

## ORIGINAL ARTICLE

# Treatment of Periodontal Disease and the Risk of Preterm Birth

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## ABSTRACT

**BACKGROUND**

Maternal periodontal disease has been associated with an increased risk of preterm birth and low birth weight. We studied the effect of nonsurgical periodontal treatment on preterm birth.

**METHODS**

We randomly assigned women between 13 and 17 weeks of gestation to undergo scaling and root planing either before 21 weeks (413 patients in the treatment group) or after delivery (410 patients in the control group). Patients in the treatment group also underwent monthly tooth polishing and received instruction in oral hygiene. The gestational age at the end of pregnancy was the prespecified primary outcome. Secondary outcomes were birth weight and the proportion of infants who were small for gestational age.

**RESULTS**

In the follow-up analysis, preterm birth (before 37 weeks of gestation) occurred in 49 of 407 women (12.0%) in the treatment group (resulting in 44 live births) and in 52 of 405 women (12.8%) in the control group (resulting in 38 live births). Although periodontal treatment improved periodontitis measures ( $P < 0.001$ ), it did not significantly alter the risk of preterm delivery ( $P = 0.70$ ; hazard ratio for treatment group vs. control group, 0.93; 95% confidence interval [CI], 0.63 to 1.37). There were no significant differences between the treatment and control groups in birth weight (3239 g vs. 3258 g,  $P = 0.64$ ) or in the rate of delivery of infants that were small for gestational age (12.7% vs. 12.3%; odds ratio, 1.04; 95% CI, 0.68 to 1.58). There were 5 spontaneous abortions or stillbirths in the treatment group, as compared with 14 in the control group ( $P = 0.08$ ).

**CONCLUSIONS**

Treatment of periodontitis in pregnant women improves periodontal disease and is safe but does not significantly alter rates of preterm birth, low birth weight, or fetal growth restriction. (ClinicalTrials.gov number, NCT00066131.)

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**A**BOUT 11% OF SINGLETON BIRTHS IN THE United States occur before 37 weeks of gestation,<sup>1</sup> and the rate of premature delivery has increased during the past 15 years. Preterm and low-birth-weight infants are at elevated risk for death, neurodevelopmental disabilities, cognitive impairment, and behavioral disorders.<sup>2-4</sup> About half of mothers delivering preterm infants have no known risk factors.<sup>5</sup> Recent studies suggest that periodontitis, an inflammatory disease caused primarily by gram-negative bacteria that destroy tooth-supporting connective tissue and bone, is associated with an increased risk of preterm birth, as well as low birth weight and preeclampsia.<sup>6-8</sup>

In rodents, subcutaneous inoculations with periodontal pathogens cause dose-dependent decreases in litter weight and elicit the production of cytokines and prostaglandins that signal preterm labor when present in amniotic fluid.<sup>9,10</sup> However, in humans, no causal link has been established between periodontitis and prematurity or low birth weight, and several epidemiologic studies have found no association.<sup>11-13</sup>

Data from two single-center clinical trials suggest that periodontal treatment during pregnancy may reduce the rate of preterm births,<sup>14,15</sup> although a recent study found no association between periodontal care during pregnancy and low birth weight.<sup>16</sup> We designed the present trial to assess whether nonsurgical periodontal treatment in pregnant women reduces the risk of delivery before 37 weeks and results in a greater birth weight and a reduced proportion of infants who are small for gestational age.

## METHODS

The Obstetrics and Periodontal Therapy (OPT) Study was a randomized, blinded, controlled trial of the effects of nonsurgical periodontal treatment during pregnancy on gestational age at birth and on birth weight. An independent data and safety monitoring board met semiannually to review the interim results. The institutional review board at each participating center approved the study; all participants provided written informed consent.

### STUDY POPULATION

We enrolled patients at Hennepin County Medical Center (MN), the University of Kentucky, the University of Mississippi Medical Center, and Harlem Hospital (NY). Potential participants were referred

by health care providers. Pregnant women who were at least 16 years of age and who were at less than 16 weeks and 6 days of gestation underwent screenings for periodontal disease in obstetrics clinics. Unlike gingivitis, periodontitis cannot be assessed by visual examination alone; it is diagnosed with the use of a probe that is inserted into the gingival crevice between the teeth and gums. Clinical attachment loss (in millimeters) is a measure of the severity of destruction of tooth-supporting connective tissue and alveolar bone. Attachment loss is typically accompanied by a deepening of the gingival crevice, the depth of which is termed probing depth. Women who had multiple probing depths of more than 4 mm and evidence of clinical attachment loss were referred for baseline examination.

To be eligible for the trial, women had to have at least 20 natural teeth and the presence of periodontal disease, which we defined as 4 or more teeth with a probing depth of at least 4 mm and a clinical attachment loss of at least 2 mm, as well as bleeding on probing at 35% or more of tooth sites. Women were ineligible if they had multiple fetuses, required antibiotic prophylaxis for periodontal procedures, had a medical condition that precluded elective dental treatment, had extensive tooth decay, or were likely to have fewer than 20 teeth after initial treatment.

### STUDY INTERVENTION

We randomly assigned participants to receive periodontal treatment either before 21 weeks or after delivery. Randomization, stratified by center with the use of permuted randomized blocks of 2 and 4, was made by a telephone call to the coordinating center.

