

# Treatment of Periodontal Disease During Pregnancy

## A Randomized Controlled Trial

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**OBJECTIVE:** To investigate whether treating periodontal disease prevents preterm birth and other major complications of pregnancy.

**METHODS:** This single-center trial was conducted across six obstetric sites in metropolitan Perth, Western Australia. Pregnant women identified by history to be at

risk ( $n=3,737$ ) were examined for periodontal disease. Approximately 1,000 women with periodontal disease were allocated at random to receive periodontal treatment commencing around 20 weeks of gestation ( $n=542$ ) or 6 weeks after the pregnancy was completed (controls;  $n=540$ ). The treatment included mechanical removal of oral biofilms together with oral hygiene instruction and motivation at a minimum of three weekly visits, with further visits if required.

**RESULTS:** There were no differences between the control and treatment groups in preterm birth (9.3% compared with 9.7%, odds ratio [OR] 1.05, 95% confidence interval [CI] 0.7–1.58,  $P=.81$ ), birth weight (3,450 compared with 3,410 g,  $P=.12$ ), preeclampsia (4.1% compared with 3.4%, OR 0.82, 95% CI 0.44–1.56,  $P=.55$ ), or other obstetric endpoints. There were four unexplained stillbirths in the control group and no pregnancy losses in the treated group ( $P=.12$ ). Measures of fetal and neonatal well-being were similar in the two groups, including abnormalities in fetal heart rate recordings ( $P=.26$ ), umbilical artery flow studies ( $P=.96$ ), and umbilical artery blood gas values ( $P=.37$ ). The periodontal treatment was highly successful in improving health of the gums ( $P<.01$ ).

**CONCLUSION:** The evidence provided by the present study does not support the hypothesis that treatment of periodontal disease during pregnancy in this population prevents preterm birth, fetal growth restriction, or preeclampsia. Periodontal treatment was not hazardous to the women or their pregnancies.

**CLINICAL TRIAL REGISTRATION:** ClinicalTrials.gov, www.clinicaltrials.gov, NCT00133926.

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**LEVEL OF EVIDENCE: I**

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Despite several decades of major improvements in diagnostic and therapeutic systems used in antenatal care, the rates of many major complications of pregnancy are not decreasing, including preterm



birth.<sup>1</sup> A vital clue as to the origin of many cases of preterm birth has come from the discovery that inflammatory pathways may be involved in a high proportion of early deliveries, suggesting the presence of infection.<sup>2</sup> Trials using antibiotics have in general failed to prevent preterm birth,<sup>3</sup> suggesting that if the inflammation is of bacterial origin, the source may be a distant site, and one that will not respond to conventional antibiotic therapy. Periodontal disease is one possibility.<sup>4</sup>

Many case series and cohort studies have shown significant associations between periodontal disease and preterm birth,<sup>5</sup> fetal growth restriction,<sup>4</sup> and preeclampsia.<sup>6</sup> Experiments using animals have also shown strong associations between periodontal pathogens and fetal death<sup>7-9</sup> and growth restriction.<sup>7</sup> The mechanisms by which an inflamed and infected periodontium could adversely affect the pregnant uterus and developing fetus are uncertain, although evidence suggests roles for translocation of periodontopathic organisms, and stimulation and release of inflammatory mediators and prostaglandins into the maternal circulation.<sup>10</sup>

Evidence from seven trials of treatment during pregnancy are now available, but many of the findings are in conflict and inconclusive.<sup>11</sup> The largest of these trials, the Obstetric and Periodontal Therapy (OPT) Study, observed no beneficial effect of periodontal treatment on preterm birth or birth weight, but did observe a possible effect of preventing stillbirth, the certainty of which was unclear.<sup>12</sup>

The purpose of the present study was to perform a randomized controlled trial of treatment of periodontal disease in midpregnancy to investigate whether such treatment may prevent preterm birth, fetal growth restriction, and preeclampsia. Our study was conducted by a single group of investigators operating from a major center, with screening and treatments at six additional sites within metropolitan Perth, Western Australia.

