OBSTETRICS

Treatment of localized periodontal disease in pregnancy does not reduce the occurrence of preterm birth: results from the Periodontal Infections and Prematurity Study (PIPS)

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OBJECTIVE: The purpose of this study was to test whether treating periodontal disease (PD) in pregnancy will reduce the incidence of spontaneous preterm delivery (SPTD) at ≤35 weeks of gestation.

STUDY DESIGN: A multicenter, randomized clinical trial was performed. Subjects with PD were randomized to scaling and root planing (active) or tooth polishing (control). The primary outcome was the occurrence of SPTD at <35 weeks of gestation.

RESULTS: We screened 3563 subjects for PD; the prevalence of PD was 50%. Seven hundred fifty-seven subjects were assigned randomly; 378 subjects were assigned to the active group, and 379 subjects were assigned to the placebo group. Active treatment did not reduce the risk of SPTD at <35 weeks of gestation (relative risk, 1.19; 95% confidence interval [CI], 0.62–2.28) or composite neonatal morbidity (relative risk, 1.30; 95% CI, 0.83–2.04). There was a suggestion of an increase in the risk of indicated SPTD at <35 weeks of gestation in those subjects who received active treatment (relative risk, 3.01; 95% CI, 0.95–4.24).

CONCLUSION: Treating periodontal disease does not reduce the incidence of SPTD.

Key words: periodontal disease, spontaneous preterm delivery

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Preterm birth, which remains a major public health issue in the United States, accounts for substantial morbidity and death. Unfortunately, the incidence of preterm birth has been largely unchanged in recent years, hovering at 12%.[1] Over the past decade, research has

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focused on associations between clinical and subclinical infections and preterm birth. This research has led to a greater understanding of potential mechanisms by which infection and the resultant inflammatory response can lead to preterm birth.[2]

Destructive periodontal disease (periodontitis) is common, with a reported prevalence of >30% in some populations. There is substantial observational evidence from a variety of populations

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that links maternal periodontal disease to preterm birth, possibly because of the maternal inflammatory response to periodontal disease.[3-7] Given the prevalence, biologic plausibility, and epidemiologic association of periodontal disease with preterm birth, we believed that an intervention that was targeted at periodontal disease treatment was an attractive 1 to examine, in the hopes of reducing the risk of preterm birth. Thus, the purpose of this study was to assess, in a randomized controlled clinical trial, whether treatment of periodontal disease in pregnancy could reduce the incidence of spontaneous preterm birth.

Materials and Methods

We performed a multicenter, randomized, controlled clinical trial of treatment of periodontal disease to reduce the incidence of preterm birth. Subjects were recruited from 3 prenatal care clinics in the metropolitan Philadelphia area. Patients between 6 and 20 weeks gestation were eligible for screening and enrollment. Gestational age was determined before random assignment in all subjects. The project estimated due date was based on a combination of last menstrual period and ultrasound, with standard pregnancy dating algorithms. Subjects were ineligible for the following reasons: periodontal treatment during the pregnancy, antibiotic use within 2 weeks, use of antimicrobial mouthwash within 2 weeks, multiple gestation, and known mitral valve prolapse.

Eligible women were screened for periodontal disease by trained research nurses or dental hygienists. Unfortunately, there is no single universally accepted measure of periodontal disease. For subjects with ≤10 natural teeth, all teeth were examined. For subjects with >10 teeth, a maxillary and mandibular quadrant was selected randomly. The random quadrants were selected in 2 steps. First step, nurses calibrated to perform the periodontal screening and recording examined every tooth in the mouth to determine eligibility. As a second step, calibrated dental hygienists, examined teeth and used a randomization code to select the random quadrant that qualified for the study.

Six attachment readings per tooth on the distobuccal, direct buccal, mesiobuccal, distolingual, direct lingual, and mesiolingual sites were taken. *Periodontal disease* was defined as attachment loss ≥3 mm on ≥3 teeth. Subjects who met this requirement were eligible for random assignment. *Moderate-severe periodontal disease* was defined as attachment loss of ≥5 mm on ≥3 teeth.

Patients with periodontal disease who returned for the scheduled treatment visit (within 2 weeks of screening) were then consented, randomly assigned, and enrolled into the study. Subjects were randomly assigned to receive either scaling and planing (active) or superficial cleaning (control). Randomization was accomplished centrally at the University of Pennsylvania, although each clinical site had its own randomization scheme. A permuted block randomization procedure was used to formulate assignment lists to assure close to equal numbers of subjects in each treatment group. A uniform block size of 4 was used.