Treatment consisted of periodontal scaling and root planing (i.e., removal of dental plaque and calculus from the tooth enamel and root) with the use of ultrasonic and hand instruments and local anesthesia as needed; up to four visits for treatment were allowed. Treatment participants also received instruction in oral hygiene; they then had monthly tooth polishing and reinstruction in oral hygiene and underwent scaling and planing as needed until delivery. Control patients received only a brief oral examination at monthly follow-ups but attended the same number of these visits as the treatment group. Patients in the control group were offered the same periodontal therapy after delivery as those in the treatment group re-

ceived. All patients received a \$20 gift certificate and an infant's toy after each visit.

#### OUTCOMES

The prespecified primary outcome was the gestational age at the end of pregnancy. Gestational age was determined at randomization on the basis of the last menstrual period or the results of ultrasonography, as described elsewhere.<sup>17</sup> Secondary outcomes included birth weight, the proportion of infants who were small for gestational age, Apgar scores, and admissions to a neonatal intensive care unit.

#### CLINICAL ASSESSMENTS, DATA COLLECTION, AND SAFETY MONITORING

Before the study began, periodontal examiners were trained by a single clinician (Dr. Michalowicz), and their techniques were standardized with the use of criteria described previously.<sup>18</sup> The standardization of the techniques of the examiners was reassessed during the study with the use of the same criteria, and we assessed the reproducibility of the results among examiners by having the examiners remeasure selected teeth in 5% of the participants; the average agreement for probing depth and measures of attachment loss (within 1 mm) was 98%.

At baseline, patients reported their pregnancy history and any medications they were taking. Examiners measured probing depth, clinical attachment loss, and bleeding on probing at six sites on each tooth; they also evaluated dental plaque<sup>19</sup> and calculus<sup>20</sup> on selected teeth. Bleeding on probing was scored as present or absent. Patients were referred to a dentist for treatment of teeth that were abscessed, fractured, or likely to become symptomatic during the study. Full-mouth periodontal assessments were repeated at 21 to 24 weeks of gestation and again at 29 to 32 weeks.

An obstetrical nurse abstracted data regarding delivery and postnatal status and risk factors for prematurity from medical records. Obstetrical adverse events were identified by a review of medical records and reports from patients. Examiners and nurses were not aware of the study-group assignments.

Patients were monitored for oral adverse events and the progression of periodontitis, which was defined as any increase in clinical attachment loss of 3 mm or more.<sup>21</sup> Treatment of progressive disease was not delayed until after delivery in either

group unless treatment was contraindicated because of advanced gestational age (middle-to-late third trimester). All patients with progressive disease at fewer than six tooth sites received root planing at those sites. Patients with six or more affected sites were referred to a consulting periodontist for treatment; affected patients in the control group received full-mouth scaling and root planing, whereas those in the treatment group could receive root planing, systemic antibiotics, and subgingival irrigation with antimicrobial solutions. For patients with progressive disease, the last periodontal measures before rescue treatment were carried forward.