## MATERIALS AND METHODS

The Smile Study was a single-center randomized controlled trial of treatment for periodontal disease in midpregnancy conducted at seven sites in one city. The protocol was approved by the ethics committees responsible for each of the study sites. Pregnant women were invited to participate in public and private antenatal clinics and offices across metropolitan Perth, Western Australia. Advertisements in the lay media and promotional material in clinical environments invited women who had concerns about the health of their gums, pain on biting, bleeding from the gums, or a history of preterm birth. We had observed in a previous study that these four items were predic-

tive of periodontal disease (unpublished observations, 2003). Women were eligible for recruitment if they were more than 16 years of age; did not have maternal cardiac disease that would warrant the need for antibiotics for periodontal examination or treatment; had not already received periodontal treatment during the current pregnancy; had no fewer than 20 natural teeth; had a single pregnancy of more than 12 and less than 20 weeks of gestational age; did not have any known fetal anomalies or other risk factors, such as hydramnios, that would place the pregnancy at imminent risk of complications; and were able to attend regularly for periodontal treatment if required.

Periodontal screening studies were conducted at King Edward Memorial Hospital, the Oral Health Centre of Western Australia, Osborne Park Hospital, Swan Districts Hospital, Armadale Hospital, Rockingham Hospital, and Joondalup Hospital. The latter five hospitals are secondary level centers across metropolitan Perth, whereas King Edward Memorial Hospital is the tertiary-level perinatal center for the state of Western Australia. Informed written consent to conduct the screening study was obtained by a research midwife. These screening studies were performed by one of five research hygienists under the supervision of two specialist periodontists (I.N. and J.S.). The examinations were a modified Community Periodontal Index of Treatment Needs study conducted in a well-equipped dental environment.<sup>13</sup> Each study took approximately 20 minutes to conduct. Periodontal disease was defined as presence of periodontal pockets of 4 mm or greater in depth at 12 or more probing sites in fully erupted teeth (typically excluding wisdom teeth). This definition was based on the results of a pilot study that showed that 15.4% of our general antenatal population had periodontal disease of this degree (unpublished observations, 2003). Periodontal pocketing was used to define the presence of periodontal disease rather than loss of clinical attachment because it better represents the microbial challenge and is the most frequently used criterion of current disease.

Pregnant women were invited to participate in the treatment study if the findings from the screening examination met the criteria for periodontal disease. Informed written consent for treatment was obtained by a research midwife or hygienist. A questionnaire was then administered to obtain data on demographic, dental, and medical aspects of the woman's health.

Randomization was conducted by a research midwife or hygienist using computer randomization software specifically designed to allocate each case at random with stratification for nulliparity, history of preterm birth, and current smoking. Women found to



have a periodontal disease were randomly allocated to receive periodontal treatment in midpregnancy (treatment group; n=542) or after the pregnancy was concluded (control group; n=540).

The women who were found to not have periodontal disease were provided with a written record of their examination but were not involved in the study thereafter.

Treatment was preceded by full periodontal examination, including precise measurement of periodontal pocket depth to 0.2 mm with a Florida probe (Florida Probe Corporation, FL). Data obtained by this system are recorded directly into a computer database.<sup>14</sup> Examination also included measurement of clinical attachment loss, bleeding after probing across the full mouth, and calculation of a modified O'Leary Plaque Index.<sup>15</sup> A treatment plan was then devised, often in consultation with a specialist periodontist, and discussed with the woman.

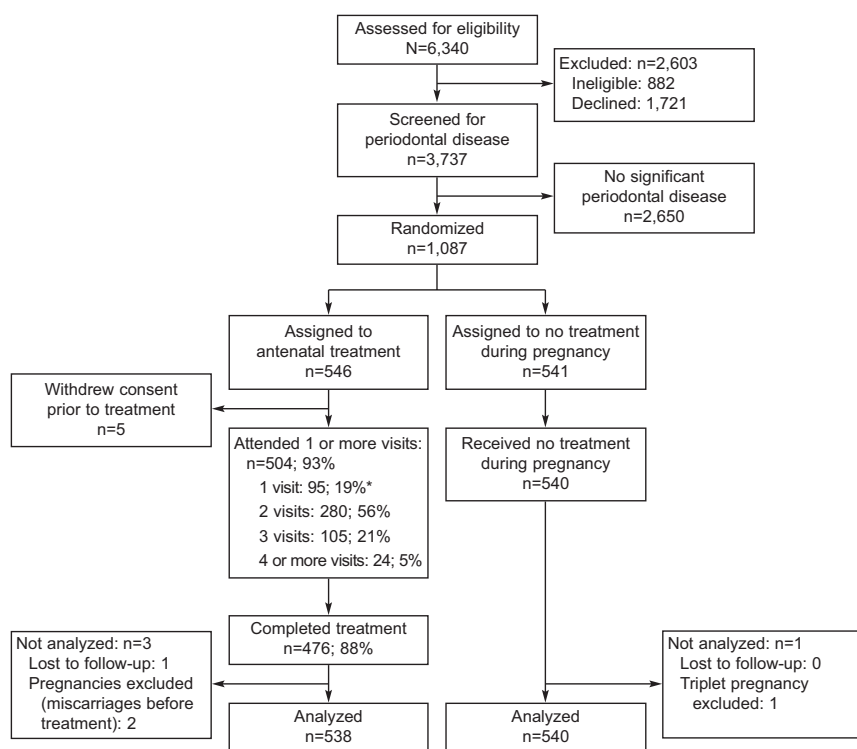
The primary objective of the treatment was to remove or control various biofilms that act as reservoirs for the bacterial load. Treatments were conducted either by the hygienists or periodontists and included nonsurgical débridement of the subgingival and supragingival plaque, removal of local predisposing factors such as calculus, root planing, and adjustment of overhanging restorations. Comprehensive oral hygiene instructions and motivation were pro-

