Periodontal Therapy Reduces the Rate of Preterm Low Birth Weight in Women With Pregnancy-Associated Gingivitis

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Periodontal Therapy May Reduce the Risk of Preterm Low Birth Weight in Women With Periodontal Disease: A Randomized Controlled Trial

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Background: Recent studies have suggested that periodontal disease is a risk factor for preterm low birth weight (PLBW). A randomized controlled trial was undertaken to help further evaluate the proposed association between periodontal disease and PLBW.

Methods: Four hundred pregnant women with periodontal disease, aged 18 to 35, were enrolled while receiving prenatal care in Santiago, Chile. Women were randomly assigned to either an experimental group (n = 200), which received periodontal treatment before 28 weeks of gestation or to a control group (n = 200) which received periodontal treatment after delivery. Previous and current pregnancies and known risk factors were obtained from patient medical records and interviews. The primary outcome assessed was the delivery at less than 37 weeks of gestation or an infant weighing less than 2,500 g.

Results: Of the 400 women enrolled, 49 were excluded from the analyses for different reasons. The incidence of PLBW in the treatment group was 1.84% (3/163) and in the control group was 10.11% (19/188), (odds ratio [OR] 5.49, 95% confidence interval [CI] 1.65 to 18.22, $P = 0.001$). Multivariate logistic regression analysis showed that periodontal disease was the strongest factor related to PLBW (OR 4.70, 95% CI 1.29 to 17.13). Other factors significantly associated with such deliveries were: previous PLBW (OR 3.98, 95% CI 1.11 to 14.21), less than 6 prenatal visits (OR 3.70, 95% CI 1.46 to 9.38), and maternal low weight gain (OR 3.42, 95% CI 1.16 to 10.03).

Conclusions: Periodontal disease appears to be an independent risk factor for PLBW. Periodontal therapy significantly reduces the rates of PLBW in this population of women with periodontal disease. *J Periodontol 2002;73:911-924.*

KEY WORDS

Clinical trials, controlled; clinical trials, randomized; infant, low birth weight; periodontal diseases/adverse effects; infant, premature; risk factors.

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Low birth weight and its 2 components, preterm birth and intrauterine growth restriction, are major predictors of perinatal mortality and morbidity.[1,2] Multiple factors have been associated with preterm delivery and low birth weight[3,4] and some authors have emphasized the heterogeneity of the causes of preterm birth.[5,6]

Convincing evidence has associated preterm birth with infection, especially genito-urinary infections, which appear to be an important factor in the premature rupture of membranes.[4,7] Several studies have linked bacterial vaginosis with preterm birth.[8-10] However, treatment of vaginosis has not led to definite conclusions on its efficacy in reducing preterm delivery[11-14] and the impact of such intervention on preterm birth rate remains unclear.[15] Results of 2 case-control studies[16,17] and a concurrent cohort study[18] showed that periodontal diseases may be a potential independent risk factor for preterm birth and low birth weight after adjusting for several known risk factors.

Periodontal diseases are a group of infectious diseases resulting in inflammation of gingival and periodontal tissues and progressive loss of alveolar bone. The periodontal infection is initiated and sustained by several bacteria, predominantly Gram-negative, anaerobic and microaerophilic bacteria that colonize the subgingival area. Host defense mechanisms play an integral role in the

pathogenesis of periodontal diseases. Tissue destruction in periodontitis is mainly due to the activation of immune cells by cell wall components of microorganisms, such as lipopolysaccharides, which potently stimulate production of host-derived enzymes, cytokines, and other pro-inflammatory mediators resulting in connective tissue destruction.[19]

Infections affecting the mother during pregnancy may produce alterations in the normal cytokine and hormone-regulated gestation, which could result in preterm labor, premature rupture of membranes, and preterm birth.[20-22] It has been postulated that the association between periodontal disease and preterm/low birth weight (PLBW) may have similar pathogenic mechanisms as other maternal infections.[23]

Identification of risk factors for preterm birth and low birth weight should help in the development of strategies to reduce the prevalence of these conditions. A randomized controlled clinical trial was undertaken to: 1) determine the relationship between periodontal disease and PLBW; 2) quantify the association between other risk factors and PLBW; and 3) determine if periodontal therapy in pregnant women with periodontal disease reduces the risk of PLBW. The main null hypothesis tested was that there are no significant differences in the incidence of PLBW in pregnant women with periodontal disease treated before 28 weeks of gestation compared to women with periodontal disease treated after delivery.