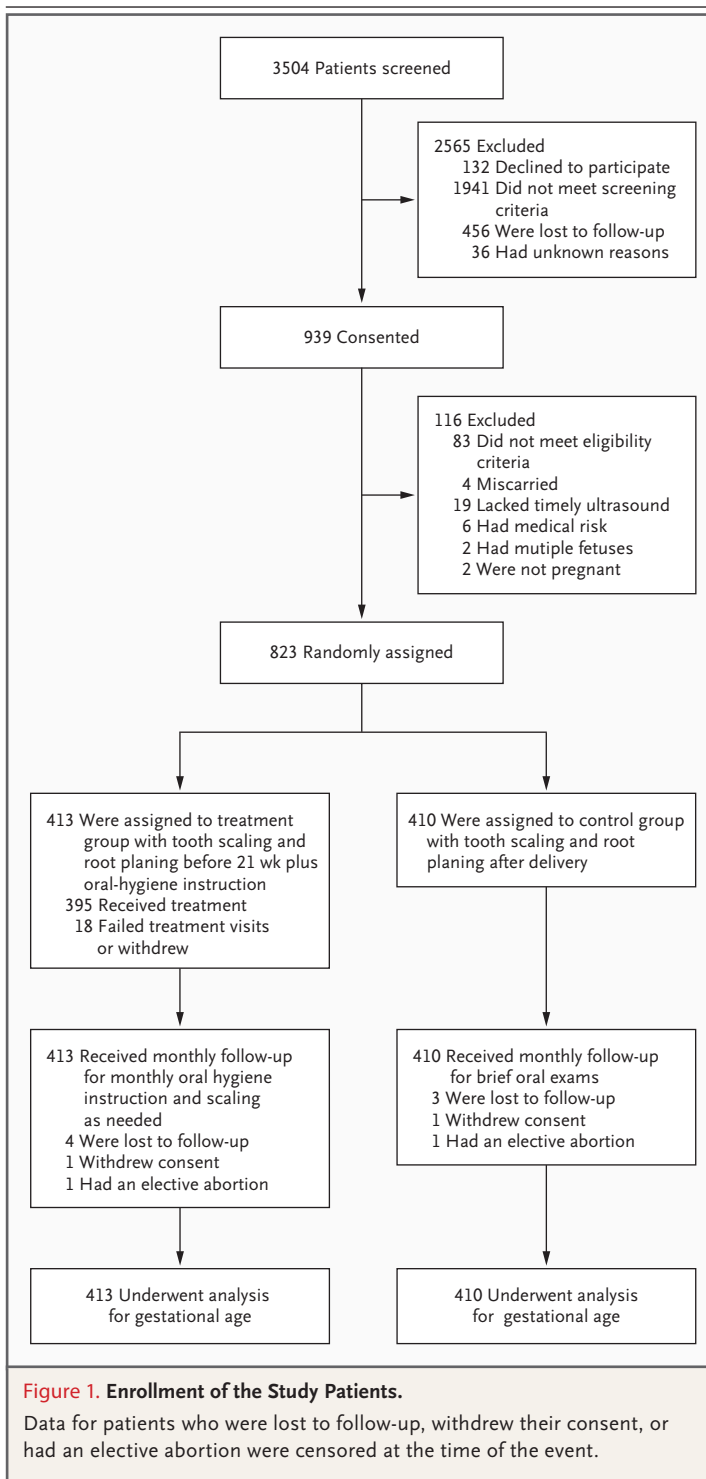
#### STATISTICAL ANALYSIS

We performed all analyses on an intention-to-treat basis unless stated otherwise. To emphasize differences in lower gestational ages, gestational ages were censored at 37 weeks.

Our primary analysis compared groups according to gestational age at delivery with the use of the log-rank test stratified by center. To calculate power, we estimated the time-to-event distribution of the control group with the use of pilot data from two enrollment centers. To estimate the desired distribution of gestational ages of the treatment group, we added to the gestational-age distribution of the control group 5, 3, and 2 weeks for gestation of 20, 25, and 30 to 35 weeks, respectively, interpolating for intermediate gestational ages. We computed power by simulating data from these distributions. With a one-sided type I error of 0.05 and allowing for a 30% loss to follow-up, calculations showed that 405 patients per group would be required to show statistical significance with a power of 90%. Adjusted analyses with the use of Cox regression added baseline risk factors, including self-reported use of alcohol or drugs, race or ethnic group, maternal age, the time since a previous pregnancy (in months), and the occurrence of selected infections.

The study's first seven birth outcomes were spontaneous abortion or stillbirth. Consequently, with the monitoring board's approval, we added a competing-risks analysis<sup>22</sup> with two event types — live birth and spontaneous abortion or stillbirth. In the competing-risks analysis, we treated these first seven events as hypothesis generating and used only later events for hypothesis testing.

All periodontal measures were analyzed with



(the center, the treatment group, the follow-up visit, and interactions); adjusted analyses used design factors plus baseline risk factors.

We performed four semiannual interim analyses for monitoring-board meetings with the use of the Lan-DeMets method and the O'Brien-Fleming alpha-spending function.<sup>23</sup> All reported P values are two-sided and not adjusted for multiple testing.

## RESULTS

We randomly assigned 823 patients to two groups — 413 to the treatment group and 410 to the control group — between March 2003 and June 2005 (Fig. 1). Eleven patients in the treatment group and eight patients in the control group were erroneously assigned after 16 weeks and 6 days but were included in the analyses. Follow-up concluded in December 2005.

Table 1 summarizes the baseline characteristics of the two groups. Of 531 patients who had a previous pregnancy ending with a live birth, 77 (14.5%) had had a previous live preterm birth. On the basis of clinical periodontal measures, most patients were judged to have generalized early-to-moderate periodontitis.

During their study pregnancy, 22% of patients were diagnosed with urinary tract infections, 12% with bacterial vaginosis, 6% with gestational diabetes, and 16% with group B streptococcal colonization. Thirteen percent reported the use of tobacco. The frequency of these findings did not differ significantly between groups.

## BIRTH OUTCOMES

The gestational age at the end of pregnancy was available for 814 of 823 women (98.9%) (Fig. 1). Eleven patients in the treatment group and eight in the control group had labor induced before 37 weeks because of hypertension, diabetes, or preeclampsia and were included in the primary analysis. In the time-to-event analysis, the groups did not differ significantly in gestational age at the end of pregnancy, which was censored at 37 weeks (hazard ratio for women in the treatment group vs. those in the control group, 0.93; 95% confidence interval [CI], 0.63 to 1.37;  $P=0.70$ ) (Fig. 2). Results did not change when women with spontaneous abortions were excluded or when indicated deliveries before 37 weeks of gestation were treated as losses to follow-up at the time of induced delivery.

the use of linear mixed models, with the change from baseline to either the 2-month or 4-month follow-up visit as the dependent variable. Initial analyses accounted only for study design factors

