as well as overall synaptogenesis.[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.[177] Thus, maternal inflammation and subsequent derangements in neuromodulators

during the periods of neurogenesis and synaptogenesis during the fetal neurodevelopment may play a pivotal role in the eventual development of adverse neurodevelopmental outcomes.

Consistent with this theory, researchers evaluated 1,791,520 children born over a 41-year period in Sweden and evaluated the association of hospitalization with any maternal infection, severe maternal infection, or a urinary tract infection with neuropsychiatric offspring outcomes including autism, depression, bipolar disorder, or psychosis.[10] While no associations were found increasing the risk for bipolar disorder or psychosis among offspring, fetal exposure to maternal infection during hospitalization increased the risk for both autism [hazard ratio (HR) 1.79, 95% CI 1.34–2.40] and depression (HR 1.24, 95% CI 1.08–1.42).[10] Thus, maternal infection and related inflammation have significant potential to lead to lifelong neurodevelopmental impairment in offspring.

Overall, periodontitis, an extrauterine maternal infection, is associated with both localized and systemic inflammation.[178] With a substantial body of evidence linking maternal inflammation with poor neurodevelopmental outcomes of offspring, these findings provide biologic plausibility for adverse neurologic outcomes of offspring exposed to maternal periodontitis.

Future Directions

While a plethora of evidence has demonstrated an association between periodontitis and preterm birth, there exist also some conflicting evidence that suggests no association may be present.[70,179] However, research tends to focus on high-income settings rather than lower income settings where higher rates of preterm birth more commonly occur. In low- and middle-income countries, causes of preterm birth are oftentimes unknown. It is in these same settings that 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.[180–182] 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.[183] 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).[184–189] 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.[1,190] 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 interventional 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.

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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

1. Liu L, Oza S, Hogan D, et al. Global, regional, and national causes of child mortality in 2000-13, with projections to inform post-2015 priorities: an updated systematic analysis. Lancet 2015;385(9966): 430–440. DOI: 10.1016/S0140-6736(14)61698-6.
2. Walani SR. Global burden of preterm birth. Int J Gynecol Obstet 2020;150(1):31–33. DOI: 10.1002/ijgo.13195.
3. Friedrich MJ. Premature birth complications top cause of death in children younger than 5 years. Journal of the American Medical Association 2015;313(3):235. DOI: 10.1001/jama.2014.18326.
4. Offenbacher S, Beck J, Lieff S, et al. Role of periodontitis in systemic health: spontaneous preterm birth. J Dent Educ 1998;62:852–858. DOI: 10.1002/j.0022-0337.1998.62.10.tb03252.x.

5. Xiong X, Buekens P, Fraser WD, et al. Periodontal disease and adverse pregnancy outcomes: a systematic review. British journal of obstetrics and gynaecology 2006;113(2):135–143. DOI: 10.1111/j.1471-0528.2005.00827.x.
6. Offenbacher S, Boggess KA, Murtha AP, et al. Progressive periodontal disease and risk of very preterm delivery. Obstet Gynecol 2006;107(1):29–36. DOI: 10.1097/01.AOG.0000190212.87012.96.
7. Boggess KA, Lieff S, Murtha AP, et al. Maternal periodontal disease is associated with an increased risk for preeclampsia. Obstet Gynecol 2003;101(2):227–231. DOI: 10.1016/S0029-7844(02)02314-1.
8. Madianos PN, Bobetsis YA, Offenbacher S. Adverse pregnancy outcomes (APOs) and periodontal disease: pathogenic mechanisms. J Clin Periodontol 2013;40 (Suppl 14):S170–S180. DOI: 10.1111/jcpe.12082.
9. Arce RM, Barros SP, Wacker B, et al. Increased TLR4 expression in murine placentas after oral infection with periodontal pathogens. Placenta 2009;30(2):156–162. DOI: 10.1016/j.placenta.2008.11.017.
10. Al-Haddad BJS, Jacobsson B, Chabra S, et al. Long-term risk of neuropsychiatric disease after exposure to infection in utero. JAMA Psychiatry 2019;76(6):594–602. DOI: 10.1001/jamapsychiatry.2019.0029.
11. Hagberg H, Mallard C, Ferriero DM, et al. The role of inflammation in perinatal brain injury. Nat Rev Neurol 2015;11(4):192–208. DOI: 10.1038/nrneurol.2015.13.
12. Hagberg H, Gressens P, Mallard C. Inflammation during fetal and neonatal life: implications for neurologic and neuropsychiatric disease in children and adults. Ann Neurol 2012;71(4):444–457. DOI: 10.1002/ana.22620.
13. Mallard C, Welin AK, Peebles D, et al. White matter injury following systemic endotoxemia or asphyxia in the fetal sheep. Neurochem Res 2003;28(2):215–223. DOI: 10.1023/A:1022368915400.
14. Kassebaum NJ, Bernabé E, Dahiya M, et al. Global burden of severe periodontitis in 1990-2010: a systematic review and meta-regression. J Dent Res 2014;93(11):1045–1053. DOI: 10.1177/0022034514552491.
15. Helmi MF, Huang H, Goodson JM, et al. Prevalence of periodontitis and alveolar bone loss in a patient population at Harvard School of Dental Medicine. BMC Oral Health 2019;19(1):254. DOI: 10.1186/s12903-019-0925-z.
16. Pihlstrom BL, Michalowicz BS, Johnson NW. Periodontal diseases. Lancet 2005;366(9499):1809–1820. DOI: 10.1016/S0140-6736(05)67728-8.
17. Antony KM, Kazembe PN, Pace RM, et al. Population-based estimation of dental caries and periodontal disease rates of gravid and recently postpartum women in Lilongwe, Malawi. AJP Rep 2019;9(3):e268–e274. DOI: 10.1055/s-0039-1695003.
