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Review

Periodontal diseases and adverse pregnancy outcomes: Is there a role for vitamin D?

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ABSTRACT

Studies have shown a relationship between maternal periodontal diseases (PDs) and premature delivery. PDs are commonly encountered oral diseases which cause progressive damage to the periodontal ligament and alveolar bones, leading to loss of teeth and oral disabilities. PDs also adversely affect general health by worsening of cardiovascular and metabolic diseases. Moreover, maternal PDs are thought to be related to increasing the frequency of preterm-birth with low birth weight (PBLBW) in new-borns. Prematurity and immaturity are the leading causes of prenatal and infant mortality and is a major public health problem around the world. Inflamed periodontal tissues generate significantly high levels of proinflammatory cytokines that may have systemic effects on the host mother and the fetus. In addition, the bacteria that cause PDs produce endotoxins which can harm the fetus. Furthermore, studies have shown that microorganisms causing PDs can get access to the bloodstream, invading uterine tissues, to induce PBLBW. Another likely mechanism that connects PDs with adverse pregnancy outcome is maternal vitamin D status. A role of inadequate vitamin D status in the genesis of PDs has been reported. Administration of vitamin D supplementation during pregnancy could reduce the risk of maternal infections and adverse pregnancy outcomes. As maternal PDs are significant risk factors for adverse pregnancy outcome, preventive antenatal care for pregnant women in collaboration with the obstetric and dental professions are required.

1. Introduction

Pregnancy induces many transitory changes in female body and compensatory modifications of various organs including the oral cavity [1–3]. Pregnant women are more likely to develop periodontitis, gingivitis, and gingival hyperplasia. How pregnancy exacerbates oral lesions is not clear, however, elevated levels of reproductive hormones are thought to be a possible link between periodontal diseases (PDs) and pregnancy [4,5]. Studies have shown the presence of estrogen and progesterone receptors in the human periodontium [6,7]; and thereby making the periodontium as a target tissue for reproductive hormones. The changes in reproductive hormones during pregnancy affect gingival inflammatory responses, possibly through influencing the chemotaxis, generation of cytokines, and antioxidants from polymorphonuclear leukocytes, gingival fibroblasts and periodontal ligament cells, and thus contributes to increased gingival inflammation [8–10]. Hormonal changes during pregnancy are likely to enhance the susceptibility of gingival inflammatory process, by changing the composition of oral biofilm, to facilitate a selective overgrowth of periodontal pathogens like *Porphyromonas gingivalis*, *Prevotella intermedia* [11], or *Campylobacter rectus* [12]. It increasingly becomes clear that the status of oral health influences general health and well-being. Maternal oral health status, in particular, has a significant impact on pregnancy outcomes and infant health [13–15]. Studies have shown that approximately 40% of pregnant women have some form of PDs [3,16–18]. Several studies have established a link between periodontal infections and different systemic disorders, including osteoporosis, diabetes mellitus, cardiovascular diseases, respiratory diseases, preeclampsia and pregnancy outcome [19–22].

PDs are chronic inflammatory diseases causing loss of periodontal

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attachment (i.e., periodontal ligaments) and alveolar bone loss. In elderly individuals, PDs are the major cause of tooth loss [23,24]. In a study conducted on 11,202 individuals of National Health and Nutrition Examination Survey (NHANES), a significant inverse association between serum levels of 25-hydroxyvitamin D and PDs was noted in both male and female patients with the age of 50 years and more [25]. Of clinical significance, studies have reported that exogenous vitamin D and calcium supplementation reduced tooth loss in elderly individuals over a period of 3 years [26]. Furthermore, when 117 cases of pregnant women with clinical moderate to severe PDs, were compared to 118 controls (pregnant women with healthy periodontal tissue), the adjusted odds ratio (95% confidence interval) for moderate to severe PDs among women with vitamin D insufficiency was 2.1 (0.99–4.5) [27]. The investigators reported that the relationship between 25-hydroxyvitamin D insufficiency and moderate to severe PDs remained significant using either < 50 nmol/l or < 37.5 nmol/l to define the insufficiency [27].

Of clinical significance, substantial evidence of an independent association between maternal PDs and adverse pregnancy outcomes, especially preterm-birth with low birth weight (PBLBW) are documented in several studies [28–30]; PBLBW deliveries were reported to be significantly associated with unhealthy maternal periodontal status in a Nigerian study conducted on 680 subjects [31,32]. In a separate study carried out in Uganda, the height-for-age status at three weeks postpartum was found to be worse among the infants whose mothers were suffering from PDs with poor oral hygiene status during their pregnancy. Efforts to reduce oral disease burdens during pregnancy should be part of antenatal care to benefit both the mother and the newborn [33].