**Table 1. Baseline Characteristics of the Study Patients.\***

Characteristic	Control Group (N=410)	Treatment Group (N=413)	P Value
Age — yr	25.9±5.5	26.1±5.6	0.56
Race or ethnic group — no. (%)†			
White	119 (29.0)	116 (28.1)	0.77
Black	182 (44.4)	190 (46.0)	0.64
Hispanic	180 (43.9)	170 (41.2)	0.43
Education — no. (%)			0.88
≤8 yr	76 (18.5)	78 (18.9)	
9–12 yr	242 (59.0)	237 (57.4)	
>12 yr	92 (22.4)	98 (23.7)	
Mean gestational age of fetus — wk	15.0±1.3	15.0±1.3	0.85
Previous pregnancies — no. (%)‡			
Any pregnancy	305 (74.4)	306 (74.1)	0.92
Live preterm birth§	44 (16.5)	33 (12.5)	0.18
Spontaneous abortion¶	94 (30.8)	108 (35.3)	0.24
Induced abortion¶	67 (22.0)	52 (17.0)	0.12
Stillbirth¶	6 (2.0)	9 (2.9)	0.44
Coexisting medical condition — no. (%)			
Diabetes	8 (2.0)	16 (3.9)	0.10
Chronic hypertension	9 (2.2)	16 (3.9)	0.16
Self-reported drug addiction	7 (1.7)	15 (3.6)	0.09
Self-reported alcohol use	8 (2.0)	8 (1.9)	0.99
Eating disorder	0	2 (0.5)	0.16
Dental status			
Number of natural teeth	26.8±1.7	26.7±1.8	0.67
Number of qualifying teeth	14.4±6.7	15.2±6.8	0.08
Percent of tooth sites that bled on probing	69.0±17.1	69.6±17.4	0.62
Percent of tooth sites with probing depth ≥4 mm	24.8±15.9	26.5±16.6	0.13

\* Plus-minus values are means ±SD.

† Race or ethnic group was reported by the patients. Some women selected more than one category and were included in all.

‡ Some patients reported more than one event.

§ Percentages are based on 266 women in the control group and 265 women in the treatment group who had had any live births.

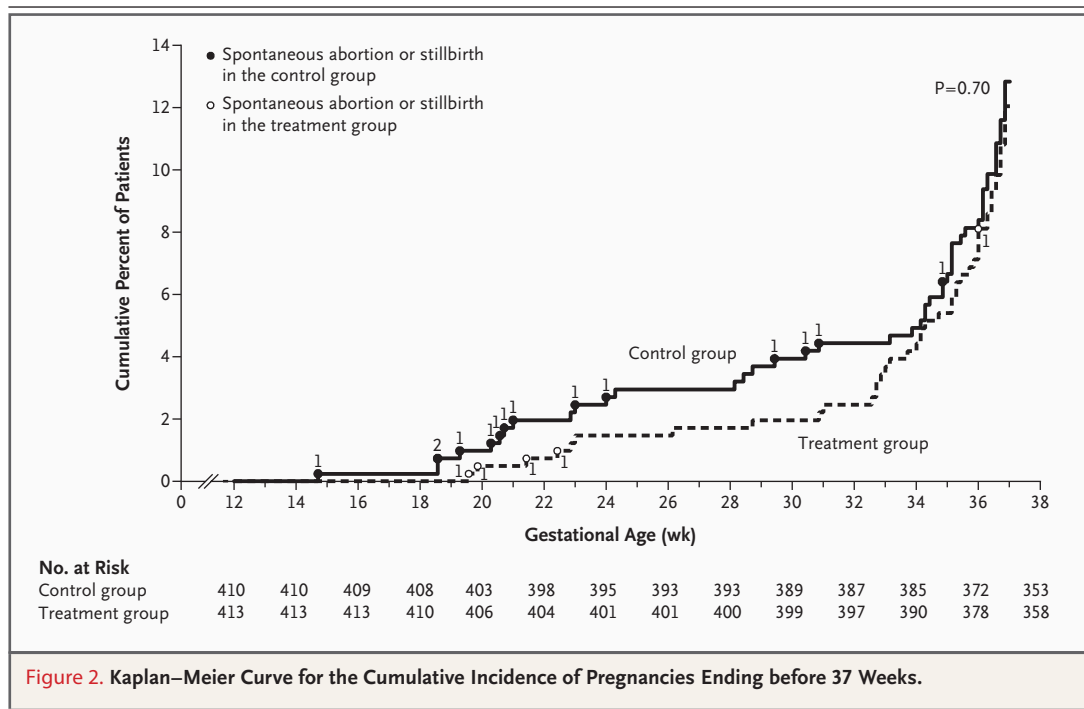
¶ Percentages are based on 305 women in the control group and 306 women in the treatment group who had had any previous pregnancies.

The groups did not differ significantly after adjustment for baseline characteristics (hazard ratio, 0.85; 95% CI, 0.55 to 1.30;  $P=0.45$ ). The effects of treatment on preterm birth did not differ significantly between centers ( $P=0.30$  for the interaction between groups according to center) or according to race or ethnic group ( $P=0.76$  for the comparison of black patients with those of all other races;

$P=0.52$  for the comparison of Hispanic patients with those of all other ethnic groups).