18. Vogt M, Sallum AW, Cecatti JG, et al. Factors associated with the prevalence of periodontal disease in low-risk pregnant women. Reprod Health 2012;9:3. DOI: 10.1186/1742-4755-9-3.
19. Nuamah I, Annan BDRT. Periodontal status and oral hygiene practices of pregnant and non-pregnant women. East Afr Med J 1998;75(12):712. PMID: 10065212.
20. Rakchanok N, Amporn D, Yoshida Y, et al. Dental caries and gingivitis among pregnant and non-pregnant women in Chiang Mai, Thailand. Nagoya J Med Sci 2010;72(1–2):43–50. DOI: 10.18999/nagjms.72.1-2.43.
21. Borrell LN, Papapanou PN. Analytical epidemiology of periodontitis. J Clin Periodontol 2005;32:132–158. DOI: 10.1111/j.1600-051X.2005.00799.x.
22. Petersen PE, Bourgeois D, Ogawa H, et al. The global burden of oral diseases and risks to oral health policy and practice the global burden of oral diseases and risks to oral health. Bull World Health Organ 2005;83(9):661–669. PMID: 16211157.
23. Chapple ILC, Genco R. Diabetes and periodontal diseases: consensus report of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases. J Clin Periodontol 2013;40:s14:S106. DOI: 10.1111/jcpe.12077.
24. Tonetti MS, Van Dyke TE. Periodontitis and atherosclerotic cardiovascular disease: consensus report of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases. J Clin Periodontol 2013;40 (Suppl 14):S24–S29. DOI: 10.1111/jcpe.12089.
25. Sharma P, Dietrich T, Ferro CJ, et al. Association between periodontitis and mortality in stages 3-5 chronic kidney disease: NHANES III and linked mortality study. J Clin Periodontol 2016;43(2):104–113. DOI: 10.1111/jcpe.12502.
26. Linden GJ, Lyons A, Scannapieco FA. Periodontal systemic associations: review of the evidence. J Clin Periodontol 2013;40 Suppl 14:S8–S19. DOI: 10.1111/jcpe.12064.
27. Hillman JD, Socransky SS, Shivers M. The relationships between streptococcal species and periodontopathic bacteria in human dental plaque. Arch Oral Biol 1985;30(11-12):791–795. DOI: 10.1016/0003-9969(85)90133-5.
28. Hajishengallis G, Darveau RP, Curtis MA. The keystone-pathogen hypothesis. Nat Rev Microbiol 2012;10(10):717–725. DOI: 10.1038/nrmicro2873.
29. Marsh PD. Dental plaque as a biofilm and a microbial community – implications for health and disease. BMC Oral Health 2006;6:S14. DOI: 10.1186/1472-6831-6-S1-S14.
30. Jenkinson HF, Lamont RJ. Oral microbial communities in sickness and in health. Trends Microbiol 2005;13(12):589–595. DOI: 10.1016/j.tim.2005.09.006.
31. Socransky SS, Gibbons RJ, Dale AC, et al. The microbiota of the gingival crevice area of man-I. Total microscopic and viable counts and counts of specific organisms. Arch Oral Biol 1963;8:275–280. DOI: 10.1016/0003-9969(63)90019-0.
32. Socransky SS, Haffajee AD, Cugini MA, et al. Microbial complexes in subgingival plaque. J Clin Periodontol 1998;25(2):134–144. DOI: 10.1111/j.1600-051X.1998.tb02419.x.
33. Silva N, Abusleme L, Bravo D, et al. Host response mechanisms in periodontal diseases. J Appl Oral Sci 2015;23(3):329–355. DOI: 10.1590/1678-775720140259.
34. Hajishengallis G, Lambris JD. Microbial manipulation of receptor crosstalk in innate immunity. Nat Rev Immunol 2011;11(3):187–200. DOI: 10.1038/nri2918.
35. Loe H, Theilade E, Jensen SB. Experimental gingivitis in man. J Periodontol 1965;36:177–187. DOI: 10.1902/jop.1965.36.3.177.
36. Theilade E, Wright WH, Jensen SB, et al. Experimental gingivitis in man. J Periodontal Res 1966;1:1–13. DOI: 10.1111/j.1600-0765.1966.tb01842.x.
37. Page RC, Schroeder HE. Pathogenesis of inflammatory periodontal disease: a summary of current work. Lab Investig 1976;34(3):235–249. PMID: 765622.
38. Anwar N, Zaman N, Nimmi N, et al. Factors associated with periodontal disease in pregnant diabetic women. Mymensingh Med J 2016;25(2):289–295. PMID: 27277362.
39. Löe H, Silness J. Periodontal disease in pregnancy I. Prevalence and severity. Acta Odontol Scand 1963;21:533–551. DOI: 10.3109/00016356309011240.
40. Hugoson A. Gingivitis in pregnant women. A longitudinal clinical study. Odontol Revy 1971;22(1):65. PMID: 5280517.
41. Kornman KS, Loesche WJ. The subgingival microbial flora during pregnancy. J Periodontal Res 1980;15(2):111–122. DOI: 10.1111/j.1600-0765.1980.tb00265.x.
42. Mariotti A. Sex steroid hormones and cell dynamics in the periodontium. Crit Rev Oral Biol Med 1994;5(1):27–53. DOI: 10.1177/10454411940050010201.
43. Deasy MJ, Vogel RI. Female sex hormonal factors in periodontal disease. Ann Dent 1976;35(3):42–46. PMID: 788632.
44. Mealey BL, Moritz AJ. Hormonal influences: effects of diabetes mellitus and endogenous female sex steroid hormones on the periodontium. Periodontol 2000 2003;32:59–81. DOI: 10.1046/j.0906-6713.2002.03206.x.
45. Vittek J, Hernandez MR, Wenk EJ, et al. Specific estrogen receptors in human gingiva. J Clin Endocrinol Metab 1982;54(3):608–612. DOI: 10.1210/jcem-54-3-608.
