10. Birks EJ, Tansley PD, Hardy J, et al. Left ventricular assist device and drug therapy for the reversal of heart failure. N Engl J Med 2006;355:1873-84.
11. Klotz S, Foronjy RF, Dickstein ML, et al. Mechanical unloading during left ventricular assist device support increases left ventricular collagen cross-linking and myocardial stiffness. Circulation 2005;112:364-74.
Copyright © 2006 Massachusetts Medical Society.

Preterm Birth and Periodontal Disease

Robert L. Goldenberg, M.D., and Jennifer F. Culhane, Ph.D.

Preterm births (those occurring before 37 weeks of gestation) make up 12.5% of births in the United States. They account for 70% of perinatal deaths and nearly half of all long-term neurologic complications — the most important adverse outcomes of pregnancy.[1] The earliest preterm births account for a disproportionate number of such adverse outcomes. Over the past several decades, despite extensive research and intensive medical and public health efforts, the rate of preterm birth has risen. Preterm birth may follow spontaneous preterm labor (in 50% of cases), membrane rupture (in 25% of cases), or the induction of labor or cesarean section triggered by maternal or fetal indications (in another 25% of cases). The increase in the rate of preterm birth is mostly attributable to an increase in the number of preterm births attributable to maternal or fetal indications and to the occurrence of multiple births associated with assisted reproductive therapies; 50% of twin births and nearly all higher-order multiple births are preterm.

Important risk factors for spontaneous preterm birth include multiple gestation, black race, low socioeconomic status, low maternal body-mass index (under 19.8, calculated as the weight in kilograms divided by the square of the height in meters), and short cervical length (under 25 mm, as measured on ultrasonography). Urogenital infections (e.g., chorioamnionitis, asymptomatic bacteriuria, and bacterial vaginosis) and infections at other sites (e.g., appendicitis, pneumonia, and periodontal disease) have all been associated with preterm birth.[2] In addition, a history of preterm birth is an important risk factor — an indication that the risk persists from one pregnancy to another. Despite the identification of these and other risk factors, the cause of most cases of preterm birth is unknown.

Periodontal disease has been identified as a risk factor for heart disease, rheumatoid arthritis, and other medical conditions, perhaps through a pathway of increased systemic inflammation. In 1996, Offenbacher et al.[3] reported a strong association between periodontal disease and the risk of preterm birth, and several subsequent reports (but not all) noted a similar association.[4-6] The reasons for the differences in findings are unclear, but in the United States, the association has appeared to be stronger and more consistent among black women and those with severe periodontal disease than among other groups of women. However, it is not known whether an observed association reflects cause and effect (periodontal disease leading to preterm birth). The presence of confounding factors (e.g., genital tract infections, low socioeconomic status, smoking, and other factors associated with both periodontal disease and preterm birth) is a possible explanation, although some studies have had persistently positive results after adjustment for multiple maternal characteristics. Periodontal disease may lead to preterm birth through seeding of the placenta or amniotic fluid by oral pathogens.[7] However, only a very small percentage of preterm births are associated with intrauterine infection with oral flora.[8] Alternatively, systemic inflammation that is initiated by periodontal disease may lead to both preterm labor and membrane rupture.[9]

With the possible exception of the use of progestational agents in women with previous preterm births, the identification of risk factors for preterm birth has not led to the development of effective interventions.[10] Lacking such options, physicians are particularly vulnerable to adopting strategies without the requisite scientific validation. The use of tocolytic agents to stop contractions, cerclage for a short cervix, and antibiotics for the treatment of bacterial vaginosis are just a few examples.[1] Against this backdrop, periodontal disease is a very attractive candidate for intervention, especially because it is readily identified and treated. The treatment of periodontal disease

has included the use of antiseptic mouthwash, various antibiotics, and periodontal cleaning and plaque removal (scaling and root planing). The last treatment is believed to be the most effective for periodontal disease. Two small studies have suggested that treatment of periodontal disease in pregnancy is feasible and may reduce the risk of preterm birth.[11,12]

In this issue of the *Journal*, Michalowicz et al.[13] report the results of a multicenter trial in which 823 pregnant women with periodontal disease were randomly assigned to undergo scaling and root planing either early in the second trimester or after delivery (the control group). Periodontal treatment during pregnancy did not result in a significant reduction in the rate of preterm birth before 37 weeks of gestation (12.0% in the treatment group and 12.8% in the control group, P=0.70), nor did it result in an upward shift in the gestational age distribution. Other outcomes, including low birth weight and the proportion of infants who were small for gestational age, also did not significantly differ between the groups.