A total of 2 patients in the treatment group and 4 in the control group had a spontaneous abortion (loss before 20 weeks); 3 patients in the treatment group and 10 in the control group had a stillbirth (loss from 20 weeks to 36 weeks and 6 days). Three patients in the treatment group and nine patients





in the control group had either a spontaneous abortion or stillbirth after the decision was made to consider the events as separate study outcomes. In the competing-risks analysis, neither the risk of live preterm birth ( $P=0.51$ ) nor of spontaneous abortion or stillbirth ( $P=0.08$ ) differed significantly between groups. When all spontaneous abortions or stillbirths (5 in the treatment group and 14 in the control group) were included in a competing-risks analysis, the  $P$  value was 0.04. The groups did not differ significantly in the rates of any secondary outcomes, including preeclampsia (Table 2).

#### COMPLIANCE AND CLINICAL PERIODONTAL OUTCOMES

Overall, 630 patients (77%) missed no more than one of the six follow-up study visits. Among participants in the treatment group, 395 (96%) received periodontal treatment, which lasted an average of 127 minutes. Periodontal treatment improved all clinical measures of disease (Table 2).

#### ADVERSE EVENTS

Treatment and control groups had a similar number of serious medical adverse events, which included hospitalization for more than 24 hours for

labor pains, hospitalization for any other reason, a congenital anomaly in the infant, spontaneous abortion, stillbirth, or neonatal death (37 patients [9.0%] in the treatment group and 41 [10%] in the control group,  $P=0.64$ ). Twenty-two events were hospitalizations in which the participant was discharged without having delivered. Infants with congenital anomalies were born to 13 women in the treatment group and 7 women in the control group. No women died; the infants of one mother in the treatment group and two in the control group died of complications from extreme prematurity.

A total of 3 patients in the treatment group and 6 in the control group had generalized clinical attachment loss, and 48 patients in the treatment group and 45 in the control group had localized clinical attachment loss after the baseline examination. Patients with generalized progression in periodontal disease were treated before delivery with the following therapies: one patient in the treatment group and two patients in the control group underwent full-mouth scaling and root planing, one patient in the control group underwent root planing and received systemic antibiotics, and one patient in the treatment group received systemic antibiotics alone. Three other

**Table 2. Birth and Clinical Periodontal Outcomes.\***

Outcome	Control Group (N=405)	Treatment Group (N=407)	P Value
Duration of pregnancy — no. (%)†			
<32 wk	18 (4.4)	10 (2.5)	0.13
<35 wk	26 (6.4)	22 (5.4)	0.56
<37 wk	52 (12.8)	49 (12.0)	0.75
Birth weight			
Total weight — g	3258±575	3239±586	0.64
<2500 g — no./total no. (%)	43/403 (10.7)	40/406 (9.9)	0.73
<1500 g — no./total no. (%)	15/403 (3.7)	8/406 (2.0)	0.14
Small for gestational age (10th percentile) — no./total no. (%)	48/391 (12.3)	51/402 (12.7)	0.91
Birth length — cm	49.9±4.1	49.9±3.8	0.84
Apgar score — no./total no. (%)‡			
<7 at 1 min	27/383 (7.0)	37/394 (9.4)	0.13
<7 at 5 min	3/383 (0.8)	4/394 (1.0)	0.74
Admission to neonatal intensive care unit — no./total no. (%)			
Total no. admitted	31/389 (8.0)	45/397 (11.3)	0.12
Length of stay >2 days	22/389 (5.7)	30/397 (7.6)	0.32
Discharged alive	30/31 (96.8)	44/45 (97.8)	1.00
Live births — no. (%)			
Total	391 (96.5)	402 (98.8)	
Preterm§			
<32 wk	5 (1.3)	6 (1.5)	1.0
<35 wk	12 (3.1)	18 (4.5)	0.35
<37 wk	38 (9.7)	44 (10.9)	0.64
Preeclampsia — no. (%)¶	20 (4.9)	31 (7.6)	0.15
Improvement in periodontal measures			
Probing depth at sites initially 4–6 mm — mm	0.38±0.02	0.88±0.02	<0.001
Probing depth at sites initially ≥7 mm — mm	1.07±0.14	1.84±0.14	<0.001
Tooth sites with clinical attachment loss ≥2 mm — %	0.84±0.85	9.72±0.87	<0.001
Tooth sites with bleeding on probing — %	2.1±0.7	22.7±0.7	<0.001

\* The numbers of patients in the study groups do not include those who withdrew from the study or were lost to follow-up. Two women who underwent elective abortions were treated as lost to follow-up at the time of the abortion. The analyses of birth weight, birth length, size for gestational age, Apgar scores, number of admissions to a neonatal intensive care unit, and the rate of preterm births included 391 patients in the control group and 402 in the treatment group (i.e., excluding women who had spontaneous abortion or stillbirth). Plus-minus values are means ±SD, unless otherwise noted.

† P values in this category were calculated with the use of Fisher's exact test.

‡ P values for Apgar scores were calculated with the use of the Wilcoxon signed-rank test.

§ This category includes all live preterm births in the specified gestational period. Percentages were calculated as a fraction of all live births.

