Linking Research to Clinical Practice

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The purpose of *Linking Research to Clinical Practice* is to present evidence-based information to clinical dental hygienists so that they can make informed decisions regarding patient treatment and recommendations. Each issue will feature a different topic area of importance to clinical dental hygienists with A BOTTOM LINE to translate the research findings into clinical application.

Progressive periodontal disease and risk of very preterm delivery

Offenbacher, Steven. Boggess, Kim A. Murtha, Amy P. Jared, Heather L. Lieff, Susan. McKaig, Rosemary G. Mauriello, Sally M. Moss, Kevin L. Beck, James D. Obstetrics & Gynecology. 107(1):29-36, 2006 Jan

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Abstract

Objective. The goal was to estimate whether maternal periodontal disease was predictive of preterm (less than 37 weeks) or very preterm (less than 32 weeks) births.

Methods. A prospective study of obstetric outcomes, entitled Oral Conditions and Pregnancy (OCAP), was conducted with 1,020 pregnant women who received both an antepartum and postpartum periodontal examination. Predictive models were developed to estimate whether maternal exposure to either periodontal disease at enrollment (less than 26 weeks) and/or periodontal disease progression during pregnancy, as determined by comparing postpartum with antepartum status, were predictive of preterm or very preterm births, adjusting for risk factors including previous preterm delivery, race, smoking, social domain variables, and other infections.

Results. Incidence of preterm birth was 11.2% among periodontally healthy women, compared with 28.6% in women with moderate-severe periodontal disease (adjusted risk ratio [RR] 1.6, 95% confidence interval [CI] 1.1-2.3). Antepartum moderate-severe periodontal disease was associated with an increased incidence of spontaneous preterm births (15.2% versus 24.9%, adjusted RR 2.0, 95% CI 1.2-3.2). Similarly, the unadjusted rate of very preterm delivery was 6.4% among women with periodontal disease progression, significantly higher than the 1.8% rate among women without disease progression (adjusted RR 2.4, 95% CI 1.1-5.2).

Conclusion. The OCAP study demonstrates that maternal periodontal disease increases relative risk for preterm or spontaneous preterm births. Furthermore, periodontal disease progression during pregnancy was a predictor of the more severe adverse pregnancy outcome of very preterm birth, independently of traditional obstetric, periodontal, and social domain risk factors.

Commentary

Newborns delivered preterm have higher levels of morbidity that may impact them throughout life. Recently, studies have begun to explore factors that are associated with preterm delivery. Many retrospective case-control studies have suggested a relationship between periodontal disease and preterm delivery and/or low birth weight babies. However, retrospective studies do not allow conclusions to be made about whether the potential cause (in this case periodontal disease) precedes the outcome (preterm delivery). This study is one of the first studies to report findings obtained during a large, prospective study (the Oral Conditions and Pregnancy study-OCAP). Prospective study designs provide a higher level of evidence since it is possible to assess whether the potential cause was present before the outcome occurred. This team of researchers examined the impact of preexisting periodontal/gingival disease and progression of disease during pregnancy on 2 important pregnancy outcomes: preterm delivery (defined as less than 37 weeks gestation); and, very preterm delivery (defined as less than 32 weeks gestation). The results suggest that the presence of periodontal disease (measured as none, mild or moderate/severe at a point prior to 26 weeks gestation) is a significant risk factor for preterm birth (<37 weeks gestation), and that this effect is independent of other known risk factors such as previous preterm pregnancies and chorioamnionitis (an inflammatory condition of the uterus during pregnancy, usually caused by a bacterial infection). It is particularly interesting that sexually transmitted diseases were not found to be related to preterm delivery, suggesting that the effect

of oral infections is distinctly different than reproductive tract infections. Disease progression (defined as ≥4 sites with an increase of 2mm or more during the pregnancy) was a significant factor for very preterm delivery (<32 weeks gestation) but not for preterm delivery (<37 weeks). In spite of this compelling evidence, it is still unknown whether the presence of periodontal disease has a causative effect on preterm delivery or whether women who have preterm delivery as well as periodontal disease might have an underlying intrinsic inflammatory or innate immunity trait that predisposes them to both conditions. No attempt was made to link periodontal organisms with those found in the uterus of women with chorioamnionitis. Irrespective, these early associations between periodontal disease and preterm delivery have implications for dental hygienists in preconception and early pregnancy counseling.

Fusobacterium nucleatum induces premature and term stillbirths in pregnant mice: implication of oral bacteria in preterm birth

Han, Yiping W. Redline, Raymond W. Li, Mei. Yin, Lihong. Hill, Gale B. McCormick, Thomas S. Infection & Immunity. 72(4):2272-9, 2004 Apr.

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Abtract

Fusobacterium nucleatum is a gram-negative anaerobe ubiquitous to the oral cavity. It is associated with periodontal disease. It is also associated with preterm birth and has been isolated from the amniotic fluid, placenta, and chorioamnionic membranes of women delivering prematurely. Periodontal disease is a newly recognized risk factor for preterm birth.

Objective. This study examined the possible mechanism underlying the link between these two diseases. F. nucleatum strains isolated from amniotic fluids and placentas along with those isolated from orally related sources invaded both epithelial and endothelial cells. The invasive ability may enable F. nucleatum to colonize and infect the pregnant uterus. Transient bacteremia caused by periodontal infection may facilitate bacterial transmission from the oral cavity to the uterus.

Methods. To test this hypothesis, we intravenously injected F. nucleatum into pregnant CF-1 mice.