Once randomly assigned, each subject received an assigned treatment by the trained dental hygienists. The following treatments were used:

Active treatment arm: scaling and root planing

This study procedure involved removing stains, plaque, and calculus above and below the gum line of the tooth. The root surface was left smooth and clean, thus removing the biofilm from the subgingival pocket that has endotoxins. After topical xylocaine was used on the gingivae, the hygienist used the rotating cup to remove stains and plaque from the supergingival portion of the tooth. The ultrasonic scaler was first used to remove the large pieces of calculus on the tooth and in the pocket between the gum and the tooth. Gracey curettes were used to clean and smooth the root surface. An explorer (dental instrument that is flexible and has a sharp tip) was run over the tooth to assure that the tooth was smooth and that the calculus had been removed. A rotating cup was used to remove plaque from the supergingival portion of the tooth with the use of minimally abrasive polishing paste.

Control treatment arm: superficial tooth cleaning procedure

This study procedure involved the removal of superficial stain and plaque from the tooth. This procedure is completely different than scaling and root planing because this cleaning was superficial. The hygienist used the rotating cup to remove stains and plaque from the supergingival portion of the tooth using minimally abrasive polishing paste. No sharp instruments were used for the subgingival removal of calculus.

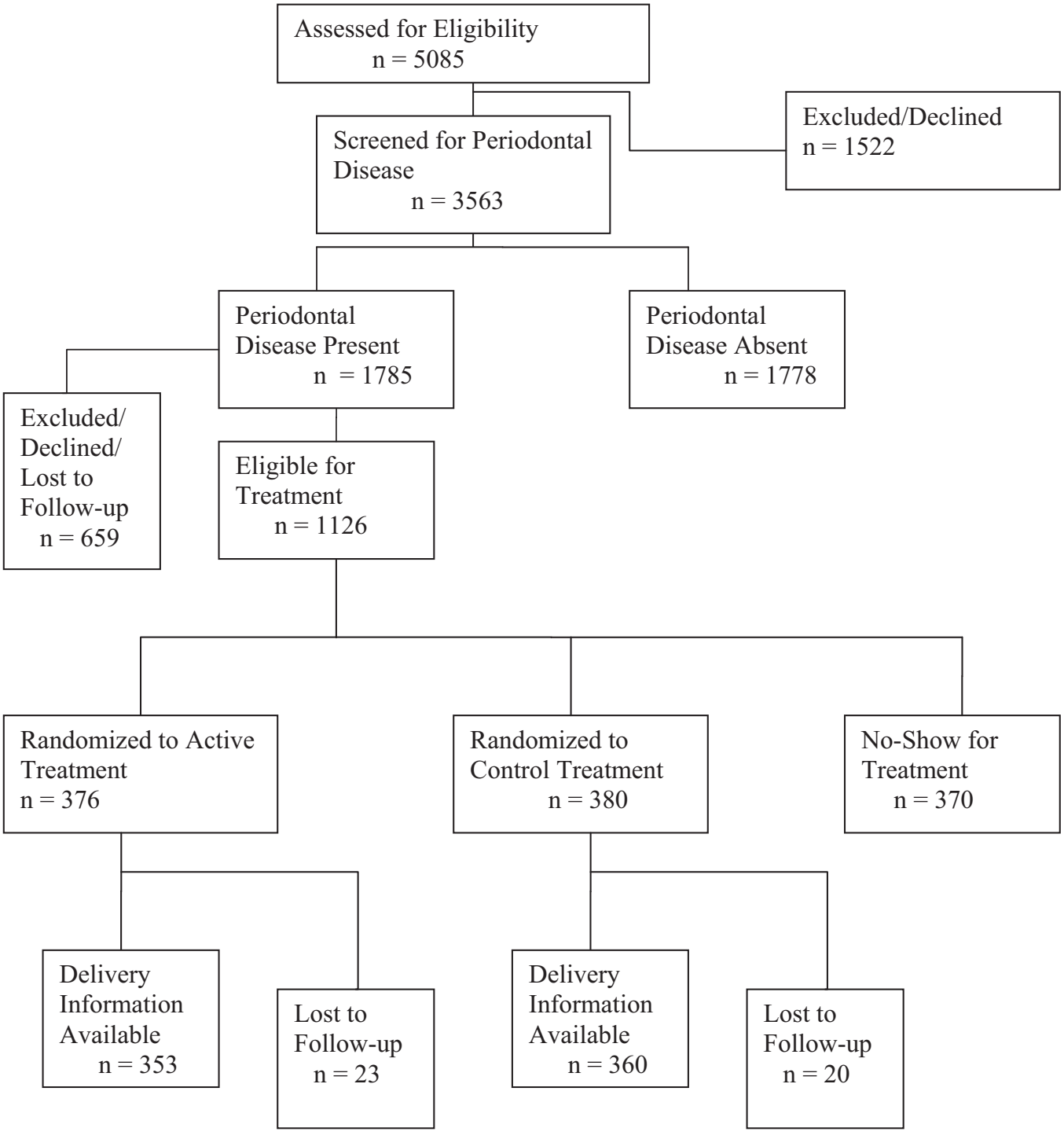
We took precautions to blind the investigators to treatment assignment. The only exception to this was the hygienists who performed either the tooth polishing (control arm) or scaling and root planing (treatment arm), who by necessity were unblinded. The members of the investigative team who assessed our primary and secondary end points were blinded to treatment assignment.