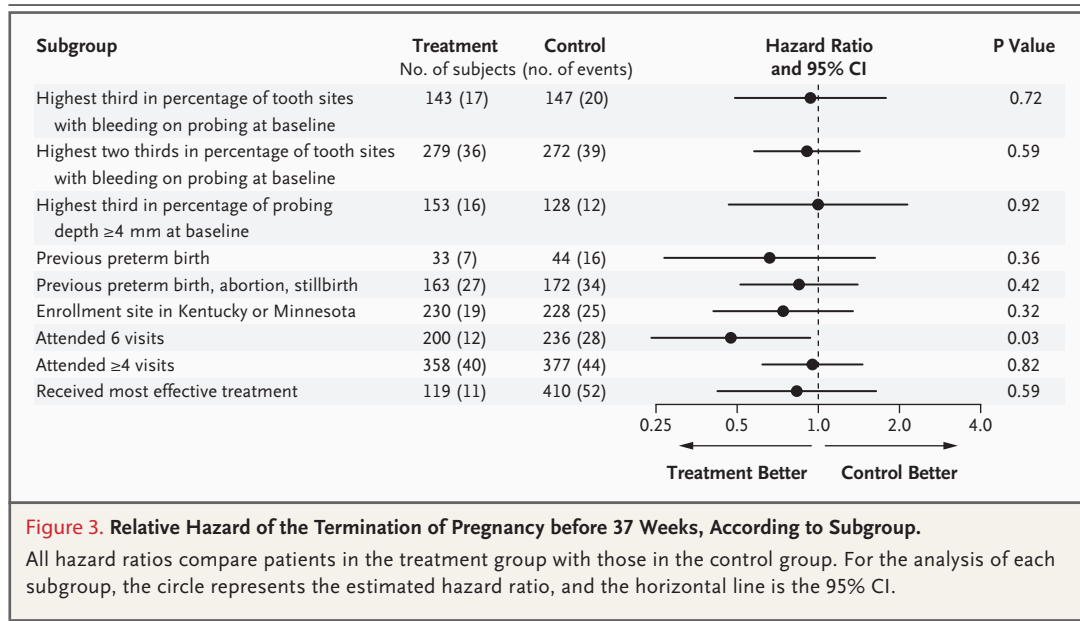
¶ This category includes patients with pregnancy-associated hypertension occurring 4 hours to 14 days after an episode of pregnancy-associated proteinuria in a woman with no previous hypertension or proteinuria; patients with pregnancy-associated hypertension in conjunction with pulmonary edema or thrombocytopenia (<100,000 platelets per cubic millimeter); and patients with the syndrome of hemolysis, elevated liver enzymes, and low platelets (HELLP).

|| Plus-minus values in this category are means ±SE. The number is the value at baseline minus the value at follow-up.

patients were treated after delivery and one declined treatment. Overall, only a small fraction of all tooth sites lost clinical attachment (0.17% in the treatment group and 0.28% in the control group,  $P=0.17$ ).

#### ADDITIONAL ANALYSES OF BIRTH OUTCOMES

We also conducted several post hoc analyses (Fig. 3). Because it is possible that treatment may improve the outcomes of pregnancy only in women with more severe disease, we performed analyses



that were limited to women with extensive gingival bleeding (the highest one third or two thirds of patients in terms of the percentage of bleeding on probing at baseline) or periodontal pocketing (the highest third of patients in terms of the percentage of sites with a probing depth  $\geq 4$  mm). In these subgroups, the risk of preterm delivery did not differ significantly between the treatment and control groups (Fig. 3). Although preterm births were more frequent in our study than in earlier trials of periodontal treatment,<sup>14,15</sup> we also performed analyses that were limited to women with previous preterm births or with a previous preterm birth, spontaneous or induced abortion, or stillbirth, and found similar results (Fig. 3).

Noncompliance with study treatment may have diluted a treatment effect. Yet we found no significant effect of periodontal treatment on the risk of preterm delivery at the two sites (Minnesota and Kentucky) with the highest compliance and the largest periodontal treatment effects or among the subgroup of patients who had four or more follow-up visits (Fig. 3).

Another possibility is that the periodontal treatment did not affect periodontitis sufficiently to affect birth outcomes. However, we also found no significant effects of treatment on preterm births in analyses comparing all patients in the control group with only the “best responders” to treatment, as defined by the highest third of proportional reduction in the percentage of bleeding on probing (i.e., a reduction of at least 40%;  $P=0.59$ )

(Fig. 3); the lowest residual percentage of bleeding on probing after treatment (35.7% or less,  $P=0.26$ ); or periodontal condition after treatment that did not meet the eligibility criteria of the study, which occurred among 178 women in the treatment group ( $P=0.48$ ).

## DISCUSSION

We found that scaling and root planing before 21 weeks of gestation plus monthly tooth polishing thereafter did not significantly alter the risk of preterm delivery before 37 weeks, increase birth weight, improve Apgar scores, or reduce either the rate of admission to a neonatal intensive care unit or the proportion of infants who were small for gestational age. Treatment improved clinical measures of periodontal disease and was not associated with adverse medical events.

These results are inconsistent with reports of two previous randomized trials of periodontal treatment during pregnancy. Jeffcoat et al.<sup>14</sup> randomly assigned 366 pregnant women to one of three groups. One group underwent scaling and planing and received metronidazole, the second group underwent simple cleaning and received placebo, and the third group underwent scaling and planing and received placebo for 7 days. Preterm birth rates (before 35 weeks and before 37 weeks of gestation) were lowest in the group that underwent root planing and received placebo but did not differ significantly among the groups.