vided at each visit. The advice included recommendations for tooth brushing and flossing after every meal and rinsing with 0.12% non-alcohol-based chlorhexidine mouthwash. Local anesthesia was used as required (1% lignocaine with 1:80,000 adrenalin up to a maximum dose of 4.4 mL per treatment visit). These treatment sessions were provided on three occasions at weekly intervals commencing around 20 weeks of gestation. Each woman was given \$10 to reimburse for travel expenses at each treatment visit.

Four weeks after the final treatment, typically at 28 weeks of gestation, a further examination was conducted to provide a quantified assessment of the success of treatment. This assessment included a clinical examination and measurements with a Florida probe. Those women in whom the treatment had not been successful were offered a further 3-week treatment regimen (107 [19.6%] women were found to require additional treatment visits).

All women in the antenatal treatment arm of the study were examined again at 32 and 36 weeks of gestation. The success of treatment was again quantified, and oral hygiene advice and motivation were provided. Systemic antibiotics were not provided for periodontal disease.

Women allocated to the postnatal (control) group were offered periodontal care after the birth, commencing 6 weeks after delivery. They had no further



**Fig. 1.** Enrollment of study patients. \*Percentages do not sum to 100 because of rounding. Newnham. *Periodontal Disease in Pregnancy*. *Obstet Gynecol* 2009.



contact with any members of the research team until their pregnancy was concluded. The postnatal care involved the same 3-week treatment protocol as for women in the antenatal treatment group. A follow-up visit was then offered 4 weeks later to assess the effectiveness of the treatment.

All medical, nursing, and perinatal pathology staff members were unaware of the treatment allocation of each woman in the study, and health care was provided according to standard protocols within each clinic and hospital. Details of all medical, obstetric, and neonatal outcomes were extracted from the medical records by research midwives who were also blinded to the treatment allocation. Twenty-four women had moved interstate or overseas, and their obstetric and neonatal outcomes were obtained by telephone (nine in the control and 15 in the antenatal treatment group, respectively). Stillbirth in Australia is defined as death of the unborn fetus after 20 completed weeks of gestation or more than 400 g birth weight.

The primary hypothesis was that treatment of periodontal disease during pregnancy reduces the rate of preterm birth from 12% to 7%. A sample size of 1,082 women was required to detect this reduction in the preterm birth rate with 80% ( $\beta=.20$ ) power while using a two-sided test of proportions at 5% significance level ( $\alpha=.05$ ).

We initially planned a study with a sample size of 1,094 women, which included an interim analysis to be conducted when 60% of the study pregnancies were completed. In August 2007, the independent data safety monitoring committee recommended proceeding without an interim analysis after data on treatment safety and pregnancy outcomes from the trial conducted by Michalowicz et al<sup>12</sup> were published.

Continuous outcomes were summarized using means and standard deviations or medians and interquartile ranges, as appropriate. Categorical outcomes were summarized using frequency distributions. Univariable comparisons of pregnancy outcomes were based on the Mann-Whitney or *t* test for continuous data and the  $\chi^2$  or Fisher exact test for categorical data. Comparison of the rate of preterm birth adjusted for parity, smoking, and history of preterm birth was performed using logistic regression analysis with odds ratios (ORs) and their 95% confidence intervals (CIs) used to summarize the treatment effect. Supplementary univariate comparisons of gestational ages at delivery between groups were based on Kaplan-Meier survival curves and the log rank test, and a proportional hazards Cox regression model was used for adjusted analyses with hazard ratios and their CIs.