46. Lewko WM, Anderson A. Estrogen receptors and growth response in cultured human periodontal ligament cells. Life Sci 1986;39(13):1201–1206. DOI: 10.1016/0024-3205(86)90352-8.
47. Kornman KS, Loesche WJ. Effects of estradiol and progesterone on Bacteroides melaninogenicus and Bacteroides gingivalis. Infect Immun 1982;35(1):256–263. DOI: 10.1128/iai.35.1.256-263.1982.

48. Carrillo-De-Albornoz A, Figuero E, Herrera D, et al. Gingival changes during pregnancy: II. Influence of hormonal variations on the subgingival biofilm. J Clin Periodontol 2010;37(3):230–240. DOI: 10.1111/j.1600-051X.2009.01514.x.
49. Yokoyama M, Hinode D, Yoshioka M, et al. Relationship between Campylobacter rectus and periodontal status during pregnancy. Oral Microbiol Immunol 2008;23(1):55–59. DOI: 10.1111/j.1399-302X.2007.00391.x.
50. Piccinni MP. T cell tolerance towards the fetal allograft. J Reprod Immunol 2010;85(1):71–75. DOI: 10.1016/j.jri.2010.01.006.
51. Björksten B, Söderström T, Damber MG, et al. Polymorphonuclear leucocyte function during pregnancy. Scand J Immunol 1978;8(3): 257–262. DOI: 10.1111/j.1365-3083.1978.tb00518.x.
52. Persellin RH, Thoi LL. Human polymorphonuclear leukocyte phagocytosis in pregnancy. Development of inhibition during gestation and recovery in the postpartum period. Am J Obstet Gynecol 1979;134(3):250–255. DOI: 10.1016/S0002-9378(16)33028-9.
53. El-Maallem H, Fletcher J. Impaired neutrophil function and myeloperoxidase deficiency in pregnancy. Br J Haematol 1980;44(3):375–381. DOI: 10.1111/j.1365-2141.1980.tb05906.x.
54. Krause PJ, Ingardia CJ, Pontius LT, et al. Host defense during pregnancy: neutrophil chemotaxis and adherence. Am J Obstet Gynecol 1987;157(2):274–280. DOI: 10.1016/S0002-9378(87)80150-3.
55. Yokoyama M, Hinode D, Masuda K, et al. Effect of female sex hormones on Campylobacter rectus and human gingival fibroblasts. Oral Microbiol Immunol 2005;20(4):239–243. DOI: 10.1111/j.1399-302X.2005.00222.x.
56. Shu L, Guan SM, Fu SM, et al. Estrogen modulates cytokine expression in human periodontal ligament cells. J Dent Res 2008;87(2):142–147. DOI: 10.1177/154405910808700214.
57. Smith JM, Shen Z, Wira CR, et al. Effects of menstrual cycle status and gender on human neutrophil phenotype. Am J Reprod Immunol 2007;58(2):111–119. DOI: 10.1111/j.1600-0897.2007.00494.x.
58. Miyagi M, Morishita M, Iwamoto Y. Effects of sex hormones on production of prostaglandin E 2 by human peripheral monocytes. J Periodontol 1993;64(11):1075–1078. DOI: 10.1902/jop.1993.64.11.1075.
59. Morishita M, Miyagi M, Iwamoto Y. Effects of sex hormones on production of interleukin-1 by human peripheral monocytes. J Periodontol 1999;70(7):757–760. DOI: 10.1902/jop.1999.70.7.757.
60. Bieri RA, Adriaens L, Spörri S, et al. Gingival fluid cytokine expression and subgingival bacterial counts during pregnancy and postpartum: a case series. Clin Oral Investig 2013;17(1):19–28. DOI: 10.1007/s00784-012-0674-8.
61. Haerian-Ardakani A, Moeintaghavi A, Talebi-Ardakani MR, et al. The association between current low-dose oral contraceptive pills and periodontal health: a matched-case-control study. J Contemp Dent Pract 2010;11(3):33–40. DOI: 10.5005/jcdp-11-3-33.
62. Khalighinejad N, Aminoshariae A, Kulild JC, et al. Apical periodontitis, a predictor variable for preeclampsia: a case-control study. J Endod 2017;43(10):1611–1614. DOI: 10.1016/j.joen.2017.05.021.
63. Kumar A, Sharma DS, Verma M, et al. Association between periodontal disease and gestational diabetes mellitus—a prospective cohort study. J Clin Periodontol 2018;45(8):920–931. DOI: 10.1111/jcpe.12902.
64. Figueiredo MGOP, Takita SY, Dourado BMR, et al. Periodontal disease: repercussions in pregnant woman and newborn health—a cohort study. PLoS One 2019;14(11):e0225036. DOI: 10.1371/journal.pone.0225036.
65. Mathew RJ, Bose A, Prasad JH, et al. Maternal periodontal disease as a significant risk factor for low birth weight in pregnant women attending a secondary care hospital in South India: a case-control study. Indian J Dent Res 2014;25(6):742–747. DOI: 10.4103/0970-9290.152184.
66. Bi WG, Emami E, Luo ZC, et al. Effect of periodontal treatment in pregnancy on perinatal outcomes: a systematic review and meta-analysis. J Matern Neonatal Med 2019;34(19):3259–3268. DOI: 10.1080/14767058.2019.1678142.
67. Offenbacher S, Katz V, Fertik G, et al. Periodontal infection as a possible risk factor for preterm low birth weight. J Periodontol 1996;67(Suppl 10):1103–1113. DOI: 10.1902/jop.1996.67.10s.1103.
68. 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. DOI: 10.14219/jada.archive.2001.0299.
69. Offenbacher S, Lieff S, Boggess KA, et al. Maternal periodontitis and prematurity. Part I: obstetric outcome of prematurity and growth restriction. Ann Periodontol 2001;6(1):164–174. DOI: 10.1902/annals.2001.6.1.164.