Because no data were reported on the effectiveness of periodontal treatment per se, we cannot compare the effect of such treatment in this study with that in ours.

In a study of Chilean women mostly from low socioeconomic strata,<sup>15</sup> periodontal therapy significantly reduced the rate of preterm birth (1.1% in the treated group vs. 6.4% in the control group,  $P=0.02$ ). Several differences between this study and ours deserve mention. Whereas the Chilean study included subjects of Spanish and Aboriginal descent, we recruited a more diverse sample from four locations in the United States. The Chilean group also had a greater average response to periodontal treatment than did patients in our study, a finding that could be associated with the use of chlorhexidine mouth rinses and systemic antibiotics (18% of patients received amoxicillin and metronidazole) in the Chilean study. Our study, by contrast, used neither agent, for the following reasons. Although chlorhexidine reduces gingival bleeding,<sup>24</sup> its effect on periodontitis is slight,<sup>25</sup> and it causes tooth staining that can unmask treatment. Systemic antibiotics, although useful adjuncts in severe periodontitis,<sup>26</sup> may resolve nonoral infections and confound the effects of local periodontal therapy on the outcomes of pregnancy. Also, the study by Jeffcoat et al. suggests that the use of systemic antibiotics after root planing does not significantly improve birth outcomes. Finally, although antibiotics that are delivered into the periodontal pocket enhance the response to root planing,<sup>27</sup> all the products that are available in the United States are tetracycline derivatives and are contraindicated during pregnancy. Nonetheless, our treatment response, in terms of mean reductions in the probing depth and attachment loss, is consistent with improvements after scaling and root planing reported in persons who are not pregnant.<sup>28,29</sup>

It is possible that we delivered periodontal care too late in pregnancy to affect birth outcomes. The timing of our care, however, was consistent with that in the two previous randomized trials. Additional studies would be needed to determine whether the provision of periodontal treatment even earlier in pregnancy or before conception might improve birth outcomes.

One theory linking periodontitis to pregnancy outcomes posits that oral bacteria seed the pla-

centa, membranes, or amniotic fluid through blood-borne routes, eliciting an inflammatory cascade that precipitates preterm labor.<sup>30</sup> We did not assess bacteremia, but recent reports cast doubt on this theory. For example, although one report showed that periodontal disease was more prevalent in mothers who delivered preterm than in those who delivered full term,<sup>7</sup> periodontal pathogens were detected in placentas of only 2 of 59 mothers who delivered preterm and of only 3 of 44 mothers delivering full term. Another study failed to detect periodontal bacteria in the amniotic fluid of women with periodontitis who delivered preterm, even though these microorganisms were frequently found in dental plaque.<sup>31</sup> Moreover, the presence of *Fusobacterium nucleatum* in dental plaque and vaginal-swab samples was not associated with the presence of the bacteria in amniotic fluid.<sup>32</sup>

Given the 95% CI of the hazard ratio for preterm delivery for patients in the treatment group, as compared with those in the control group (0.63 to 1.37), we cannot rule out a modest increase or decrease in the risk of preterm delivery with periodontal treatment. We observed a nonsignificant reduction in spontaneous abortion or stillbirth with periodontal treatment. Other reports have linked periodontal disease<sup>12,33</sup> and other nonuterine maternal infections<sup>34,35</sup> with an increased risk of miscarriage. However, we view this finding with particular caution because only 19 patients in our study had either a spontaneous abortion or stillbirth and because we began evaluating rates of earlier pregnancy losses (using a competing-risks analysis) only after seven such events had occurred.

In summary, the treatment of periodontitis in pregnant women was safe and effective in improving periodontal disease. However, it did not significantly alter the rates of preterm birth, low birth weight, fetal growth restriction, or preeclampsia.

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

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## APPENDIX

In addition to the authors, the following investigators participated in the OPT Study: *University of Minnesota, Minneapolis* — A. Deinard, H. Voelker, J. Osborn, I. Olson, Y. He, Q. Cao, L. Wolff, E. Delmore, S. Wewerka; *Hennepin County Medical Center, Minneapolis* — L. Simpson, J. Anderson, K. Meyer, J. Danielson, T. Thompson; *University of Kentucky, Lexington* — D. Dawson, A. Buell, D. Mischel, P. Stein, L. Cunningham; *University of Mississippi, Jackson* — S. Vance, G. Young, A. Garner, N. Wood, K. Holmes; and *Harlem Hospital-Columbia University, New York* — S. Lassiter, J. Mays, J. Jackson, E. Rijo, M. Bolden, C. Spicer.