Primary data analysis was performed on the intention-to-treat principle. Secondary subgroup analyses of dose response effects to treatment compared pregnancy outcomes according to the disease severity and treatment compliance during pregnancy (noncompliant women in the treatment group were excluded from this analysis). Results of this analysis were similar to those obtained when using the intention-to-treat approach and are not shown. SPSS (SPSS Inc., Chicago IL) statistical software was used for data analysis.  $P<.05$  was considered statistically significant.

## RESULTS

A total 6,340 women were invited to participate in the study between February 2005 and December 2007,

**Table 1. Characteristics of the Women and Their Pregnancies at Trial Entry**

	Treatment Group (n=538)	Control Group (n=540)	P
Maternal age (y)*	30.5 (5.5)	30.5 (5.5)	.842
Race			.897
White	394 (73.2)	400 (74.1)	
Asian	88 (16.4)	87 (16.1)	
Aboriginal	23 (4.3)	22 (4.1)	
African	23 (4.3)	17 (3.1)	
Hispanic	5 (0.9)	7 (1.3)	
Other	5 (0.9)	7 (1.3)	
Highest education (y)†			.077
Less than 10	8 (1.5)	13 (2.4)	
11–12	251 (46.7)	277 (51.3)	
More than 12	146 (27.1)	113 (20.9)	
University degree	128 (23.8)	135 (25.0)	
Body mass index (kg/m <sup>2</sup> )*	25.0 (5.5)	24.9 (5.4)	.864
Smoking during pregnancy			
At recruitment	152 (28.0)	152 (28.0)	.941
During treatment	95 (17.7)	95 (17.7)	.831
Alcohol during pregnancy	78 (14.5)	75 (13.9)	.793
Illicit drug use	14 (2.6)	13 (2.4)	.842
Nulliparous	236 (43.9)	233 (43.1)	.812
Previous pregnancies			
Previous preterm birth	40 (13.2)	34 (11.1)	.412
Any abortions	153 (50.7)	143 (46.6)	.314
Any spontaneous abortions	102 (33.2)	102 (33.8)	.932
Any stillbirths	11 (3.6)	12 (3.9)	.863
Preexisting diabetes	7 (1.3)	14 (2.6)	.126
Preexisting hypertension	8 (1.5)	11 (2.1)	.509
Preeclampsia (current pregnancy)	18 (3.4)	22 (4.1)	.551
Gestational hypertension (current pregnancy)	53 (10.1)	59 (11.1)	.607

Data are n (%) unless otherwise indicated.

P values for group comparisons are based on *t* tests for continuous data and  $\chi^2$  or Fisher exact tests for categorical data.

\* Mean (SD).

† Percentage totals less than 100% are due to missing data (highest education).





with the final pregnancy concluding in June 2008 (Fig. 1). The women were approached either directly by research midwives within a clinical environment, or they responded by telephone to promotional material in the lay press. Of these, 3,737 women were recruited and received a screening examination of their periodontal status. These examinations identified 1,087 women (29.1%) with periodontal disease, each of whom then provided consent to participate in the treatment arm of the study. Five hundred forty-one women were allocated at random to receive periodontal treatment commencing 6 weeks after the pregnancy was concluded (control group), and 546 women were allocated at random to receive treatment commencing at 21 weeks of gestation (treatment group). Five women assigned to antenatal treatment withdrew their consent before treatment commenced. One woman was excluded when found at 19 weeks of gestation to have a multiple pregnancy. Two women had spontaneous abortions after recruitment and be-

fore their first screening examination. Follow-up data were available for all women except one in the antenatal group, who was known to have left Australia to give birth in her country of origin.

The two groups were similar in baseline maternal characteristics (Table 1): 71.6% of the women were Caucasian, 98.0% had received more than 9 years of education, the mean prepregnancy body mass index was 24.9 kg/m<sup>2</sup>, and 45.1% had experienced a previous spontaneous or induced pregnancy loss. There were no differences between the two groups in rates of preeclampsia ( $P=.551$ , OR 0.82, 95% CI 0.44–1.56) or gestational hypertension ( $P=.607$ , OR 0.88, 95% CI 0.59–1.31).