70. Davenport ES, Williams CECS, Sterne JAC, et al. Maternal periodontal disease and preterm low birthweight: case-control study. J Dent Res 2002;81(5):313–318. DOI: 10.1177/154405910208100505.
71. Corbella S, Taschieri S, Del Fabbro M, et al. Adverse pregnancy outcomes and periodontitis: a systematic review and meta-analysis exploring potential association. Quintessence Int (Berl) 2016;47(3):193–204. DOI: 10.3290/j.qi.a34980.
72. Ide M, Papapanou PN. Epidemiology of association between maternal periodontal disease and adverse pregnancy outcomes – systematic review. J Clin Periodontol 2013;40 Suppl 14:S181–S94. DOI: 10.1111/jcpe.12063.
73. Baskaradoss JK, Geevarghese A, Al Dosari AAF. Causes of adverse pregnancy outcomes and the role of maternal periodontal status – a review of the literature. Open Dent J 2012;6:79–84. DOI: 10.2174/1874210601206010079.
74. Corbella S, Taschieri S, Francetti L, et al. Periodontal disease as a risk factor for adverse pregnancy outcomes: a systematic review and meta-analysis of case-control studies. Odontology 2012;100(2):232–240. DOI: 10.1007/s10266-011-0036-z.
75. Konopka T, Paradowska-Stolarz A. Periodontitis and risk of preterm birth and low birthweight–a meta-analysis. Ginekol Pol 2012;83(6):446–453. PMID: 22880465.
76. Shanthi V, Vanka A, Bhambal A, et al. Association of pregnant women periodontal status to preterm and low-birth weight babies: a systematic and evidence-based review. Dent Res J (Isfahan) 2012;9(4):368–380. PMID: 23162575.
77. Offenbacher S, Beck JD, Jared HL, et al. Effects of periodontal therapy on rate of preterm delivery: a randomized controlled trial. Obstet Gynecol 2009;114(3):551–559. DOI: 10.1097/AOG.0b013e3181b1341f.
78. 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. DOI: 10.1056/NEJMoa062249.
79. López NJ, Smith PC, Gutierrez J. Periodontal therapy may reduce the risk of preterm low birth weight in women with peridotal disease: a randomized controlled trial. J Periodontol 2002;73(8):911–924. DOI: 10.1902/jop.2002.73.8.911.
80. Romero R, Espinoza J, Kusanovic JP, et al. The preterm parturition syndrome. BJOG An Int J Obstet Gynaecol 2006;113 (Suppl 3): 17–42. DOI: 10.1111/j.1471-0528.2006.01120.x.
81. Gilles HM, Lawson JB, Sibelas M, et al. Malaria, anaemia and pregnancy. Ann Trop Med Parasitol 1969;63(2):245–263. DOI: 10.1080/00034983.1969.11686625.
82. Osman NB, Folgosa E, Gonzales C, et al. Genital infections in the aetiology of late fetal death: an incident case-referent study. J Trop Pediatr 1995;41(5):258–266. DOI: 10.1093/tropej/41.5.258.
83. Benedetti TJ, Valle R, Ledger WJ. Antepartum pneumonia in pregnancy. Am J Obstet Gynecol 1982;144(4):413–417. DOI: 10.1016/0002-9378(82)90246-0.
84. Madinger NE, Greenspoon JS, Ellrodt AG. Pneumonia during pregnancy: has modern technology improved maternal and fetal outcome? Am J Obstet Gynecol 1989;161(3):657–662. DOI: 10.1016/0002-9378(89)90373-6.
85. Hibbard L, Thrupp L, Summeril S, et al. Treatment of pyelonephritis in pregnancy. Am J Obstet Gynecol 1967;98(5):609–615. DOI: 10.1016/0002-9378(67)90172-X.
86. Cunningham FG, Morris GB, Mickal A. Acute pyelonephritis of pregnancy: a clinical review. Obstet Gynecol 1973;42(1):112–117. PMID: 4720190.
87. Herd N, Jordan T. An investigation of malaria during pregnancy in Zimbabwe. Cent Afr J Med 1981;27:62–68. PMID: 7261055.

88. Kalanda BF, Verhoeff FH, Chimsuku L, et al. Adverse birth outcomes in a malarious area. Epidemiol Infect 2006;134(3):659–666. DOI: 10.1017/S0950268805005285.
89. Patrick MJ. Influence of maternal renal infection on the foetus and infant. Arch Dis Child 1967;42(222):208–213. DOI: 10.1136/adc.42.222.208.
90. Wren BG. Subclinical renal infection and prematurity. Med J Aust 1969;2(12):596–600. DOI: 10.5694/j.1326-5377.1969.tb107290.x.
91. Munn MB, Groome LJ, Atterbury JL, et al. Pneumonia as a complication of pregnancy. J Matern Neonatal Med 1999;8(4):151. DOI: 10.1002/(sici)1520-6661(199907/08)8:4<151::aid-mfm2>3.0.co;2-h.
92. Kaul AK, Khan S, Martens MG, et al. Experimental gestational pyelonephritis induces preterm births and low birth weights in C3H/HeJ mice. Infect Immun 1999;67(11):5958–5966. DOI: 10.1128/iai.67.11.5958-5966.1999.
93. Romero R, Mazor M, Munoz H, et al. The preterm labor syndrome. Ann N Y Acad Sci 1994;734:414–429. DOI: 10.1111/j.1749-6632.1994.tb21771.x.
94. Minkoff H. Prematurity: infection as an etiologic factor. Obstet Gynecol 1983;62(2):137–144. PMID: 6346172.
95. Romero R, Mazor M, Ying King Wu, et al. Infection in the pathogenesis of preterm labor. Semin Perinatol 1988;12(4):262–279. DOI: 10.5555/uri:pii:0146000588900456.
96. Romero R, Sirtori M, Oyarzun E, et al. Infection and labor. V. Prevalence, microbiology, and clinical significance of intraamniotic infection in women with preterm labor and intact membranes. Am J Obstet Gynecol 1989;161(3):817–824. DOI: 10.1016/0002-9378(89)90409-2.