MATERIALS AND METHODS

Study Population

The population study consisted of pregnant women who were invited to participate in the study while receiving routine prenatal care in Consultorio Carol Urzúa of Peñalolén, a district of Santiago, Chile. Women were of low socioeconomic status and received free uniform prenatal care at that clinic, which belongs to the National Public Health Service System, under the technical supervision of the Ministry of Health. Every year, about 1,100 pregnant women receive prenatal care at the facility.

The prenatal care program applied by the Public Health Services in Chile was designed by the Ministry of Health's Expert Panel on the Content of Prenatal Care. The program includes regular examinations, screening for pregnancy complications, nutritional advice, laboratory tests for risk assessments, stress reduction, education about the symptoms of preterm labor, correction of identified risk factors, and referral to the high-risk obstetric clinic when necessary.

As part of the recruitment process for the study, the midwives who were in charge of the prenatal care clinics referred to the investigators all the women, aged 18 to 35, who were receiving prenatal care. Eight hundred twenty-nine (829) women who had completed 9 weeks of gestation gave verbal consent to determine their periodontal status.

The patients medical records were thoroughly examined, relevant data were extracted and eligibility for the study was determined. The recruitment of patients was done over a 20-month period.

Inclusion criteria. Otherwise healthy pregnant women, aged 18 to 35, with a singleton gestation, between 9 and 21 weeks of gestation, with periodontal disease and with fewer than 18 natural teeth were identified for inclusion in the study.

Exclusion criteria. Exclusion criteria included history of congenital heart disease requiring prophylactic antibiotics for invasive procedures, existing diabetes before pregnancy, current use of corticosteroids, chronic renal disease, and the intention to deliver at a hospital other than that of the study.

Patient selection, periodontal therapy, and maintenance treatment were done in a dental clinic located in the building in which the prenatal care was given. An informed written consent was obtained from each volunteer and the study protocol was approved by the institutional review board.

Sample Size

Assuming a probability of preterm low birth weight of 20% in the control group and a probability of 10% in the treatment group, we believed that 280 women in each group might detect a significant difference of PLBW between groups (P <0.050; 2-sided) with a power of 80%. The results of the incidence of PLBW in the study groups were reviewed after completing 160 deliveries in each group with the understanding the trial would end early for ethical reasons if the observed P value of the differences between the groups was <0.05 as, indeed, did occur. There were 400 women enrolled in the study when at least 160 deliveries had occurred in each group.

Measurement of Periodontal Status

Upon entering the study all women received a full-mouth periodontal examination and the following variables were determined: oral hygiene status, gingival inflammation, probing depth (PD), and clinical attachment level (CAL). Oral hygiene status was assessed as the percentage of surfaces demonstrating plaque. Dichotomous measures of supragingival plaque accumulation were made by running a periodontal probe at the cervical surface of each tooth. The presence of plaque was positive when a continuous band of plaque was found in contact with the gingival tissue on the cervical portion of mesial, buccal, distal, and lingual tooth surfaces.

Probing depth and attachment level measurements were made at the mesiobuccal, buccal, distobuccal, distolingual, lingual, and mesiolingual positions of every tooth with the exception of third molars. The CAL was

measured using the cemento-enamel junction as a reference point.

Bleeding on probing (BOP) was assessed on the 6 sites at which PD was determined and deemed positive if it occurred within 15 seconds after probing. BOP was expressed as the percentage of sites showing bleeding. Gingival redness was determined on 2 gingival units per tooth. It was deemed positive when gingival redness involved all the marginal and/or the attached gingiva of the lingual or buccal gingiva of a tooth. Gingival redness was expressed as the percentage of gingival units showing redness.

Clinical measurements were recorded to the nearest millimeter using a calibrated periodontal probe by 2 calibrated examiners who are periodontists. Calibration sessions to measure agreement between the examiners were conducted and intra- and inter-examiner reliability was recorded until satisfactory agreement was reached. The reproducibility expressed as proportion of agreement between clinical scores was 91% for probing depth and bleeding. For attachment level and gingival redness the proportion of agreement between examiners was 88% and 86%, respectively.

The examination also included recording of the number of teeth present, with carious lesions, missing, and with fillings (DMFT index), and any other notable features in the oral cavity; e.g., soft tissue abnormalities, pericoronitis.