Four fetuses in the control group were stillborn (Tables 2 and 3). All four were from pregnancies that were uncomplicated, and their mothers were all married, had more than 12 years of education, and were nonsmokers. In each case, the perinatal pathologist classified the cause of stillbirth as unknown, and there

**Table 2. Birth and Newborn Outcomes**

	Treatment Group (n=538)	Control Group (n=540)	<i>P</i>
Pregnancy outcomes			
Stillbirth	—	4 (0.7)	.124
Neonatal death	—	1 (0.2)	.501
Preterm birth	52 (9.7)	50 (9.3)	.812
Gestational age at delivery (wk)*	39.6 (38.4–40.4)	39.6	.548
Onset of labor†			
Spontaneous	258 (48.0)	244 (45.2)	.436
Induced	132 (24.5)	158 (29.3)	
Augmented	57 (10.6)	55 (10.2)	
No labor	79 (14.7)	77 (14.3)	
Mode of delivery†			
Spontaneous vaginal	276 (51.3)	280 (51.9)	.488
Assisted vaginal	88 (16.4)	79 (14.6)	
Elective cesarean	71 (13.2)	64 (11.9)	
Emergency cesarean	93 (17.3)	111 (20.6)	
Fever greater than 37°C in labor‡	37 (7.1)	47 (8.9)	.283
Primary postpartum hemorrhage (greater than 1,000 mL)*	27 (5.2)	37 (7.0)	.220
Retained placenta‡	12 (2.3)	13 (2.4)	.866
Secondary postpartum hemorrhage‡	5 (1.0)	7 (1.3)	.579
Newborn outcomes			
Male	269 (50.1)	262 (48.5)	.605
Birth weight (g)*	3,410 (3,057–3,760)	3,450 (3,111–3,800)	.117
Fraction of expected birth weight*	1.03 (0.93–1.10)	1.03 (0.95–1.12)	.103
Birth weight less than 10th percentile	52 (9.6)	39 (7.2)	.152
Head circumference (cm)*	35 (33–36)	35 (34–36)	.123
Length (cm)*	50 (48–52)	50 (49–52)	.615
Sepsis necessitating antibiotics‡	25 (4.7)	17 (3.1)	.201

Data are n (%) unless otherwise indicated.

*P* values for group comparisons are based on Mann-Whitney tests for continuous data and  $\chi^2$  or Fisher exact tests for categorical data.

\* Median (interquartile range).

† Percentage totals less than 100% are due to missing data (onset of labor, mode of delivery).

‡ Percentage calculations exclude missing data.



**Table 3. Details of the Pregnancies Resulting in Stillbirth**

Case	Gestational Age (wk)	Birth Weight (g)	Regular Dental Visits	Pain on Biting	Avoid Eating on Some Teeth	Bleeding Gums During Brushing	No. of Teeth	Periodontal Disease* (%)
1	26	770	As needed	Rarely	Rarely	Daily	29	11.5
2	27	800	As needed	Never	Never	Daily	28	11.9
3	38	2,800	Never	Weekly	Weekly	Daily	30	15.6
4	40	4,350	Annual	Not given	Never	Daily	24	36.1

All four pregnancies were uneventful, no abnormalities were found during postmortem examination, and all placentas were described as unremarkable. Oral health characteristics reported by women at recruitment and assessed during the screening examination are shown.

\* Percentage of tooth sites with probing depth 4 mm or greater.

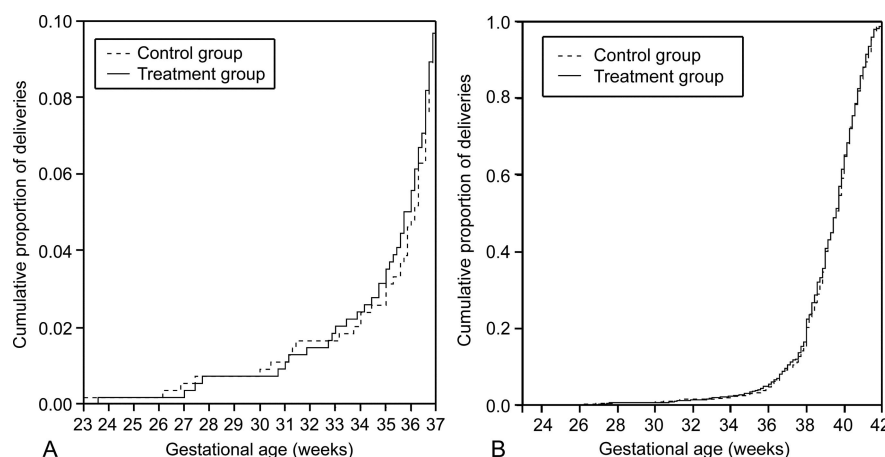
were no features of inflammation in the fetus or placenta. All four mothers had given histories of daily occurrences of bleeding from their gums during tooth brushing, and on periodontal examination each had bleeding, inflammation, and plaque levels classified as moderate. There was a single neonatal death, occurring at 1 hour of age after preterm birth at 22 weeks of gestation. The pregnancy had been complicated by antepartum hemorrhage and was in the control group. Except for a single case of loss to follow-up where the neonatal outcome was unknown, all remaining 538 women allocated to the treatment group completed their pregnancies and were discharged to home with a live infant.