97. Gonçalves LF, Chaiworapongsa T, Romero R. Intrauterine infection and prematurity. Ment Retard Dev Disabil Res Rev 2002;8(1):3–13. DOI: 10.1002/mrdd.10008.
98. Zahl PA, Bjerknes C. Induction of decidua-placental hemorrhage in mice by the endotoxins of certain gram-negative bacteria. Proc Soc Exp Biol Med 1943;54(3):329. DOI: 10.3181/00379727-54-14424.
99. Elovitz MA, Mrinalini C. Animal models of preterm birth. Trends Endocrinol Metab 2004;15(10):479–487. DOI: 10.1016/j.tem.2004.10.009.
100. Fidel PL, Romero R, Wolf N, et al. Systemic and local cytokine profiles in endotoxin-induced preterm parturition in mice. Am J Obstet Gynecol 1994;170(5 Pt 1):1467–1475. DOI: 10.1016/S0002-9378(94)70180-6.
101. Hirsch E, Saotome I, Hirsch D. A model of intrauterine infection and preterm delivery in mice. Am J Obstet Gynecol 1995;172(5):1598–1603. DOI: 10.1016/0002-9378(95)90503-0.
102. Gibbs RS, McDuffie RS, Kunze M, et al. Experimental intrauterine infection with Prevotella bivia in New Zealand White rabbits. Am J Obstet Gynecol 2004;190(4):1082–1086. DOI: 10.1016/j.ajog.2003.10.700.
103. McKay DG, Wong TC. The effect of bacterial endotoxin on the placenta of the rat. Am J Pathol 1963;42(3):357–377. PMID: 19971021.
104. Kullander S. Fever and parturition an experimental study in rabbits. Acta Obstet Gynecol Scand 1977;66:77–85. DOI: 10.3109/00016347709156356.
105. McDuffie RS, Sherman MP, Gibbs RS. Amniotic fluid tumor necrosis factor-a and interleukin-1 in a rabbit model of bacterially induced preterm pregnancy loss. Am J Obstet Gynecol 1992;167(6):1583–1588. DOI: 10.1016/0002-9378(92)91745-V.
106. Gravett MG, Witkin SS, Haluska GJ, et al. An experimental model for intraamniotic infection and preterm labor in rhesus monkeys. Am J Obstet Gynecol 1994;171(6):1660–1667. DOI: 10.1016/0002-9378(94)90418-9.
107. Wang H, Hirsch E. Bacterially-induced preterm labor and regulation of prostaglandin-metabolizing enzyme expression in mice: the role of toll-like receptor 41. Biol Reprod 2003;69(6):1957–1963. DOI: 10.1095/biolreprod.103.019620.
108. Fidel P, Ghezzi F, Romero R, et al. The effect of antibiotic therapy on intrauterine infection-induced preterm parturition in rabbits. J Matern Neonatal Med 2003;14(1):57–64. DOI: 10.1080/jmf.14.1.57.64.
109. Romero R, Oyarzun E, Mazor M, et al. Meta-analysis of the relationship between asymptomatic bacteriuria and preterm delivery/low birth weight. Obstet Gynecol 1989;73(4):576–582. PMID: 2927852.
110. Smaill FM, Vazquez JC. Antibiotics for asymptomatic bacteriuria in pregnancy. Cochrane Database Syst Rev 2019;2019(11):CD000490. DOI: 10.1002/14651858.CD000490.pub4.
111. Fazeli A, Bruce C, Anumba DO. Characterization of Toll-like receptors in the female reproductive tract in humans. Hum Reprod 2005;20(5):1372–1378. DOI: 10.1093/humrep/deh775.
112. Elovitz MA, Wang Z, Chien EK, et al. A new model for inflammation-induced preterm birth: the role of platelet-activating factor and toll-like receptor-4. Am J Pathol 2003;163(5):2103–2111. DOI: 10.1016/S0002-9440(10)63567-5.
113. Abrahams VM, Bole-Aldo P, Kim YM, et al. Divergent trophoblast responses to bacterial products mediated by TLRs. J Immunol 2004;173(7):4286–4296. DOI: 10.4049/jimmunol.173.7.4286.
114. Vadillo Ortega F, Avila Vergara MA, Hernández Guerrero C, et al. [Apoptosis in trophoblast of patients with recurrent spontaneous abortion of unidentified cause]. Ginecol Obstet Mex 2000;68:122–131. PMID: 10808617.
115. Murthi P, Kee MW, Gude NM, et al. Fetal growth restriction is associated with increased apoptosis in the chorionic trophoblast cells of human fetal membranes. Placenta 2005;26(4):329–338. DOI: 10.1016/j.placenta.2004.07.006.
116. Huppertz B, Hemmings D, Renaud SJ, et al. Extravillous trophoblast apoptosis – a workshop report. Placenta 2005;26:S46. DOI: 10.1016/j.placenta.2005.02.002.
117. Romero R, Mazor M, Tartakovsky B. Systemic administration of interleukin-1 induces preterm parturition in mice. Am J Obstet Gynecol 1991;165(4 Pt 1):969–971. DOI: 10.1016/0002-9378(91)90450-6.
118. Watari M, Watari H, DiSanto ME, et al. Pro-inflammatory cytokines induce expression of matrix-metabolizing enzymes in human cervical smooth muscle cells. Am J Pathol 1999;154(6):1755–1762. DOI: 10.1016/S0002-9440(10)65431-4.
119. Fortunato SJ, Menon R, Lombardi SJ. Role of tumor necrosis factor-α in the premature rupture of membranes and preterm labor pathways. Am J Obstet Gynecol 2002;187(5):1159–1162. DOI: 10.1067/mob.2002.127457.