We ensured that procedures for screening and treatment were standardized and monitored. Before the study started, a study investigator (M.J.) conducted training sessions that included demonstrations and 1-on-1 tutorials for each research nurse/dental hygienist. During the study, University of Pennsylvania dentists made weekly visits to each of the recruitment sites and randomly performed periodontal screens on 10% of the patients who were being screened for study eligibility by the hygienists/nurses.

Outcome: determination of preterm births

After active or control treatment was received, patients were observed and received prenatal care by their primary obstetricians, who were also blinded to study treatment allocation; this care was entirely at the subjects' and providers' discretion. The primary study outcome for this clinical trial was the occurrence of spontaneous preterm birth at <35 weeks of gestation. A "spontaneous" preterm birth is 1 that occurs because of either idiopathic preterm labor or from preterm premature rupture of the amniotic membranes, according to standard

FIGURE
Flow diagram of trial participation



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diagnostic criteria. The clinical outcomes were determined by a review of the patient's inpatient delivery medical record. There were a number of secondary outcomes that also were of interest for this study, including subtypes of preterm birth (spontaneous, indicated), delivery at <37 weeks of gestation, delivery at <32 weeks of gestation, gestational age at delivery, and birthweight. We also considered major neonatal adverse outcomes (respiratory distress syndrome, chronic lung disease, necrotizing enterocolitis, grade III/IV IVH, sepsis, death) and, for analytic purposes, com-

bined these into "composite neonatal morbidity/death."

A priori sample size calculations assumed a type I error of 5%, a power of 80%, and a prevalence of preterm delivery at <35 weeks of gestation of 7%. In addition, a decrease in preterm delivery of 50% for preterm birth at <35 weeks of gestation was considered clinically relevant. Given these assumptions, we estimated that 636 patients would be needed per treatment group. In addition, our sample size was inflated by 5% for interim analysis[8] and an additional 5% to account for potential loss to follow-up evaluation. Therefore, the goal was to recruit 700 subjects per treatment group, for a total of 1400 subjects for the randomized trial. Because of temporal restraints that were mandated by the mechanism of funding, enrollment stopped after 3 years of recruitment, which was well before we reached our target sample size. This report presents the results from 757 participants: 378 women who were assigned randomly to active treatment, and 379 women who were assigned to control treatment. This was approximately 54% of the planned recruitment.

Comparisons between those women who were assigned randomly to active treatment vs control treatment were performed with standard bivariate statistics. Dichotomous outcomes were compared with Fisher's exact test or χ^2 test, where appropriate. Relative risks and 95% confidence intervals (CIs) also were reported. Continuous outcomes were compared with unpaired *t* tests, as appropriate. The intent-to-treat principle was used for the primary analysis.