Diagnoses of Periodontal Disease

The presence of 4 or more teeth with 1 or more sites with PD ≥4 mm and with clinical attachment loss ≥3 mm at the same site was diagnosed as periodontal disease. Women were randomly assigned to either the experimental group, which received periodontal therapy before 28 weeks of gestation or to the control group which received therapy after delivery. Randomization was done equalizing periodontal disease as the relevant variable and PD was selected as the variable describing periodontal disease. Patients were assigned to 1 of 2 categories: those with a mean PD <2.5 mm and those with a mean PD ≥2.5 mm. Patients were matched on the basis of the mean PD. Each patient of the matched pair was allocated to the treatment or the control group by a coin toss.

Recording of Maternal Characteristics

Demographic factors such as age, marital status, and educational level as well as detailed data about previous and current pregnancies were obtained from the patient medical records and from interviews during prenatal visits. A medical, obstetrical, and social history was taken according to the protocol of the prenatal care program for each patient. Information on known risk factors and obstetric factors were collected and included the following:

In relation to pregnancy history: number carried to full term, number of previous preterm deliveries, number of low weight births, number of previous pregnancies aborted, and number of live births.

In relation to the current pregnancy: maternal age at the time of study entry, onset of prenatal care, nutritional status, tobacco use, alcohol consumption, use of illicit drugs, sexually transmitted diseases, asymptomatic bacteriuria, urinary infections, vaginosis or any other maternal infectious disease, number of prenatal visits, intrauterine growth restriction, fetal death, gestational age, and birth weight.

Prenatal care included the following procedures: blood pressure measurements, urine tests, blood tests, recording of maternal weight and height, and physical and pelvic examinations. At each prenatal visit, an evaluation of nutritional status was done to determine if weight gain was adequate. A normal standard of the weight-to height proportion established for Chilean women was used for the evaluation of nutrition status. At every week of gestation, pregnant women should gain weight within the recommended range for her weight-to height proportion. The nomogram by Rosso and Mardones[24] was used to assess whether weight gain was adequate. Underweight women received supplementary nutrition.

As a uniform prenatal care protocol was applied to all the women of this study, theoretically all of them received adequate care. However, there were women who began the prenatal care at different times in their gestational period, and/or who did not adhere to the scheduled prenatal visits. In order to assess if prenatal care had been adequate, the number of weeks of gestation at the beginning of prenatal care and the number of prenatal visits were used as assessment criteria. Prenatal care was categorized as starting routine care before 12 weeks of gestation, between 13 and 20 weeks of gestation, and after 20 weeks of gestation. A woman who smoked 5 or more cigarettes per day was considered a smoker. The number of alcoholic drinks consumed per week and use of any illegal drugs were also recorded. Antibiotic therapy during the gestational period, including dates and indications, was also recorded. According to the prenatal care program protocol, women with symptomatic or asymptomatic bacteriuria (urine culture with >100,000 c.f.u.), were treated with nitrofurantoin for 10 days. Vaginal swabs for Gram-stained smears and for microbiological assessment from women who presented vaginal discharge with a fishy odor were taken. The presence of bacterial vaginosis was determined by Gram stain assessment.[25] Detection of *Trichomonas vaginalis* was done by wet mount and monilia by potassium hydroxide preparation. All women with vaginosis were treated with locally applied antibiotics, either metronidazole, clotrimazole, or nistatine, according to the results of microbiological examinations.

Periodontal Therapy

Periodontal therapy consisted of plaque control instructions, scaling, and root planing performed under local anesthesia. At the beginning of treatment, each woman was instructed to rinse once a day with 0.12% chlorhexidine. Periodontal therapy was completed before 28 weeks of gestation and maintenance therapy was provided every 2 to 3 weeks until delivery. Another complete periodontal examination was given after finishing the therapy. All measurements for a given woman were performed by the same examiner. Carious lesions were treated and all teeth indicated for extraction were extracted from both groups.

Women in the control group were monitored every 4 to 6 weeks during the gestational period to determine any change in their periodontal condition and another periodontal examination was performed after 28 weeks of gestation.

Assessment of Pregnancy Outcomes

Primary outcomes measured were preterm birth and low birth weight as they have been used in other studies aimed to determine association between adverse pregnancy outcomes and periodontal disease.[16,17,26] Preterm birth was defined as spontaneous delivery at less than 37 completed weeks of gestation[27] that followed spontaneous labor or spontaneous rupture of membranes, as there is considerable evidence that the risk factors for both are similar and the distinction is artificial.[28] Low birth weight (LBW) was assessed as positive when the infant had a birth weight under 2,500 g.[27] The birth outcome which occurred after 37 completed weeks of gestation or the birth of an infant with a weight ≥2,500 g was defined as normal.