120. Athayde N, Edwin SS, Romero R, et al. A role for matrix metalloproteinase-9 in spontaneous rupture of the fetal membranes. Am J Obstet Gynecol 1998;179(5):1248–1253. DOI: 10.1016/S0002-9378(98)70141-3.
121. Maymon E, Romero R, Pacora P, et al. Evidence of in vivo differential bioavailability of the active forms of matrix metalloproteinases 9 and 2 in parturition, spontaneous rupture of membranes, and intra-amniotic infection. Am J Obstet Gynecol 2000;183(4):887–894. DOI: 10.1067/mob.2000.108878.
122. Romero R, Chaiworapongsa T, Espinoza J, et al. Fetal plasma MMP-9 concentrations are elevated in preterm premature rupture of the membranes. Am J Obstet Gynecol 2002;187(5):1125–1130. DOI: 10.1067/mob.2002.127312.
123. Osmers RGW, Adelmann-Grill BC, Rath W, et al. Biochemical events in cervical ripening dilatation during pregnancy and parturition. J Obstet Gynaecol (Lahore) 1995;21(2):185–194. DOI: 10.1111/j.1447-0756.1995.tb01092.x.
124. Rath W, Winkler M, Kemp B. The importance of extracellular matrix in the induction of preterm delivery. J Perinat Med 1998;26(6):437. DOI: 10.1515/jpme.1998.26.6.437.
125. Hirsch E, Muhle RA, Mussalli GM, et al. Bacterially induced preterm labor in the mouse does not require maternal interleukin-1 signaling. Am J Obstet Gynecol 2002;186(3):523–530. DOI: 10.1067/mob.2002.120278.
126. Hirsch E, Filipovich Y, Mahendroo M. Signaling via the type I IL-1 and TNF receptors is necessary for bacterially induced preterm labor in a murine model. Am J Obstet Gynecol 2006;194(5):1334–1340. DOI: 10.1016/j.ajog.2005.11.004.

127. Romero R, Tartakovsky B. The natural interleukin-1 receptor antagonist prevents interleukin-I-induced preterm delivery in mice. Am J Obstet Gynecol 1992;167(4 Pt 1):1041–1045. DOI: 10.1016/S0002-9378(12)80035-4.
128. Andrews WW, Hauth JC, Goldenberg RL, et al. Amniotic fluid interleukin-6: correlation with upper genital tract microbial colonization and gestational age in women delivered after spontaneous labor versus indicated delivery. Am J Obstet Gynecol 1995;173(2):606–612. DOI: 10.1016/0002-9378(95)90290-2.
129. Romero R, Avila C, Santhanam U, et al. Amniotic fluid interleukin 6 in preterm labor: association with infection. J Clin Invest 1990;85(5):1392–1400. DOI: 10.1172/JCI114583.
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.
131. Hillier SL, Witkin SS, Krohn MA, et al. The relationship of amniotic fluid cytokines and preterm delivery, amniotic fluid infection, histologic chorioamnionitis, and chorioamnion infection. Obstet Gynecol 1993;81(6):941–948. PMID: 8497360.
132. Gomez R, Romero R, Galasso M, et al. The value of amniotic fluid interleukin-6, white blood cell count, and gram stain in the diagnosis of microbial invasion of the amniotic cavity in patients at term. Am J Reprod Immunol 1994;32(3):200–210. DOI: 10.1111/j.1600-0897.1994.tb01115.x.
133. Messer J, Eyer D, Donato L, et al. Evaluation of interleukin-6 and soluble receptors of tumor necrosis factor for early diagnosis of neonatal infection. J Pediatr 1996;129(4):574–580. DOI: 10.1016/S0022-3476(96)70123-3.
134. Athayde N, Romero R, Maymon E, et al. Interleukin 16 in pregnancy, parturition, rupture of fetal membranes, and microbial invasion of the amniotic cavity. Am J Obstet Gynecol 2000;182(1 Pt 1):135–141. DOI: 10.1016/S0002-9378(00)70502-3.
135. Pacora P, Romero R, Maymon E, et al. Participation of the novel cytokine interleukin 18 in the host response to intra-amniotic infection. Am J Obstet Gynecol 2000;183(5):1138–1143. DOI: 10.1067/mob.2000.108881.
136. Hanna N, Hanna I, Hleb M, et al. Gestational age-dependent expression of IL-10 and its receptor in human placental tissues and isolated cytotrophoblasts. J Immunol 2000;164(11):5721–5728. DOI: 10.4049/jimmunol.164.11.5721.
137. Sadowsky DW, Novy MJ, Witkin SS, et al. Dexamethasone or interleukin-10 blocks interleukin-1beta-induced uterine contractions in pregnant rhesus monkeys. Am J Obstet Gynecol 2003;188(1):252–263. DOI: 10.1067/mob.2003.70.
138. Terrone DA, Rinehart BK, Granger JP, et al. Interleukin-10 administration and bacterial endotoxin-induced preterm birth in a rat model. Obstet Gynecol 2001;98(3):476–480. DOI: 10.1016/S0029-7844(01)01424-7.
139. Rodts-Palenik S, Wyatt-Ashmead J, Pang Y, et al. Maternal infection-induced white matter injury is reduced by treatment with interleukin-10. Am J Obstet Gynecol 2004;191(4):1387–1392. DOI: 10.1016/j.ajog.2004.06.093.
140. Aagaard K, Ma J, Antony KM, et al. The placenta harbors a unique microbiome. Sci Transl Med 2014;6(237):237ra65. DOI: 10.1126/scitranslmed.3008599.
141. Bearfield C, Davenport ES, Sivapathasundaram V, et al. Possible association between amniotic fluid micro-organism infection and microflora in the mouth. British journal of obstetrics and gynaecology 2002;109(5):527–533. DOI: 10.1111/j.1471-0528.2002.01349.x.
142. 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. DOI: 10.1128/JCM.44.4.1475-1483.2006.