Although the occurrence of adverse events before 32 weeks of gestation was not a prespecified outcome, it was less common in the treatment group than in the control group. An effect of treatment on early adverse outcomes is plausible, since observational studies suggest that periodontal disease is much more strongly associated with late miscarriage, stillbirth, and early spontaneous preterm birth than with preterm birth in general. On the basis of these observations and the data reported by Michalowicz and colleagues, one could hypothesize that periodontal treatment might preferentially reduce these other outcomes but not late preterm birth. In future studies, major adverse outcomes might include late miscarriage, early stillbirth, and spontaneous preterm birth before 32 weeks, rather than all preterm births before 37 weeks. Although such studies would require a much larger cohort of subjects, they would provide critical information for supporting or debunking this intervention. This observation draws attention to a very serious issue related to research on preterm birth: the need to refine outcome variables. Depending on the risk factor under study, trials should be designed to reduce preterm birth in specific etiologic and gestational-age categories.

What else might explain the negative findings of Michalowicz et al.? First, periodontal disease may not be in the causal pathway to preterm birth, and even if it is, treatment of periodontal disease during pregnancy simply may not reduce the rate of preterm birth. We have hypothesized that once the inflammatory cascade is activated during pregnancy, interventions targeting this pathway may be ineffective in reducing the rate of preterm birth.[14] Treatment during pregnancy may be too late; it is possible that treatment either before pregnancy (in nulliparous women) or in the period between pregnancies (for multiparous women, especially those with a history of preterm birth) may yield more promising results.

We are aware of three other ongoing trials of scaling and root planing in pregnancy to treat periodontal disease and reduce preterm birth,[15-17] all of which have enrolled more patients than did the study by Michalowicz et al. The results of these studies will help clarify whether periodontal treatment has any role in reducing the rate of preterm birth. In the meantime, the findings of Michalowicz et al. do not support the provision of periodontal treatment in pregnancy for the purpose of reducing preterm birth.

No potential conflict of interest relevant to this article was reported.

From the Department of Obstetrics and Gynecology, Drexel University, Philadelphia.

1. Goldenberg RL, Rouse DJ. The prevention of premature birth. N Engl J Med 1998;339:313-20.
2. Goldenberg RL, Hauth JC, Andrews WW. Intrauterine infection and preterm delivery. N Engl J Med 2000;342:1500-7.
3. 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:1103-13.
4. Jeffcoat MK, Geurs NC, Reddy MS, Cliver SP, Goldenberg RL, Hauth JC. Periodontal infection and preterm birth: results of a prospective study. J Am Dent Assoc 2001;132:875-80.
5. Davenport ES, Williams CE, Sterne JA, Murad S, Sivapathasundram V, Curtis MA. Maternal periodontal disease and preterm low birthweight: case-control study. J Dent Res 2002;81:313-8.
6. Moore S, Ide M, Coward PY, et al. A prospective study to investigate the relationship between periodontal disease and adverse pregnancy outcome. Br Dent J 2004;197:251-8.
7. Feldman JD, Kontaxis EN, Sherman MP. Congenital bacteremia due to Capnocytophaga. Pediatr Infect Dis 1985;4:415-6.
8. Goepfert AR, Jeffcoat MK, Andrews WW, et al. Periodontal disease and upper genital tract inflammation in early spontaneous preterm birth. Obstet Gynecol 2004;104:777-83.
9. El-Shazly S, Maksheed M, Azizieh F, Raghupathy R. Increased expression of pro-inflammatory cytokines in placentas of women undergoing spontaneous preterm delivery or premature rupture of membranes. Am J Reprod Immunol 2004;52:45-52.
10. Meis PJ, Klebanoff M, Thom E, et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. N Engl J Med 2003;348:2379-85. [Erratum, N Engl J Med 2003; 349:1299.]