Since the definition of preterm birth depends on accurate pregnancy dating, both obstetric and neonatal criteria were used. Estimation of gestational age was based on the last menstrual period, ultrasound examinations, sequential physical examinations, and post-natal examination. All women had an ultrasonographic examination between 9 to 24 weeks for gestational age dating and to rule out congenital anomalies. The criterion used to determine the gestational age was based on menstrual dates if it differed by less than 2 weeks from that determined by an ultrasound examination performed at ≤16 weeks of gestation. If the patient was unsure of her last menstrual period or there was more than a 2-week discrepancy between the gestational age based on menstrual dates and the ultrasound examination, the determination of gestational age was based on the ultrasound assessment if this examination had been done before 16 weeks of gestation. In the few cases in which the patient had no recorded last menstrual dates, or the ultrasound examination had been performed after 16 weeks of gestation, the obstetrical estimate was based on clinical judgment and on the pediatrician's estimate based on the Ballard et al. neonatal assessment.[29] Labor and delivery management decisions were made by the resident staff and attending physicians at the hospital. They had no knowledge that the patients were participating in a research study.

The records of patients who delivered before 37 completed weeks of gestation or who had infants weighing less than 2,500 g were reviewed by the obstetrician researcher of the study (JG) before a final gestational age assignment was made. An infant born at term (≥37 weeks of gestation) with a birth weight less than 2500 g was diagnosed as having an intrauterine growth restriction if the birth weight was in the tenth percentile for gestational age determined on the nomogram for Chilean newborn infants.[30] The obstetrician was masked from the mother's periodontal data.

Women who had a medically indicated preterm delivery that followed pregnancies complicated by maternal medical or obstetric disorders; e.g., preeclampsia or eclampsia, polyhidramnios, gestational diabetes, or placenta previa were excluded from the analysis.

Statistical Analysis

Women who delivered before 37 weeks of gestation (PTB) or had a low-birth-weigh infant (LBW) were grouped in the preterm/low-birth-weight group (PLBW) for the analyses of data to identify the risk factors. The analyses included descriptive statistics and both univariate and multivariate logistic regression analyses. Categorical variables were compared by the chi square test or Fisher's exact test and continuous variables by the unpaired *t* test. Multivariable logistic regression models were developed to identify the risk factors for PLBW starting with all variables included in a univariate analysis. A stepwise, multiple logistic regression was performed. Unadjusted and adjusted odds ratios were calculated with 95% confidence limits. Data to determine the odds ratios for PTB, LBW, and PLBW were analyzed on an intention-to-treat basis, regardless of compliance with protocol. The intention-to-treat analysis involved all patients who were randomly assigned and from whom the pregnancy outcomes were available. Odds ratios for PTB, LBW, and PLBW were also determined per protocol analysis. Statistical analysis was performed using a software program.‡ Statistical significance was defined as $P < 0.05$.

RESULTS

Of the 400 women enrolled, 49 (37 in the treatment group and 12 in the control group) women (12.7%) were excluded from the multivariate logistic regres-

‡ SAS, Version 6.12, Cary, NC.

sion analyses for different reasons. Of the 37 women excluded from the treatment group, 8 had spontaneous abortions; 5 had indicated preterm deliveries due to preeclampsia (n = 1), gestational diabetes (n = 1), placenta previa (n = 2), or polyhydramnios (n = 1); 18 withdrew from the periodontal treatment because they felt nauseous and uncomfortable during the treatment; and 6 were lost to follow up because they moved from the residential area and parturition data were not available. The 18 women who withdrew from periodontal therapy had a normal parturition but their periodontal status before delivery could not be assessed because they were not available for a new periodontal examination. Figure 1 shows the flow diagram of the progress through the phases of the study.

Of the 12 women in the control group who were excluded from the analyses, 6 had spontaneous abortions, 2 had indicated preterm deliveries due to preeclampsia (n = 1) and polyhidramnios (n = 1), and 4 were lost to follow up because they moved from the residential area. Three-hundred and fifty-three women finished the study, 163 in the treatment group and 188 in the control group.

Twenty-nine women in the treatment group (18%) had severe aggressive periodontitis and were given metronidazole 250 mg plus amoxicillin 500 mg 3 times a day for 7 days in addition to the mechanical treatment. Antibiotics were always prescribed in women with severe periodontitis after they had completed at least 16 weeks of gestation.