TABLE 1
Characteristics of study participants

Variable	Treatment: Active (n = 376)	Treatment: Control (n = 380)	*P* value
Average age, y[a]	24.1 ± 5.2	24.4 ± 5.7	.41
Race[b]			.41
White	3.2 (12)	1.9 (7)	
Black	87.5 (329)	87.3 (331)	
Other	9.3 (35)	10.8 (41)	
Hispanic	8.2 (31)	9.2 (35)	.63
Education[b]			.04
High school or lower	71.5 (269)	64.7 (246)	
Some college or college degree	28.5 (107)	35.3 (134)	
Marital status[b]			.88
Married	11.7 (44)	12.4 (47)	
Single, never married	85.6 (322)	84.5 (321)	
Other	2.7 (10)	3.2 (12)	
Site[b]			1.00
Hospital of the University of PA	55.9 (210)	56.1 (213)	
Pennsylvania Hospital	22.3 (84)	22.1 (84)	
Einstein Hospital	21.8 (82)	21.8 (83)	
Screening assessment of severity of preterm delivery[b]			.90
Mild periodontal disease	45.2 (168)	44.7 (169)	
Moderate/severe periodontal disease	54.8 (204)	55.3 (209)	
History of preterm delivery[b]			.62
Previous preterm delivery	11.7 (44)	12.9 (49)	
No previous preterm delivery	88.3 (332)	87.1 (331)	

[a] Data are given as mean ± SD; the probability value was determined with the *t* test; [b] Data are given as percentage (n); probability values were determined with the χ^2 test.

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RESULTS

A total of 5085 pregnant women were assessed for eligibility, of which 3563 women were screened for periodontal diseases (Figure). Among those screened, the prevalence of periodontal disease was 50% (1765/3563 women); 1126 women were eligible for random assignment. Of these, 370 subjects did not return for the randomization visit, which left 756 subjects who were ultimately assigned randomly: 376 women to scaling and root planing and 380 women to control treatment. The mean gestational age at screening was 13.1 weeks, and the mean gestational age at treatment was 16.5 weeks.

Characteristics at randomization were similar between those in the active and control groups (Table 1). The only exception was that a greater proportion of those women who were assigned randomly to active treatment were of high school education or lower. Approximately one half of the subjects were enrolled from the Hospital of the University of Pennsylvania, with similar enrollment numbers from the other 2 sites (Pennsylvania Hospital and Albert Einstein Medical Center). Importantly, the groups were balanced with respect to gestational age, periodontal disease severity, and history of a preterm delivery.

There was no evidence that active treatment improved pregnancy outcomes (Table 2). There was no difference in the incidence of spontaneous preterm birth at <35 or <37 weeks of gestation or of preterm birth overall at <35 or <37 weeks of gestation between the 2 treatment groups. There was a trend towards an increase in the risk of an indicated preterm birth (occurring because of maternal or fetal indications for delivery, such as preeclampsia, fetal growth re-

TABLE 2
Outcomes

Outcome measure	Treatment		*P* value	Relative risk (95% CI)
	Active	Control		
Gestational age: live births only	n = 359	n = 361		
Average gestational age, wk	38.6 (2.8)	38.8 (2.3)	.47	
Gestational age <35 weeks, %	8.6	5.5	.11	1.56 (0.91–2.68)
Spontaneous preterm delivery, %	5.3	4.4	.59	1.19 (0.62–2.28)
Indicated preterm delivery, %	3.3	1.1	.05	3.01 (0.98–9.27)
Gestational age <37 weeks, %	16.2	13.0	.24	1.24 (0.87–1.77)
Spontaneous preterm delivery, %	10.6	10.3	.88	1.03 (0.67–1.59)
Indicated preterm delivery, %	5.6	2.8	.06	2.01 (0.95–4.24)
Birthweight: live births only	n = 357	n = 359		
Average birthweight, g	3076.1	3143.8	.14	
Birthweight <2500 g, %	13.5	9.8	.12	1.38 (0.92–2.08)
Birthweight <1500 g, %	3.1	1.7	.22	1.84 (0.69–4.93)
Adverse pregnancy/neonatal outcomes	n = 376	n = 380		
Stillbirth, %	2.1	2.4	.82	0.90 (0.35–2.30)
Miscarriage, %	4.0	3.2	.54	1.26 (0.60–2.66)
Composite neonatal morbidity/mortality, %	10.6	8.2	.24	1.30 (0.83–2.04)

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striction) at both <35 and <37 weeks of gestation in those randomly assigned to active treatment. No difference was noted in mean birthweight or proportion of low birthweight (birthweight, <2500 g) or very low birthweight (birthweight, <1500 g) newborn infants. Most importantly, there was no difference in composite neonatal morbidity/mortality rates between the groups. Table 3 represents an analysis of treatment efficacy that was based on parity. Interestingly, there were no differences in treatment outcomes in nulliparous patients. There was an increased risk of indicated preterm birth in those who were multiparous.