11. Jeffcoat MK, Hauth JC, Geurs NC, et al. Periodontal disease and preterm birth: results of a pilot intervention study. J Periodontol 2003;74:1214-8.
12. Lopez NJ, Smith PC, Gutierrez J. Periodontal therapy may reduce the risk of preterm low birth weight in women with periodontal disease: a randomized controlled trial. J Periodontol 2002;73:911-24.
13. Michalowicz BS, Hodges JS, DiAngelis AJ, et al. Treatment of periodontal disease and the risk of preterm birth. N Engl J Med 2006;355:1885-94.
14. Goldenberg RL, Culhane JF. Prepregnancy health status and the risk of preterm delivery. Arch Pediatr Adolesc Med 2005; 159:89-90.
15. Newnham JP, Doherty D, McGeachie J, Swain J, Newnham IA. Prevention of preterm birth by treatment of periodontal disease. ClinicalTrials.gov. (Accessed October 12, 2006, at http://www.clinicaltrials.gov/ct/show/NCT00133926?order=7.)
16. Offenbacher S, Cochran DL, Dudley DJ, Hauth JC, Reddy MS, Murtha AP. MOTOR: maternal oral therapy to reduce obstetric risk. ClinicalTrials.gov. (Accessed October 12, 2006, at http://www.clinicaltrials.gov/ct/show/NCT00097656?order=1.)
17. Macones GA, Clothier BA. Periodontal infection and prematurity study. ClinicalTrials.gov. (Accessed October 12, 2006, at http://www.clinicaltrials.gov/ct/show/NCT00116974?order=1.)
Copyright © 2006 Massachusetts Medical Society.

Retraction: Sudbø J et al. DNA Content as a Prognostic Marker in Patients with Oral Leukoplakia. N Engl J Med 2001;344:1270-8 and Sudbø J et al. The Influence of Resection and Aneuploidy on Mortality in Oral Leukoplakia. N Engl J Med 2004;350:1405-13

Gregory D. Curfman, M.D., Stephen Morrissey, Ph.D., and Jeffrey M. Drazen, M.D.

On February 9, 2006, we published an Expression of Concern[1] about two articles we had published by Jon Sudbø et al.[2,3] In the Expression of Concern, we indicated that we were awaiting the results of an investigation by Dr. Sudbø's institution. That investigation was undertaken by a commission appointed by the Rikshospitalet–Radiumhospitalet Medical Center and the University of Oslo. The commission's report was filed on June 30, 2006, in Norwegian (http://www.rikshospitalet.no/content/res_bibl/6621.pdf), and we received an official English translation on September 1, 2006 (see the Supplementary Appendix, available with the full text of this article at www.nejm.org).

In early September, we sent copies of the translated report to all the authors of the two *Journal* articles by Jon Sudbø et al. We asked each author to respond before September 30, 2006. We have now received responses from all authors except Asle Sudbø. Each of the responding authors, except Jon Sudbø, has indicated that the data that form the foundation for the articles have been called into question by the findings of the commission, and each of them has requested that the articles be retracted. Jon Sudbø alone does not agree with the commission's report. Given the weight of evidence offered in the commission's report and the requests of most of the authors of the articles, we retract both articles.

1. Curfman GD, Morrissey S, Drazen JM. Expression of concern: Sudbø J et al. DNA content as a prognostic marker in patients with oral leukoplakia. N Engl J Med 2001;344:1270-8 and Sudbø J et al. The influence of resection and aneuploidy on mortality in oral leukoplakia. N Engl J Med 2004;350:1405-13. N Engl J Med 2006;354:638.
2. Sudbø J, Kildal W, Risberg B, Koppang HS, Danielsen HE, Reith A. DNA content as a prognostic marker in patients with oral leukoplakia. N Engl J Med 2001;344:1270-8.
3. Sudbø J, Lippman SM, Lee JJ, et al. The influence of resection and aneuploidy on mortality in oral leukoplakia. N Engl J Med 2004;350:1405-13.
Copyright © 2006 Massachusetts Medical Society.