## REFERENCES

- Martin JA, Hamilton BE, Sutton PD, Ventura SJ, Menacker F, Munson ML. Births: final data for 2003. *Natl Vital Stat Rep* 2005;54:1-116.
- MacDorman MF, Martin JA, Mathews TJ, Hoyert DL, Ventura SJ. Explaining the 2001-02 infant mortality increase: data from the linked birth/infant death data set. *Natl Vital Stat Rep* 2005;53:1-22.
- Bhutta AT, Cleves MA, Casey PH, Craddock MM, Anand KJ. Cognitive and behavioral outcomes of school-aged children who were born preterm: a meta-analysis. *JAMA* 2002;288:728-37.
- Vohr BR, Wright LL, Dusick AM, et al. Neurodevelopmental and functional outcomes of extremely low birth weight infants in the National Institute of Child Health and Human Development Neonatal Research Network, 1993-1994. *Pediatrics* 2000;105:1216-26.
- Iams JD, Goldenberg RL, Mercer BM, et al. The Preterm Prediction Study: can low-risk women destined for spontaneous preterm birth be identified? *Am J Obstet Gynecol* 2001;184:652-5.
- Bogges KA, Lief S, Murtha AP, Moss K, Beck J, Offenbacher S. Maternal periodontal disease is associated with an increased risk for preeclampsia. *Obstet Gynecol* 2003;101:227-31.
- 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.
- Offenbacher S, Bogges KA, Murtha AP, et al. Progressive periodontal disease and risk of very preterm delivery. *Obstet Gynecol* 2006;107:29-36. [Erratum, *Obstet Gynecol* 2006;107:1171.]
- Collins JG, Windley HW III, Arnold RR, Offenbacher S. Effects of a Porphyromonas gingivalis infection on inflammatory mediator response and pregnancy outcome in hamsters. *Infect Immun* 1994;62:4356-61.
- Yeo A, Smith MA, Lin D, et al. Campylobacter rectus mediates growth restriction in pregnant mice. *J Periodontol* 2005;76:551-7.
- 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.
- 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.
- Noack B, Klingenberg J, Weigelt J, Hoffmann T. Periodontal status and preterm low birth weight: a case control study. *J Periodontol Res* 2005;40:339-45.
- 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.
- 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.
- Hujoel PP, Lydon-Rochelle M, Robertson PB, del Aguila MA. Cessation of periodontal care during pregnancy: effect on infant birthweight. *Eur J Oral Sci* 2006;114:2-7.
- Carey JC, Klebanoff MA, Hauth JC, et al. Metronidazole to prevent preterm delivery in pregnant women with asymptomatic bacterial vaginosis. *N Engl J Med* 2000;342:534-40.
- Pihlstrom BL, Wolff LF, Bakdash MB, et al. Salt and peroxide compared with conventional oral hygiene. I. Clinical results. *J Periodontol* 1987;58:291-300.
- Loe H. The gingival index, the plaque index and the retention index systems. *J Periodontol* 1967;38:Suppl:610-6.
- Greene JC, Vermillion JR. The simplified oral hygiene index. *J Am Dent Assoc* 1964;68:7-13.
- Thomson WM, Slade GD, Beck JD, Elter JR, Spencer AJ, Chalmers JM. Incidence of periodontal attachment loss over 5 years among older South Australians. *J Clin Periodontol* 2004;31:119-25.
- Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. *Ann Stat* 1988;16:1141-54.
- DeMets DL, Lan KK. Interim analysis: the alpha spending function approach. *Stat Med* 1994;13:1341-52.
- Loe H, Schiott CR, Karring G, Karring T. Two years oral use of chlorhexidine in man. I. General design and clinical effects. *J Periodontol Res* 1976;11:135-44.
- Bonito AJ, Lux L, Lohr KN. Impact of local adjuncts to scaling and root planing in periodontal disease therapy: a systematic review. *J Periodontol* 2005;76:1227-36. [Erratum, *J Periodontol* 2006;77:326.]
- Mombelli A, Samaranayake LP. Topical and systemic antibiotics in the management of periodontal diseases. *Int Dent J* 2004;54:3-14.
- Pavia M, Nobile CG, Angelillo IF. Meta-analysis of local tetracycline in treating chronic periodontitis. *J Periodontol* 2003;74:916-32.
- Cobb CM. Clinical significance of non-surgical periodontal therapy: an evidence-based perspective of scaling and root planing. *J Clin Periodontol* 2002;29:Suppl 2:6-16.
- Preshaw PM, Hefti AF, Jepsen S, Etienne D, Walker C, Bradshaw MH. Subantimicrobial dose doxycycline as adjunctive treatment for periodontitis: a review. *J Clin Periodontol* 2004;31:697-707.
- Gibbs RS. The relationship between infections and adverse pregnancy outcomes: an overview. *Ann Periodontol* 2001;6:153-63.
- Dortbudak O, Eberhardt R, Ulm M, Persson GR. Periodontitis, a marker of risk in pregnancy for preterm birth. *J Clin Periodontol* 2005;32:45-52.
- Bearfield C, Davenport ES, Sivapathasundaram V, Allaker RP. Possible association between amniotic fluid micro-organism infection and microflora in the mouth. *BJOG* 2002;109:527-33.
- Farrell S, Ide M, Wilson RF. The relationship between maternal periodontitis, adverse pregnancy outcome and miscarriage in never smokers. *J Clin Periodontol* 2006;33:115-20.
- Omwandho CO, Gruessner SE, Tinneberg HR. Early pregnancy loss and neonatal deaths associated with Klebsiella pneumonia infection: a mini review of possible occupational health risk. *Arch Gynecol Obstet* 2006;273:258-60.
- Andersen B, Nielsen TF. Appendicitis in pregnancy: diagnosis, management and complications. *Acta Obstet Gynecol Scand* 1999;78:758-62.

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