We performed a planned subanalysis to see whether certain subgroups (specified a priori) benefited from active treatment (Table 4). For women

TABLE 3
Primary outcomes stratified by nulliparity

Outcome measure	Nulliparous women				Multiparous women			
	Active treatment	Control treatment	*P* value	Rel Risk (95% CI)	Active treatment	Control treatment	*P* value	Relative risk (95% CI)
Average gestational age, wk[a]	38.8 ± 3.0	38.8 ± 2.7	.96		38.5 ± 2.6	38.7 ± 1.9	.26	
Gestational age <35 wk, %	7.4 (11)	7.3 (10)	.97	1.02 (0.45–2.32)	9.5 (20)	4.5 (10)	.04	2.12 (1.02–4.43)
Spontaneous preterm delivery	5.4 (8)	4.4 (6)	.69	1.23 (0.44–3.47)	5.2 (11)	4.5 (10)	.72	1.17 (0.51–2.69)
Indicated preterm delivery	2.0 (3)	2.9 (4)	.71[b]	0.69 (0.16–3.05)	4.3 (9)	0 (0)	.001[b]	20.2 (1.18–344.32)[c]
Gestational age <37 wk, %	15.5 (23)	13.1 (18)	.56	1.18 (0.67–2.09)	16.6 (35)	13.0 (29)	.28	1.28 (0.81–2.02)
Spontaneous preterm delivery	10.8 (16)	8.8 (12)	.56	1.23 (0.61–2.51)	10.4 (22)	11.2 (25)	.81	0.93 (0.54–1.61)
Indicated preterm delivery	4.7 (7)	4.4 (6)	.89	1.08 (0.37–3.13)	6.2 (13)	1.8 (4)	.02[b]	3.45 (1.14–10.41)

CI, confidence interval.
Except when indicated otherwise, the probability values were determined with the χ^2 test, and relative risks were determined by the Mantel-Haenzel method.

[a] Data are given as mean ± SD, and probability values were determined by *t* test; [b] Probability value was determined by Fisher's exact method; [c] Relative risk was determined by the logit method, with a 0.5 correction applied to cells with zero counts.

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TABLE 4
Odds of preterm birth

	Gestational age <35 wk		Gestational age <37 wk	
Key subgroups	**Odds ratio (95% CI)**	***P* value**	**Odds ratio (95% CI)**	***P* value**
All patients	1.61 (0.90–2.88)	.11	1.29 (0.85–1.95)	.23
Site				
Hospital of the U of Pennsylvania	1.98 (0.86–4.54)	.11	1.30 (0.73–2.32)	.37
Pennsylvania Hospital	1.00 (0.24–4.14)	1.00	1.97 (0.82–4.76)	.13
Einstein Hospital	1.51 (0.55–4.19)	.43	0.84 (0.36–1.96)	.69
Screening assessment of preterm delivery severity				
Mild	1.20 (0.50–2.86)	.68	1.59 (0.86–2.94)	.14
Moderate-severe	2.06 (0.93–4.56)	.07	1.08 (0.61–1.91)	.79
History of preterm delivery				
Previous preterm delivery	4.48 (1.14–17.60)	.03	1.61 (0.62–4.21)	.33
No previous preterm delivery	1.24 (0.64–2.41)	.52	1.24 (0.78–1.98)	.36

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with a history of a previous preterm birth (n = 93), there was an increase in the risk of preterm birth at <35 weeks of gestation in those in the active treatment arm compared with those in the control treatment arm (odds ratio, 4.48; 95% CI, 1.14–17.6). This difference was mainly due to a difference in indicated preterm births in the active treatment group. There was also a trend towards an increased risk of preterm birth at <35 weeks of gestation in those women with moderate-severe periodontal disease who received active treatment.