143. Muwazi L, Rwenyonyi CM, Nkamba M, et al. Periodontal conditions, low birth weight and preterm birth among postpartum mothers in two tertiary health facilities in Uganda. BMC Oral Health 2014;14:42. DOI: 10.1186/1472-6831-14-42.
144. Sánchez AR, Bagniewski S, Weaver AL, et al. Correlations between maternal periodontal conditions and preterm low birth weight infants. J Int Acad Periodontol 2007;9(2):34–41. PMID: 17506382.
145. Yeo BK, Lim LP, Paquette DW, et al. Periodontal disease–the emergence of a risk for systemic conditions: pre-term low birth weight. Ann Acad Med Singapore 2005;34(1):111–116. PMID: 15726229.
146. Johnson S, Evans TA, Draper ES, et al. Neurodevelopmental outcomes following late and moderate prematurity: a population-based cohort study. Arch Dis Child Fetal Neonatal Ed 2015;100(4):F301–F308. DOI: 10.1136/archdischild-2014-307684.
147. Poulsen G, Wolke D, Kurinczuk JJ, et al. Gestational age and cognitive ability in early childhood: a population-based cohort study. Paediatr Perinat Epidemiol 2013;27(4):371–379. DOI: 10.1111/ppe.12058.
148. Kerstjens JM, De Winter AF, Bocca-Tjeertes IF, et al. Developmental delay in moderately preterm-born children at school entry. J Pediatr 2011;159(1):92–98. DOI: 10.1016/j.jpeds.2010.12.041.
149. Boyle EM, Poulsen G, Field DJ, et al. Effects of gestational age at birth on health outcomes at 3 and 5 years of age: population based cohort study. British Medical Association 2012;344:e896. DOI: 10.1136/bmj.e896.
150. Cserjési R, Van Braeckel KNJA, Butcher PR, et al. Functioning of 7-year-old children born at 32–35 weeks' gestational age. Pediatrics 2012;130(4):e838–e846. DOI: 10.1542/peds.2011-2079.
151. Talge NM, Holzman C, Wang J, et al. Late-preterm birth and its association with cognitive and socioemotional outcomes at 6 years of age. Pediatrics 2010;126(6):1124–1131. DOI: 10.1542/peds.2010-1536.
152. Mackay DF, Smith GCS, Dobbie R, et al. Gestational age at delivery and special educational need: retrospective cohort study of 407,503 schoolchildren. PLoS Med 2010;7(6):e1000289. DOI: 10.1371/journal.pmed.1000289.
153. Lipkind HS, Slopen ME, Pfeiffer MR, et al. School-age outcomes of late preterm infants in New York City. Am J Obstet Gynecol 2012;206(3):222.e1–e6. DOI: 10.1016/j.ajog.2012.01.007.
154. Quigley MA, Poulsen G, Boyle E, et al. Early term and late preterm birth are associated with poorer school performance at age 5 years: a cohort study. Arch Dis Child Fetal Neonatal Ed 2012;97(3):F167–F173. DOI: 10.1136/archdischild-2011-300888.
155. Mathiasen R, Hansen BM, Nybo Andersen AMN, et al. Gestational age and basic school achievements: a national follow-up study in Denmark. Pediatrics 2010;126(6):e1553–e1561. DOI: 10.1542/peds.2009-0829.
156. Chyi LJ, Lee HC, Hintz SR, et al. School outcomes of late preterm infants: special needs and challenges for infants born at 32–36 weeks gestation. J Pediatr 2008;153(1):25–31. DOI: 10.1016/j.jpeds.2008.01.027.
157. Potijk MR, De Winter AF, Bos AF, et al. Higher rates of behavioural and emotional problems at preschool age in children born moderately preterm. Arch Dis Child 2012;97(2):112–117. DOI: 10.1136/adc.2011.300131.
158. Favrais G, Van De Looij Y, Fleiss B, et al. Systemic inflammation disrupts the developmental program of white matter. Ann Neurol 2011;70(4):550–565. DOI: 10.1002/ana.22489.
159. Smith PLP, Hagberg H, Naylor AS, et al. Neonatal peripheral immune challenge activates microglia and inhibits neurogenesis in the developing murine hippocampus. Dev Neurosci 2014;36(2):119–131. DOI: 10.1159/000359950.
160. Boksa P. Effects of prenatal infection on brain development and behavior: a review of findings from animal models. Brain Behav Immun 2010;24(6):881–897. DOI: 10.1016/j.bbi.2010.03.005.
161. Tahraoui SL, Marret S, Bodénant C, et al. Central role of microglia in neonatal excitotoxic lesions of the murine periventricular white matter. Brain Pathol 2001;11(1):56–71. DOI: 10.1111/j.1750-3639.2001.tb00381.x.
162. Rousset CI, Chalon S, Cantagrel S, et al. Maternal exposure to LPS induces hypomyelination in the internal capsule and programmed cell death in the deep gray matter in newborn rats. Pediatr Res 2006;59(3):428–433. DOI: 10.1203/01.pdr.0000199905.08848.55.

163. Covey MV, Loporchio D, Buono KD, et al. Opposite effect of inflammation on subventricular zone versus hippocampal precursors in brain injury. Ann Neurol 2011;70(4):616–626. DOI: 10.1002/ana.22473.
164. Lively S, Schlichter 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.
165. Golan H, Levav T, Mendelsohn A, et al. Involvement of tumor necrosis factor alpha in hippocampal development and function. Cereb Cortex 2004;14(1):97–105. DOI: 10.1093/cercor/bhg108.
166. Aloe L, Properzi F, Probert L, et al. Learning abilities, NGF and BDNF brain levels in two lines of TNF-α transgenic mice, one characterized by neurological disorders, the other phenotypically normal. Brain Res 1999;840(1-2):125–137. DOI: 10.1016/S0006-8993(99)01748-5.