The two groups were similar in duration of pregnancy, either when expressed as the rate of preterm birth ( $P=.812$ , OR 1.05, 95% CI 0.7–1.58) or when compared using estimated Kaplan-Meier cumulative probabilities of delivery (Figure 2) ( $P=.548$ , hazard ratio 1.02, 95% CI 0.91–1.15) and median gestational age at delivery (Table 2). Factors simultaneously associated with an increased risk of preterm delivery included history of preterm delivery ( $P=.002$ , OR 2.71, 95% CI 1.42–5.17), pre-eclampsia ( $P<.001$ , OR 17.56, 95% CI 8.75–35.24),

threatened abortion ( $P=.011$ , OR 2.83, 95% CI 1.26–6.34), and antepartum hemorrhage ( $P<.001$ , OR 3.75, 95% CI 1.91–7.36). Risk of preterm delivery for nulliparous women was similar to that of parous women who had no history of preterm delivery ( $P=.838$ , OR 1.05, 95% CI 0.64–1.72).

The type of onset of labor was similar for each group ( $P=.436$ ). Birth weights were similar in the two groups when expressed either as mean birth weight ( $P=.117$ ) or expected birth weight for gestational age using charts derived from the local population ( $P=.103$ ).

There were no differences between the two groups in measures of fetal welfare or health of the newborn (Table 4). These measures included incidence of nonreassuring fetal heart rate traces ( $P=.264$ ), the need for delivery based on abnormal fetal heart rate patterns ( $P=.687$ ), the presence of meconium in amniotic fluid ( $P=.522$ ), cesarean delivery for fetal distress ( $P=.720$ ), Apgar scores less than 7 at 1 or 5 minutes ( $P=.403$  and  $P=.988$ , respectively), the need for resuscitation of the newborn ( $P=.133$ ), umbilical artery pH ( $P=.371$ ),  $P_{CO_2}$  ( $P=.867$ ) and base excess ( $P=.864$ ) values, or the need for admission to the



**Fig. 2.** Kaplan-Meier curves of the cumulative incidence of deliveries according to gestational age. There were no differences between the treatment and control groups ( $P=.55$ , hazard ratio 1.02, 95% confidence interval 0.91–1.15). **A.** Survival plots limited to preterm deliveries and highlighting group differences. **B.** All deliveries combined. Newnham. *Periodontal Disease in Pregnancy*. *Obstet Gynecol* 2009.



**Table 4. Tests of Fetal and Neonatal Well-Being**

	Treatment Group (n=538)	Control Group (n=540)	<i>P</i>
<b>Fetal</b>			
AFI measured*	285 (55.2)	307 (58.6)	.275
AFI less than 5 cm	6 (2.1)	9 (2.9)	.521
AFI more than 25 cm	2 (0.7)	6 (1.9)	.288
Umbilical artery S/D ratios measured*	186 (35.6)	190 (35.8)	.941
Abnormal S/D ratios	8 (4.3)	8 (4.2)	.965
Electronic FHR monitoring in labor*	308 (59.3)	317 (60.2)	.790
Nonreassuring	115 (37.3)	102 (32.2)	.175
Decision on delivery based on electronic FHR monitoring*			
No	42 (37.2)	32 (32.0)	.687
Partially	25 (22.1)	22 (22.0)	
Yes	46 (40.7)	46 (46.0)	
Scalp pH measured in labor*	14 (2.7)	17 (3.2)	.614
Meconium in amniotic fluid*	76 (14.6)	85 (16.0)	.522
Nonreassuring fetal heart rate pattern in labor**†	61 (13.3)	64 (13.6)	.894
Cesarean delivery for nonreassuring fetal heart rate pattern**†	35 (7.7)	39 (8.3)	.720
<b>Neonatal</b>			
Apgar score less than 7			
1 min*	61 (11.7)	53 (10.1)	.403
5 min*	8 (1.5)	8 (1.5)	.988
Resuscitation*			
None	309 (59.1)	354 (66.7)	.133
Suction	76 (14.5)	61 (11.5)	
Oxygen	74 (14.1)	67 (12.6)	
Bag and mask	56 (10.7)	42 (7.9)	
Intubation	8 (1.5)	7 (1.3)	
Umbilical artery cord blood			
n	279	292	
pH‡	7.27 (7.22–7.31)	7.28 (7.22 to 7.32)	.371
PCO <sub>2</sub> ‡	53.9 (47.0 to 60.1)	53.0 (47.3 to 60.6)	.867
PO <sub>2</sub> ‡	18.0 (13.2 to 22.0)	17.1 (16.2 to 22.0)	.390
Base excess‡	−2.6 (−4.6 to 0.4)	−2.4 (−4.5 to 0.4)	.864
Ventilation*	6 (1.1)	4 (0.8)	.544
CPAP*	14 (2.7)	11 (2.1)	.518
Oxygen*	12 (2.3)	10 (1.9)	.641
SCN admission*	66 (12.6)	51 (9.6)	.119