2. Periodontal diseases and adverse pregnancy outcomes

Pregnancy-related complications with PBLBW are significant public health problems, as such complications are associated with increased mortality, and long-term disability [17,34,35]. More than 20 years ago, Offenbacher et al. (1996) provided the evidence of an association between periodontal pathogens and preterm birth; the investigators found that the mothers with PBLBW newborns had significantly worse PDs than those who gave birth to normal weight infants [36,37]. The investigators estimated PDs from full-mouth examination data on clinical attachment levels and probing depths on six sites per tooth; in addition, bleeding on probing was measured and expressed as the percentage of sites exhibiting this response. From the analyzed data Offenbacher et al. estimated that 18.2% of all PLBW cases may be attributable to PDs, and speculated that PDs in pregnant women might be contributing to more cases of PBLBW than either smoking or alcohol intake. Since then, other studies have also found similar associations [38,39]. Although the etiology of PBLBW is not precisely known, premature decidual activation by microorganisms and/or inflammatory mediators is one of the likely mechanisms [39–41].

Further studies found an association between oral infections, particularly gum diseases and PBLBW [42–44]. Offenbacher and colleagues hypothesized that PDs expose the pregnant host to gram-negative pathogens (e.g., *Porphyromonas gingivalis*, *Tannerella forsythia* and *Campylobacter rectus*), lipopolysaccharide (endotoxin) and inflammatory mediators (IL-1, TNF-α, etc.) which are likely to affect fetal growth to induce adverse pregnancy outcomes. Published studies have claimed that mothers with PDs were 7.5 times more likely to have a PBLBW infant or other pregnancy-related complications [2,12,16,35,45–48]. Jeffcoat and colleagues also found a similar positive association between maternal PDs and PBLBW in the USA, and the mothers with severe PDs were 4–7 times more likely to deliver a preterm newborn relative to mothers with good oral health status [49,50]. It is important to mention that a few studies did not detect a correlation between maternal PDs and pregnancy outcomes [51,52]. In a case-control multicenter study on 1108 women with preterm deliveries, spontaneous preterm birth or preterm premature rupture of membranes was not associated with periodontitis [53]. In a separate case-control study conducted on 59 German Caucasian pregnant women with a high risk for a PBLBW infant, periodontitis was not among the detectable risk factor for PBLBW [54]. Such discrepancies in different clinical studies might be explained by the use of various parameters of adverse pregnancy outcomes, and how PDs were defined in terms of disease patterns and severities.

Intervention studies provide evidence that reducing maternal periodontal infection and inflammation may decrease premature delivery. Non-randomized trials concluded that mothers with PBLBW newborns had significantly higher levels of subgingival pathogens, and the investigators speculated that mechanical periodontal therapy alone might reduce PBLBW deliveries in pregnant women with periodontitis [55,56]. A meta-analysis concluded that treatment of PDs with scaling and root planing did not reduce the incidence of preterm birth, and the investigators recommended that pregnant women should be informed that such treatment during pregnancy is unlikely to reduce the risk of PBLBW infants [57].

Of importance, *Fusobacterium nucleatum* from the oral flora has been detected in the amniotic fluid of pregnant women with premature delivery [35,58–60]; an association between *Capnocytophaga* and intrauterine infection are also reported. It is, therefore, becoming increasingly evident that some of the organisms responsible for genital tract infections leading to preterm delivery could be derived from the mouth of the affected individuals. Bacterial insults are likely to change the microenvironment of the uterine cavity and eventually induce premature labor and delivery of vulnerable PBLBW newborns [38,46,61,62].

Bloodborne gram-negative bacteria or inflammatory mediators (lipopolysaccharides and cytokines), may be transported to the uterus and cervix to augment the inflammatory response, and induce premature labor and delivery [38,52,63–65]. Periodontal infection (gram-negative infection) may also induce such inflammatory responses, and thereby can cause premature rupture of membranes with PBLBW newborns [38,47,66,67]. Maternal PDs may act synergistically with other maternal risk factors to cause premature delivery. Of relevance, poor pregnancy outcomes, including PBLBW newborns, and infant mortality, are usually associated with late or no prenatal care, smoking, consumption of alcohol, obesity, maternal age, poor nutrition, and low socioeconomic status (Table 1) [68–70]. Preeclampsia (a common hypertensive disorder during pregnancy) is an independent risk factor for both maternal and infant morbidity and mortality. Boggess and colleagues reported that maternal exposure to PDs might be related to the occurrence of preeclampsia, as severe maternal PDs during pregnancy has been associated with an increased risk for preeclampsia [1,71,72].

Table 1
Factors influencing adverse pregnancy outcomes.

Partial list of the factors associated with adverse pregnancy outcome
Age of mother
Diabetes Mellitus
Frequent alcohol consumption
Infections
Lack of availability and access to preconception care
Malnutrition (not taking vitamins with folic acid)
Multiparity
Obesity
Periodontal diseases
Poor sanitation
Pregnancy at an early age
Presence of chronic medical conditions
Prolonged reproductive period
Sexually transmitted diseases and HIV
Smoking
Use of drugs