Comment

The association between periodontal disease and preterm birth has been observed in several studies. Jeffcoat et al[9] performed a prospective cohort study of >1300 women at the University of Alabama at Birmingham. Subjects were enrolled at 21-24 weeks of gestation, and information on many risk factors for preterm birth was collected. An adjusted analysis in this study suggested a positive association between moderate-severe periodontal disease and preterm birth at <37 weeks of gestation (odds ratio, 4.5; 95% CI, 2.2–9.2), <35 weeks of gestation (odds ratio, 5.3; 95% CI, 2.1–13.6), and <32 weeks of gestation (odds ratio, 7.1; 95% CI, 1.7–27.4). Offenbacher et al,[6] in a prospective cohort study of >1000 women, also found an increase risk of preterm birth at <37 weeks of gestation in women with periodontal disease (relative risk, 2.0; 95% CI, 1.2–3.2). Other studies have not found an association.[10] A recent metaanalysis by Vergnes and Sixou, which included 17 studies, suggested a 2.8-fold increased risk of preterm birth in those women with periodontal disease.[6]

Current research is aimed at determining the effectiveness of periodontal disease treatment on reducing the risk of preterm birth. There have been 2 published clinical trials on periodontal disease treatment and preterm birth, with conflicting results. Michalowicz et al[11] published a randomized trial of 823 women with periodontal disease in pregnancy and compared antepartum treatment to postpartum treatment. In the primary analysis, there was no difference between the groups in terms of preterm birth. However, there was a trend toward a reduction in preterm birth at <32 weeks of gestation in those women who were treated during pregnancy. Lopez et al[12] enrolled >800 women to an randomized controlled trial of treatment of periodontal disease during pregnancy (compared with after delivery) and found a marked reduction in the rates of preterm birth.

This study did not find any suggestion of a benefit to treatment of periodontal disease in pregnancy in terms of rates of preterm birth or neonatal outcomes.[12] The overall rates of preterm birth at <37 and <35 weeks of gestation were similar between the treatment groups in our study. Of note, however, we did find a suggestion that treatment was associated with a trend towards an increase in indicated preterm births at both <35 and <37 weeks of gestation.

The reason that the results of our clinical trial differ somewhat from previous work is unclear, although there are several possibilities. The first possibility has to do with our definition of periodontal disease. Periodontal diseases are composed of 2 major diseases: gingivitis (in particular pregnancy gingivitis), which is reversible inflammation of the gingiva, and periodontitis, the topic of this investigation, which involves destruction of the hard and soft tissues that support the teeth. Unfortunately there is no widely accepted definition for periodontitis, and no clear cut-off points for mild, moderate, and severe periodontal disease or for localized and generalized disease. Still, our definition of periodontal disease was similar to that used in the

other clinical trials. In our study, of those women who were screened, 50% were noted to be positive for periodontal disease. This is higher than what has been reported in the past and higher than that reported in the other clinical trials. We did have rigorous quality assurance measures in place to be certain of proper diagnosis, but it is possible that our diagnostic criteria and quadrant-based approach may explain our findings partially. Future analyses will address other cut-off points that have been customized to the population that we studied. The second possibility is that earlier treatment may be more beneficial, although our gestational age at treatment was similar to that of the study by Michalowicz et al.[11] A third possibility is that our "control" (tooth polishing only) may actually be considered a minimal treatment. Although it seems unlikely that this would play are large role in explaining our results (especially the trend in differences in indicated preterm deliveries), it is possible that this choice of control blunted differences in treatment efficacy. The final possibility is that the population difference (such as the ethnic breakdown of our population) may partially explain our results, compared with others.

Our initial sample size estimate called for the recruitment of 1400 women (700 per group). However, because of limitations in the duration of the study with this funding mechanism, the study was halted with 54% of the subjects enrolled. Because of this, there is concern that not finding a treatment effect for the reduction of preterm birth may be due to type II error. In our a priori sample size estimate, we assumed that the incidence of spontaneous preterm delivery at <35 weeks of gestation in the control group would be 7.0%, and we designed the study to have 80% power to detect a 50% reduction in spontaneous preterm birth in those women in the active treatment group. However, although the observed rate of spontaneous preterm deliveries at <35 weeks of gestation in the control group was lower than anticipated, the rate of spontaneous preterm deliveries in the active group was slightly increased in our study, relative to the control group (4.4% in the control group and 5.3% in the active group). A post hoc power calculation revealed that, with the number of subjects in this study and the rate of spontaneous preterm delivery in the control subjects, we have 80% power to detect a 60% reduction in the rate of spontaneous preterm birth at <35 weeks of gestation. The results are even more striking if we consider a post hoc power calculation for preterm birth overall at <35 weeks of gestation or of overall preterm birth at <37 weeks gestation, where we have 80% power to detect a relative risk of 0.45 and 0.65, respectively.

