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Review Article

Periodontitis and pregnancy outcomes

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ABSTRACT

Placental and Periodontal environment have common aspects which suggests that periodontal microorganisms that enter the circulation and seed the placenta may find a niche that can support infection. When periodontal pathogens are being assessed, the timing of the seeding of the placenta for their possible contribution to adverse pregnancy outcomes can be challenging to determine. Samples from the placenta are generally taken at the time of delivery, and therefore when infection occurred, it is unknown. If a woman is considering becoming pregnant, and periodontitis is present, periodontal treatment should occur prior to the pregnancy as seeding occurs in the first trimester. The presence of periodontal bacteria (i.e. F. nucleatum and P. gingivalis) in the placenta does not itself constitute evidence of cause and effect regarding adverse pregnancy outcomes.

1. Introduction

Infection and inflammatory response associated with periodontitis can adversely affect a number of systemic diseases and conditions has changed the narrative about the importance of identifying and treating oral diseases. Periodontitis identified as a potential risk factor for many of diseases and there is strongest evidence for cardiovascular diseases, diabetes mellitus and adverse pregnancy outcomes. These conditions were the focus of the World Workshop in Periodontics in 2012 and adverse pregnancy outcomes differs from the other associations in that young women are potentially affected and pregnancy is not "chronic" by considering the 9-month gestation period.[1] Further, the relationship of periodontitis and adverse pregnancy outcomes is one of the associations highlighted in a review of "Periodontal Medicine" during the past 100 years.[2]

The association of adverse health outcomes and periodontitis has been focused on hematogenous spread of specific periodontal bacterial pathogens and the contribution of the periodontitis response to the total systemic inflammatory burden.[2]

Reports that pregnant women with periodontitis were at increased risk for adverse pregnancy outcomes has generated significant interest. Adverse outcomes are pre-labor or premature rupture of membranes, spontaneous abortion, pre-term labor and delivery and low birthweight. For purposes of discussion, these conditions will be grouped together and referred to as adverse pregnancy outcomes, which continues to be recognized as a global health problem of enormous significance. It is estimated that 11% of all births fall into adverse pregnancy outcomes.[3] The prevalence of adverse pregnancy outcomes in the United States has changed little in the in the past 10-15 years and was 10% in 2018.[4] Many risk factors for adverse pregnancy outcomes have been identified, including both older and younger maternal age, diabetes and the metabolic syndrome, hypertension and cardiovascular

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disease, smoking and alcohol consumption, recreational drug use and low socioeconomic status.[5] Nevertheless, more than half of all cases of adverse pregnancy outcomes do not have an identifiable risk factor[3] In addition to immediate post-partum complications such as immature lung development and the increased risk of infection, the consequences of adverse pregnancy outcomes can affected the health of the individual for life, and include neuro developmental deficits (cerebral palsy, attention deficit-hyperactivity disorder, visual impairment, anxiety and depression), as well as increased risk for chronic diseases including cardiovascular disease, diabetes mellitus and hypertension.[6] Historically, great interest in this association was generated by publication in 1996 of a study by Offenbacher and colleagues.[7] They compared women who experienced an adverse outcome with a matched group of females who did not experience such an outcome. After controlling for known risk factors for adverse pregnancy outcomes like tobacco use or consumption of alcohol, periodontitis was a significant risk factor for these outcomes, with an odds ratio of 7.9. This report was followed by many other publications assessing this association. Subsequently, a summation of the available data was presented in systematic reviews, and ultimately by a publication that summarized these systemic reviews.[8] A total of 23 systematic reviews were included, which were published between 2002 and 2016, and these included from 3 to 45 original studies. The conclusions in the systemic review were:

1. There were no reports linking periodontal disease or periodontal treatment with death of the mother, or perinatal mortality.
2. Focusing on the systematic reviews that included the studies with a lower risk of bias, the following associations were observed between periodontitis and specific adverse outcomes:
   Preterm birth: relative risk = 1.6 (based on 17 publications with a total of 6,741 patients).
   Low birthweight: relative risk = 1.7 (based on 10 publications with a total of 5,693 patients).
   Pre-eclampsia: a condition seen in pregnant women, associated with hypertension and elevated levels of protein in the urine. Relative risk = 2.2 (based on 15 studies with a total of 5,111 patients)
   Preterm low birth weight: relative risk = 3.4 (based on 4 studies with a total of 2,263 patients).
3. We also calculated estimates of the population-attributable fraction of the effect of periodontal disease on these adverse outcomes. Here the estimates of the population-attributable fraction is the percentage of affected individuals whose condition is considered to be a due to the presence of periodontitis.

1. Preterm birth: 5-38%
2. Low birthweight: 6-41%
3. Pre-eclampsia: 10-55%

We concluded that "pregnant women with periodontal disease are at increased risk of developing pre-eclampsia and delivering a preterm and/or low birthweight baby". They urged dentists and obstetricians to be aware of this linkage, and that preventive strategies and appropriate treatments need to be developed.