AFI, amniotic fluid index; S/D, systolic/diastolic ratio; FHR, fetal heart rate; CPAP, continuous positive airway pressure; SCN, special care nursery.

Data are n (%) unless otherwise indicated. *P* values for group comparisons are based on Mann-Whitney tests for continuous data and  $\chi^2$  or Fisher exact tests for categorical data.

\* Percentage calculations exclude missing data.

† Excluding elective cesarean delivery.

‡ Median (interquartile range).

special care nursery ( $P=.119$ , OR 1.36, 95% CI 0.92–2.01).

The mean gestational age at the time of the periodontal screening examination was 18.2 weeks (Table 5). There were no differences between the two groups at recruitment in measures of inflammation ( $P=.459$ ), plaques ( $P=.506$ ), bleeding on probing ( $P=.361$ ), and percentage of tooth sites with probing depth of 4 mm or greater ( $P=.788$ ).

Four hundred seventy-six women (88.3%) in the treatment group completed their treatment (Fig. 1). Among the 63 women who did not complete their treatment, 35 did not attend any of their scheduled visits. The success of treatment was measured around 28 weeks of gestation (Table 6). There were significant improvements in all clinical measures of disease after treatment.



**Table 5. Periodontal Characteristics at the Screening Examination**

	Treatment Group (n=538)	Control Group (n=540)	P
Gestational age at screening (wk)*	18.1 (2.3)	18.2 (2.2)	.451
Number of natural teeth*	28.8 (2.3)	28.7 (2.3)	.293
Inflammation†			.459
Minimal	8 (1.5)	3 (0.6)	
Mild	106 (19.7)	102 (18.9)	
Moderate	274 (50.9)	291 (53.9)	
Heavy	108 (20.0)	110 (20.4)	
Severe	36 (6.7)	29 (5.4)	
Plaque‡			.506
Minimal	9 (1.7)	5 (0.9)	
Mild	150 (27.8)	173 (32.0)	
Moderate	251 (46.6)	237 (43.9)	
Heavy	104 (19.3)	101 (18.7)	
Severe	18 (3.3)	20 (3.7)	
Bleeding on probing†			.361
Minimal	12 (2.2)	5 (0.9)	
Mild	120 (22.3)	111 (20.6)	
Moderate	266 (49.4)	274 (50.7)	
Heavy	116 (21.5)	122 (22.6)	
Severe	18 (3.3)	24 (4.4)	
% of tooth sites with probing depth 4 mm or greater‡	14.8 (10.4–22.5)	14.9 (10.7–22.1)	.788

Data are n (%) unless otherwise indicated.

\* Mean (standard deviation).

† Percentage totals less than 100% due to missing data (inflammation, plaque, bleeding on probing).

‡ Median (interquartile range).

## DISCUSSION

The purpose of this study was to investigate whether treatment of periodontal disease during midpregnancy prevents complications of pregnancy. Periodontal treatment did not prevent, or cause, preterm birth, fetal growth restriction, or preeclampsia. All other measures of pregnancy outcome were similar in the two groups, with the possible exception of perinatal death. There were four stillbirths and one neonatal death in the control group and no pregnancy losses in the treatment group.