A post hoc power calculation does not take into account the fact that we surprisingly observed an increased rate of spontaneous and overall preterm birth in those who received active treatment. Another way to frame the potential impact of the early end to the study is to consider what the difference in preterm birth rate would need to be in the remaining 46% of the sample (if recruitment were to continue) to show a benefit of active treatment. If we consider spontaneous preterm births at <35 weeks of gestation, to have found a benefit to active treatment, there would need to be a reversal in the rate of preterm birth in the control vs active group (in the remaining 46% of the sample), such that we would have to experience no additional spontaneous preterm deliveries at <35 weeks of gestation for the active treatment arm and observe an additional 20 spontaneous preterm deliveries at <35 weeks of gestation in the group that received the placebo treatment. Put another way, if the study were to have continued, we would have needed to observe a relative risk of 0.05 for spontaneous preterm delivery at <35 weeks of gestation (a 95% reduction in risk in those women in the active treatment group) in the remaining 46% of the sample. Although possible, this seems extremely unlikely. Therefore, we are confident that a type II error does not account for our negative findings.

Despite the null findings regarding a reduction in spontaneous preterm birth, a concerning finding of this study is the trend toward an increased risk of indicated preterm birth in those women who were actively treated for periodontal disease in pregnancy. This was found both for deliveries that were categorized at <35 and <37 weeks of gestation. The indicated preterm births occurred primarily because of severe preeclampsia and fetal growth restriction, and the proportions of these indications were similar in those women who received active treatment and those women who received control treatment. Although this was a prespecified secondary end point, it may represent nothing more than a type I error, particularly because the finding is of borderline statistical significance and moderate effect size. Alternatively, 1 speculative biologic explanation for this finding is that treatment induces a transient systemic increase in proinflammatory mediators and/or oxidative stress. In theory, this pathway could lead to adverse effects on the placenta, which would result in conditions such as fetal growth restriction and preeclampsia. This latter hypothesis of an association between periodontitis and indicated preterm birth must be investigated further before it is considered more than just speculation. If this association is borne out in other studies, then one must weigh the benefits of improved oral health vs the small increase in indicated preterm births. In our opinion, if the association between active treatment and indicated preterm delivery is true, then active treatment should not be performed during pregnancy but should be delayed until after delivery.

Another intriguing finding is that the odds of preterm birth at <35 weeks of gestation in those who receive active treatment is increased markedly in those women with a previous preterm birth, relative to those women without a previous preterm birth. Although this also may represent a type I error, it is worthy of additional study.

In summary, the results of this study do not support the use of screening and treating periodontal disease in pregnancy that is aimed at reducing preterm birth. Of concern, active treatment of periodontitis in pregnancy may even increase risk for some subtypes of preterm birth. ■

REFERENCES

1. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. Lancet 2008;371:75-84.

2. Parry S, Strauss J. Premature rupture of the fetal membranes. N Engl J Med 1998;338:663-70.

3. Jeffcoat MK, Geurs NC, Reddy MS, Goldenberg RL, Hauth JC. Current evidence regarding periodontal disease as a risk factor in preterm birth. Ann Periodontol 2001;6:183-8.

4. 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.

5. 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.

6. 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.

7. Offenbacher SBK, Murtha AP, Jared HL, et al. Progressive periodontal disease and risk of very preterm delivery. Obstet Gynecol 2006;107:29-36.

8. Kim K, Demets D. Sample size determination for group sequential clinical trials with immediate response. Stat Med 1992;11:1391-9.

9. Jeffcoat M, Geurs N, Reddy M, Cliver S, Goldenerg R, Hauth J. Peridontal infection and preterm birth: results of a prospective study. J Am Dent Assoc 2001;132:875-80.

10. Vergnes JN, Sixou M. Preterm low birth weight and maternal periodontal status: a meta-analysis. Am J Obstet Gynecol 2007;196:135.e1-7.

11. 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.

12. Lopez N, Smith P, Gutierrez J. Periodontal therapy may reduce the risk of preterm low birthweight in women with periodontal disease: a randomized controlled trial. J Peridontol 2002;73:911-24.