A review published in 2016 included 15 randomized controlled trials, with a total of 7,161 patients. Comparisons included more intense versus less intense periodontal treatment and periodontal treatment versus no treatment.[9]

In general, the quality of the evidence was low, meaning that the evaluated studies contained flaws. Many of the studies did not consider all variables that have been associated with adverse pregnancy outcomes. Their conclusions were that no reduction in adverse outcomes were observed (i.e. preterm birth at <32 weeks, <35 weeks, <37 weeks) with the provision of conservative periodontal therapy, generally in the second trimester. They did conclude that there was evidence that periodontal therapy could decrease the occurrence of low birthweight babies. These authors argued for better studies that included both periodontal outcomes and obstetrical outcomes.

In a systematic review that examined the effect of periodontal treatment on adverse pregnancy outcomes was published in 2018. There were 18 systematic reviews of which 13 included a meta-analysis.[10] While descriptive reviews suggested that periodontal therapy was associated with improved pregnancy outcomes, when considering those reviews with a meta-analysis (to gauge the magnitude of the effect), differences due to the periodontal treatment were not significant.

Taken together, the available evidence indicates a fascinating dichotomy. There is an association between the presence of periodontal disease/periodontitis and adverse pregnancy outcomes. However, treatment studies (with treatment generally provided in the second trimester) did not have a marked effected on these obstetrical outcomes. However, a recent report in the American Journal of Obstetrics & Gynecology may provide an explanation for this dichotomy.[11] Review by Fischer and colleagues[11] proposes a mechanistic explanation. They first emphasize that adverse pregnancy outcomes continues to be a global problem with life-long consequences for affected babies, as well as their family and society in general. These authors argue that the relationship between periodontitis and adverse pregnancy outcomes should not be dismissed because of the available clinical treatment data.

They emphasize the potential importance of periodontal bacteria that may be essential to the periodontitis- adverse pregnancy outcomes relationship, specifically *Fusobacterium ucleatum* and *Porphyromonas gingivalis. F. nucleatum* has been the microbiological focus

of this relationship.[12] They also include *P. gingivalis* since it possesses a range of virulence factors that may contribute to poor health outcomes. They first address the key question of why conservative periodontal therapy trials failed to have a significant effect on improving pregnancy outcomes. These trials provided periodontal therapy during the second trimester. The treatment provided was scaling and root planing which disrupts the subgingival biofilm. As the treatment is provided to patients with evidence of periodontitis, tissue inflammation would very likely have been present prior to the second trimester, the sulcular epithelium would be ulcerated and the likelihood exists for hematogenous spread of the subgingival microorganisms to have occurred early in the pregnancy. Further, they note that microbiologically there are similarities between the microflora of the oral cavity and that of the placenta. Infection and subsequent inflammation of the urinary tract and vagina have been associated with adverse pregnancy outcomes, and both periodontitis and vaginosis are associated with developed of an anaerobic environment, which will favor colonization by pathogenic microflora. Colonization of the placenta by pathogenic bacteria leads to an inflammatory response, which is likely a key component of the periodontitis- adverse pregnancy outcomes relationship.

Use of various laboratory approaches to identify the presence of the suspected pathogen (i.e. polymerase chain reaction) is likely inadequate. What must be determined is whether the organisms are just transient, or whether true infection has been established. Also questioned is how the placental samples are collected, and whether contamination of the samples occurred (for example by maternal blood), or even if sample processing may have contributed to a false positive reading. In the future, studies of this association need to be focused on careful collection of placental samples. These studies should also determine the intensity of the infection that would be associated with an adverse outcome. As noted, identification of periodontal bacteria is not in itself adequate evidence of cause and effect. A more detailed analysis is needed, which may mean identification of specific bacterial strains or other molecular characteristics associated with virulence. To further support a pathogenic association, samples from both the oral cavity and placenta should be collected to check for homology.

2. Conclusions

Woman who ask about the periodontitis- adverse pregnancy outcomes relationship, or are of child-bearing age can be told of an association between the presence of periodontitis and adverse pregnancy outcomes. Patients can be told that the published treatment studies, where periodontal therapy is provided to pregnant patients with periodontitis during the second trimester, have generally not reduced the occurrence of adverse pregnancy outcomes. This treatment has generally improved the status of the periodontium, without adverse effects on the mother or fetus. Woman should be urged to maintain a healthy mouth during pregnancy, since pregnancy is often associated with increased inflammatory response in the periodontium.[13] Based on the review of Fischer and colleagues[11], if possible, women of child-bearing age who are considering becoming pregnant and have evidence of periodontitis should be urged to have periodontal treatment before becoming pregnant. This represents something of a challenge, as there is evidence that pregnant women are not adequately familiar with the importance of oral health during pregnancy.[14]

There is a need for oral health care providers to communicate the periodontitis- adverse pregnancy outcomes relationship to other health professionals that care of women who are pregnant.[15]

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4. Conflict of Interest

None.

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