Meta-analysis of the first seven trials of periodontal treatment during pregnancy revealed a possible reduction in preterm birth and incidence of low birth weight.<sup>11</sup> These findings from randomized trials added to observations from observational studies<sup>4,16</sup> indicating associations between periodontal disease and preterm birth. The results of the present study and those of the next largest trial<sup>12</sup> are not supportive

**Table 6. Responses to Periodontal Treatment**

Treatment Group (n=538)	First Treatment (n=504)	After Treatment (n=354)	P
Gestational age at visit (wk)	21 (20–21)	28 (28–28)	
% of sites with depth 4 mm or greater	[Range 14–25] 13.8 (7.6–21.4)	[Range 26–29] 3.3 (1.2–7.0)	<.001
% of sites with depth 5 mm or greater	2.4 (0.7–5.6)	0.6 (0–1.6)	<.001
% of sites with depth 6 mm or greater	1.6 (0.5–3.9)	0 (0–1.1)	<.001
% sites bleeding on probing	70.2 (54.3–84.0)	28.7 (17.9–42.5)	<.001

Data are median (interquartile range).

of the hypothesis, with both trials providing strong evidence that treatment of periodontal disease is ineffective in preventing early birth. There are many differences, however, between many of the randomized controlled trials that have been reported.<sup>11</sup> Only three of the seven trials reported adequate randomization procedures, and only three trials were blinded. Within these various trials was a diversity of patient populations.

The first reported trial involved women of Spanish and local aboriginal descent who were of low socioeconomic status.<sup>17</sup> Preterm birth was less frequent in those who had been allocated to receive periodontal therapy (1.1% in the treatment group, 6.4% in the control group,  $P=.02$ ). The second trial was a pilot study, conducted at the University of Alabama in Birmingham.<sup>18</sup> Three hundred sixty-six women were randomly assigned to scaling and root planing, with or without metronidazole, or dental prophylaxis and placebo. Eighty-five percent of women in this trial were African-American. The trial provided some preliminary evidence that periodontal treatment may prevent preterm birth, and that adjunctive treatment with metronidazole is not of benefit and may be harmful. The largest trial reported until now was the OPT Study conducted in the United States and reported in 2006, which observed preterm birth in 12% of women in the treatment group and 12.8% in the control group, a difference that was not statistically significant.<sup>12</sup>

The finding in the present study of four stillbirths in the control group and none in the treatment group would not in itself be grounds to expect that the treatment was protective for the fetus because the





numbers were relatively small, the difference did not achieve statistical significance, and this was not a primary endpoint of the study. There is, however, evidence from other sources suggesting that such a protective effect may be real. First, the finding is consistent with that observed in the next largest randomized controlled trial of periodontal treatment during pregnancy, the OPT Study, reported by Michalowicz et al.<sup>12</sup> In that trial, 3 of 407 patients in the treatment group and 10 of 405 patients in the control group had a stillbirth. The authors viewed this finding with particular caution because the numbers were relatively small. If the numbers of stillbirths in the study by Michalowicz et al and the present study are combined by meta-analysis, the reduction in stillbirth after periodontal treatment is statistically significant ( $P=.02$ , OR 4.00, 95% CI 1.22–13.10). These two randomized controlled trials have been chosen for this meta-analysis because they are the only ones that share similar study designs.

Second, we have observed previously that women with a history of recent perinatal loss are more likely to have periodontal disease. In a case-control study of 53 women whose pregnancy had resulted in perinatal death compared with 111 matched controls, those women who had experienced a perinatal loss were more likely to have periodontal disease (OR 2.34, 95% CI 1.05–5.47).<sup>19</sup>

Third, the lethal effects of periodontal pathogens in causing fetal death are well established in animal models, including both hamsters<sup>7,8</sup> and sheep.<sup>9</sup>

Stillbirth, however, was not a primary endpoint of the present study. Despite our previous observations that periodontal disease may increase the risk of fetal death, we were unable to design our study with stillbirth as a primary outcome. To perform such a study would require a sample size that is unachievable within the range of contemporary research funding and opportunity. Hence, the value of combining results from similar studies becomes evident. The OPT Study had design features generally similar to those of the present study,<sup>12</sup> suggesting that results from the two trials can be combined with relative confidence. Meta-analysis of the first seven published randomized controlled trials of periodontal treatment during pregnancy, however, did not provide reassurance that stillbirth may be prevented by such treatment.<sup>11</sup>

In conclusion, the evidence provided by the present study does not support the hypothesis that treatment of periodontal disease in midpregnancy prevents preterm birth, fetal growth restriction, or

preeclampsia. A possible beneficial effect in preventing a proportion of stillbirths remains uncertain. Several other randomized controlled trials are currently in progress, and meta-analyses of the results of all studies can be expected to provide conclusive evidence in the future. Studies also need to be performed to investigate any possible benefits from periodontal treatment before conception. In the meantime, the information available to us at this time suggests that periodontal treatment during pregnancy is safe for the woman and her pregnancy, and that any beneficial effects for the child are either nonexistent or likely to be restricted to certain populations or subgroups that have yet to be defined with certainty.

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