Results. The injection resulted in premature delivery, stillbirths, and nonsustained live births. The bacterial infection was restricted inside the uterus, without spreading systemically. F. nucleatum was first detected in the blood vessels in murine placentas. Invasion of the endothelial cells lining the blood vessels was observed. The bacteria then crossed the endothelium, proliferated in surrounding tissues, and finally spread to the amniotic fluid. The pattern of infection paralleled that in humans.

Conclusion. This study represents the first evidence that F. nucleatum may be transmitted hematogenously to the placenta and cause adverse pregnancy outcomes. The results strengthen the link between periodontal disease and preterm birth. Our study also indicates that invasion may be an important virulence mechanism for F. nucleatum to infect the placenta.

Commentary

This study is one of the first to examine the potential mechanism by which periodontal organisms may affect adverse pregnancy outcomes such as preterm delivery. An innovative mouse-model design was used to determine if *Fusobacterium nucleatum*, a common organism associated with periodontitis, can invade the placental barrier. *F. nucleatum* was selected as the organism to examine in the study as previous research has shown that it can be isolated from the blood stream of individuals with periodontal disease. Relying on Koch's postulates for proof of association, the researchers isolated several strains of *F. nucleatum* from the oral cavity of women who had prematurely delivered their babies, cultured these strains, and injected various concentrations into pregnant mice at the gestation phase equivalent to 28 and 32 weeks in human gestation. Two additional solutions (containing *E. coli*, which is known as a non-invasive microbe, or a phosphate-buffered saline) were injected into other pregnant mice to serve as 2 controls. Preterm births, still births, and fetal death rates were high in the mice that had been injected with *F. nucleatum*. In contrast, all mice injected with either the *E. coli* solution or phosphate-buffered saline delivered normal, healthy mice pups.

In a parallel study conducted at the same time, pregnant mice were again injected with *F. nucleatum* and live organisms obtained from their spleen, liver, and placentas 6 hours after the injection. At 24 hours post injection, the microbes were not detectable in the liver or spleen, suggesting they had been eliminated from both organs, but they had established stable colonization in the placentas. Given that Koch's postulates for establishing causation were met, the authors concluded that *F. nucleatum* is a causative agent for adverse fetal outcomes and these outcomes are analogous to those found in humans.

Additionally, immunohistochemical analysis of placental tissue was conducted to determine where the organisms were located at 24, 48, and 72 hours following injection of either the *F. nucleatum* or control solution. These analyses showed that the organism cultures penetrated the endothelia and were capable of infecting the placental membranes, similar to chorioamnionitis in humans after 72 hours.

It is important to note that the researchers did not attempt to make the bacterial challenge given to the pregnant mice equivalent to that which would be found in bacteremia of periodontal origin in humans. While the study does substantiate a causative link between the organism injected at high levels and preterm birth and fetal death, the results must be considered in light of the methodology used. As a "proof of concept," the study provides the evidence that may facilitate our understanding of the relationship between periodontal organisms and preterm delivery or adverse pregnancy outcomes. However, caution must be used in generalizing these results to humans since the concentrations of *F. nucleatum* solutions intravenously injected into the mice were very high and are not comparable to those found in periodontally related bacteremia. Additionally, only one organism was examined in this study.

The Bottom Line

Although much attention has been given to the possible role that periodontal disease may play in adverse pregnancy outcomes, the evidence showing a causative link is still lacking. The 2 studies reviewed above represent some of the best "early evidence" available to date; however, there are still many unanswered questions that need to be addressed before researchers and clinicians alike can substantiate a causative relationship. Based on this critical appraisal, the following conclusions and recommendations can be made to clinicians:

- The rate of preterm delivery (<37 weeks) in this sample of pregnant women who were receiving prenatal care at Duke University's Obstetric Clinic was 11.2% for periodontally healthy individuals, 19.0% for women with mild periodontal disease, and 28.6% for women with moderate-severe disease. Data for other populations may vary from these estimates.

- "The increased risk for preterm delivery was 1.6 times greater for individuals with moderate-severe periodontal disease compared to periodontally healthy women.

- Pregnant women who had progressive periodontal/gingival breakdown during their pregnancy were 2.4 times more likely to have very preterm delivery (<32 weeks gestation).

- It is unknown whether periodontal disease predisposes women to preterm delivery or whether some underlying immunological or inflammatory defect makes women predisposed to both conditions.

- At least one periodontal organism has been shown, using an animal model, to be capable of invading vascular cells and being transmitted to the placental tissues in pregnant mice.

- The animal model "proof of concept" results are likely not directly relevant to periodontally induced bacteremia in pregnant humans since the concentration of bacteria was high and directly injected intravenously into pregnant mice.

- These study results do not provide any guidance as to what is the best clinical intervention to follow when providing dental hygiene care to pregnant women with periodontal disease. However, preconception oral health care and counseling is warranted and in line with current guidelines for reducing risk factors (in this case chronic infection) in women prior to conception.

Summary

Until additional evidence is obtained on the role of periodontal disease in pregnancy outcomes AND how best to treat pregnant women with disease, the best course of action for the dental hygiene clinician is to provide pre-conception care aimed at reducing and controlling gingival/periodontal inflammation. In the absence of preconception care, early pregnancy counseling should be aimed at empowering the pregnant women to employ good plaque control through an understanding of how hormones play in exacerbating existing disease. Use of scare tactics (attributing potential adverse pregnancy outcomes to periodontal disease) should be avoided as there is insufficient evidence to date.