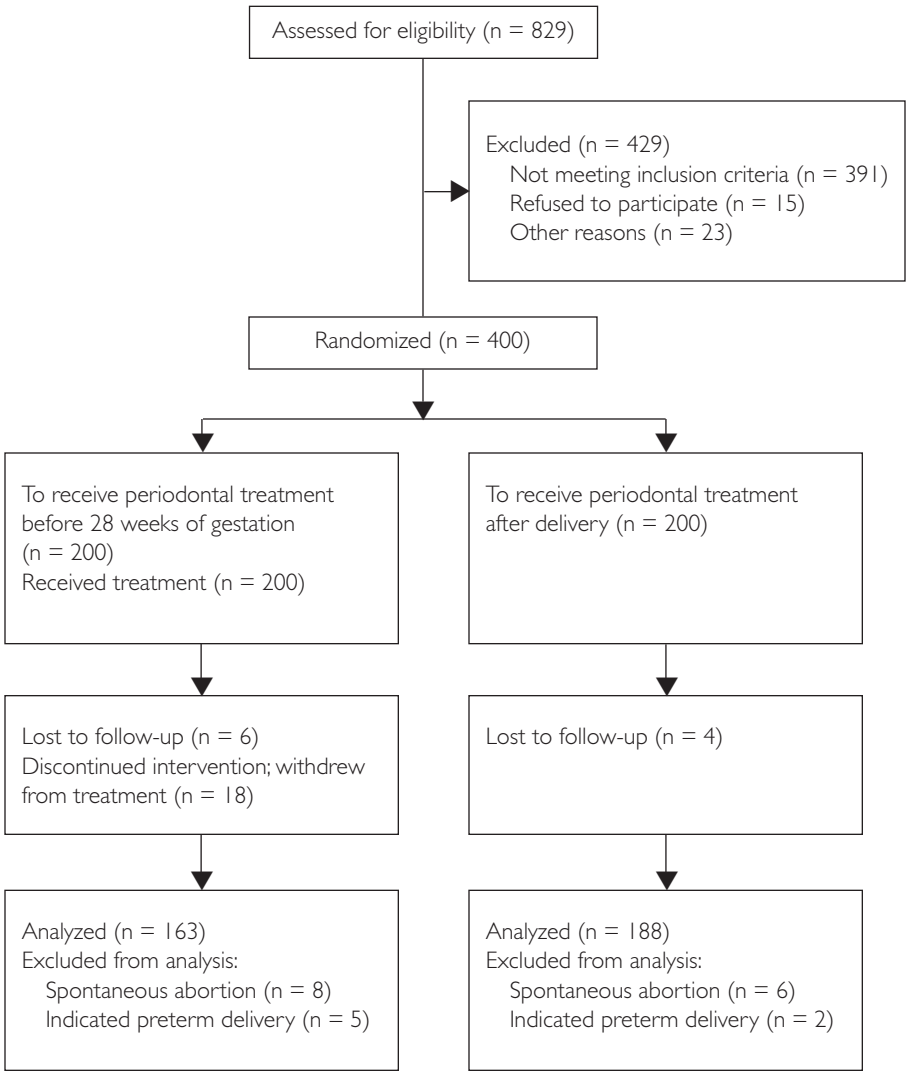

Figure 1.
Flow diagram.

The women in the present study were typically those of the Chilean population of low socioeconomic status. This is a mixture of Spanish and local aboriginal descent, predominantly Caucasian and with no black racial genetic component.[31] The mean age was 27.56 (SD ±4.38) years, 24.5% were single, 62.4% had less than 12 years of education, 24.5% smoked, and 23.6% were primiparous. The total number of multiparous women in both groups was 269, and 21 had a history of previous PLBW.

Table 1 shows the distribution of maternal characteristics of women in both groups at baseline. The treatment group had a mean age one year older than that of the control group ($P = 0.04$), as well as a higher percentage of single women ($P = 0.001$). The distribution of all other variables showed no significant differences between the groups. Alcohol consumption as a variable was eliminated from the study since 88% of the women did not drink alcohol during the gestational period and the remaining women drank less than 3 drinks a week.

Table 2 shows the distribution of women according to age. The majority of women in both groups was between 26 to 35 years old, with no statistical differences in the distribution by age in either group. The treatment group had a significantly higher mean gestational age (39.6 ± 1.2 versus 39 ± 2, $P = 0.002$), a higher infant mean weight (3,501 g ± 429 versus 3,344 ± 598, $P = 0.004$), and a significantly higher mean number of prenatal visits (9.4 ± 1.8 versus 7.9 ± 2.3) than the control group. Table 3 shows the periodontal characteristics of women in the treatment group at baseline and after receiving periodontal therapy, and

Table 1.