167. Dunn D, Wallon M, Peyron F, et al. Mother-to-child transmission of toxoplasmosis: risk estimates for clinical counselling. Lancet 1999;353(9167):1829–1833. DOI: 10.1016/S0140-6736(98)08220-8.
168. Pass RF, Anderson B. Mother-to-child transmission of cytomegalovirus and prevention of congenital infection. J Pediatric Infect Dis Soc 2014;3 Suppl 1(Suppl 1):S2–S6. DOI: 10.1093/jpids/piu069.
169. Valentine GC, Seferovic MD, Fowler SW, et al. Timing of gestational exposure to Zika virus is associated with postnatal growth restriction in a murine model. Am J Obstet Gynecol 2018;219(4):403.e1–403.e9. DOI: 10.1016/j.ajog.2018.06.005.
170. Goeden N, Velasquez J, Arnold KA, et al. Maternal inflammation disrupts fetal neurodevelopment via increased placental output of serotonin to the fetal brain. J Neurosci 2016;36(22):6041–6049. DOI: 10.1523/JNEUROSCI.2534-15.2016.
171. Chameau P, Inta D, Vitalis T, et al. The N-terminal region of reelin regulates postnatal dendritic maturation of cortical pyramidal neurons. Proc Natl Acad Sci USA 2009;106(17):7227–7232. DOI: 10.1073/pnas.0810764106.
172. Vichier-Guerre C, Parker M, Pomerantz Y, et al. Impact of selective serotonin reuptake inhibitors on neural crest stem cell formation. Toxicol Lett 2017;281:20–25. DOI: 10.1016/j.toxlet.2017.08.012.
173. Fricker AD, Rios C, Devi LA, et al. Serotonin receptor activation leads to neurite outgrowth and neuronal survival. Mol Brain Res 2005;138(2):228–235. DOI: 10.1016/j.molbrainres.2005.04.016.
174. Khozhai LI, Otellin VA. Synaptogenesis in the dorsal raphe nucleus of the medulla oblongata in rats in conditions of serotonin deficiency. Neurosci Behav Physiol 2013;43(8):984–988. DOI: 10.1007/s11055-013-9840-y.
175. Gaspar P, Cases O, Maroteaux L. The developmental role of serotonin: news from mouse molecular genetics. Nat Rev Neurosci 2003;4(12):1002–1012. DOI: 10.1038/nrn1256.
176. Shah R, Courtiol E, Castellanos FX, et al. Abnormal serotonin levels during perinatal development lead to behavioral deficits in adulthood. Front Behav Neurosci 2018;12:114. DOI: 10.3389/fnbeh.2018.00114.
177. Muller CL, Anacker AMJ, Veenstra-VanderWeele J. The serotonin system in autism spectrum disorder: from biomarker to animal models. Neuroscience 2016;321:24–41. DOI: 10.1016/j.neuroscience.2015.11.010.
178. Loos BG, Craandijk J, Hoek FJ, et al. Elevation of systemic markers related to cardiovascular diseases in the peripheral blood of periodontitis patients. J Periodontol 2000;71(10):1528–1534. DOI: 10.1902/jop.2000.71.10.1528.
179. Fogacci MF, Cardoso E de OC, Barbirato D da S, et al. No association between periodontitis and preterm low birth weight: a case–control study. Arch Gynecol Obstet 2018;297(1):71–76. DOI: 10.1007/s00404-017-4556-9.
180. Grembowski D, Fiset L, Milgrom P, et al. Does fluoridation reduce the use of dental services among adults? Med Care 1997;35:454–471. DOI: 10.1097/00005650-199705000-00004.
181. Grembowski D, Fiset L, Spadafora A, et al. Fluoridation effects on periodontal disease among adults. J Periodontal Res 1993;28(3):166–172. DOI: 10.1111/j.1600-0765.1993.tb01065.x.
182. Maupomé G, Gullion CM, Peters D, et al. A comparison of dental treatment utilization and costs by HMO members living in fluoridated and nonfluoridated areas. J Public Health Dent 2007;67(4):224–233. DOI: 10.1111/j.1752-7325.2007.00033.x.
183. Jia B, Zong L, Lee JY, et al. Maternal supplementation of low dose fluoride alleviates adverse perinatal outcomes following exposure to intrauterine inflammation. Sci Rep 2019;9(1):2575. DOI: 10.1038/s41598-018-38241-8.
184. De Cock P, Mäkinen K, Honkala E, et al. Erythritol is more effective than xylitol and sorbitol in managing oral health endpoints. Int J Dent 2016;2016:9868421. DOI: 10.1155/2016/9868421.
185. Mäkinen KK, Isotupa KP, Kivilompolo T, et al. Comparison of erythritol and xylitol saliva stimulants in the control of dental plaque and mutans streptococci. Caries Res 2001;35(2):129–135. DOI: 10.1159/000047444.
186. Mäkinen KK, Isotupa KP, Kivilompolo T, et al. The effect of polyol-combinant saliva stimulants on S. mutans levels in plaque and saliva of patients with mental retardation. Spec care Dent 2002;22(5):187–193. DOI: 10.1111/j.1754-4505.2002.tb00269.x
187. Mäkinen KK, Saag M, Isotupa KP, et al. Similarity of the effects of erythritol and xylitol on some risk factors of dental caries. Caries Res 2005;39(3):207–215. DOI: 10.1159/000084800.
188. Söderling EM, Hietala-Lenkkeri AM. Xylitol and erythritol decrease adherence of polysaccharide-producing oral streptococci. Curr Microbiol 2010;60(1):25–29. DOI: 10.1007/s00284-009-9496-6.
189. Yao J, Zhang JL, Wu YQ, et al. Contrasting study of erythritol and xylitol on Streptococcus mutans. Hua Xi Kou Qiang Yi Xue Za Zhi 2009;27(6):603–605. PMID: 20077891.
190. Blencowe H, Cousens S, Oestergaard MZ, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet 2012;379(9832):2162–2172. DOI: 10.1016/S0140-6736(12)60820-4.