Characteristics of Patients at Baseline

Characteristic	Treatment Group (N = 163)	Control Group (N = 188)	*P* Value
Mean age	28 ± 4.5	27 ± 4.3	0.04
Percentage of single women	30.6	19.2	0.001
Parity	1.2 ± 0.9	1.4 ± 1.1	0.13
Percentage of women:			
Primiparous	21.47	25	0.43
With <12 years of education	33.4	40.8	0.18
With previous PLBW	4.3	7.4	0.21
With previous abortion	13.5	13.8	0.92
Who smoked	25.7	23.4	0.60
With urinary infection	18.4	14.9	0.37
With antibiotic therapy due to urinary infection	16.6	14.4	0.56
With vaginosis	25.1	17	0.061
Underweight	12.1	11.9	0.91
Normal weight	28.6	23	0.28
Overweight	20.2	24.6	0.39
Obese	39	40.8	0.81

Percentage or mean ± standard deviation. *P* values of the differences between both groups.

Table 2.

Distribution of Patients by Age

	Treatment Group		Control Group		Total		
	(N = 163)		(N = 188)		(N = 351)		
Age	N	%	N	%	N	%	*P* Value
18-20	12	7.3	12	6.3	24	6.8	0.47
21-25	42	25.7	55	29.2	97	27.5	0.87
26-30	54	33.1	72	38.8	126	36.1	0.63
31-35	55	33.7	49	26	104	29.6	0.52

P value of the differences between the treatment and the control group.

those of women in the control group at baseline and after 28 weeks of gestation. Women in both groups had moderate to severe marginal periodontitis, without significant differences between the groups at baseline. After receiving periodontal therapy, women in the treatment group showed periodontal parameters compatible with periodontal health and all the periodontal parameters showed statistically significant lower values than those of women in the control group (Table 3). The periodontal characteristics of women in the control group did not change significantly throughout pregnancy.

There were 22 preterm/low-weight-birth-infants (6.26%) in the 351 live births. Of these, 14 were due to premature birth (3.98%) and 8 were low-birth-weight infants (2.27%). The incidence of preterm birth (PTB), low birth weight (LBW), and of preterm/low birth weight (PLBW) are shown in Table 4 using the intention-to-treat analysis and per protocol analysis. The results of both analyses showed that women with periodontal disease had more than 5 times the incidence of PLBW and of PTB compared with women without periodontal disease. The rate of LBW was also higher in women with periodontal disease, but the difference was not statistically significant.

Table 5 shows the odds ratios for PTB, LBW, and PLBW in women with periodontal disease using the intention-to-treat analysis, and per protocol analysis. The results of both analyses show that the odds ratios of having a PTB or a PLBW for women with periodontal disease are higher than 5. The P values and the 95% confidence intervals show that the relationship between periodontal disease and these pregnancy outcomes is statistically significant. Even though the odds ratio for LBW in women with periodontal disease is higher than 6 using both the intention-to-treat and per protocol analyses, the odds ratios are not reliable due to the 95% confidence intervals including 1.

Infants with PLBW in the treatment group had a higher mean gestational age (34.4 ± 2.4 weeks versus 33.6 ± 4) and a higher mean birth weight (2,353 g ± 112 versus 2,156 ± 562) than in the control group, but the differences were not significant.

Five preterm births in the control group and the 2 preterm births in the treatment group were associated with premature rupture of membranes. Of the 2 PTB in the treatment group associated with premature rupture of membranes, one was complicated by acute maternal pyelonephritis which began at 31 weeks of gestation and the preterm delivery occurred at 32.5 weeks and the second was associated with recurrent vaginosis which began at 28 weeks of gestation and lasted until delivery, due to the lack of compliance to the antibiotic treatment.

None of the PLBW in the control group was complicated by placental abruption, trauma, urinary infection, vaginosis, venereal disease, substance abuse, clinical chorioamnionitis, birth deffects, genetic syndromes, or chromosomal aneupliody. None of the women received tocolytic agents or non-steroidal anti-inflammatory drugs.

Table 3.

Periodontal Characteristics of Treatment Group (N = 163) at Baseline and After Therapy and of Control Group (N = 188) at Baseline and After 28 Weeks of Gestation

Characteristic	Treatment Group at Baseline	Control Group at Baseline	*P* Value	Treatment Group After Therapy	Control Group After 28 Weeks of Gestation	*P* Value
N teeth	25.6 ± 2.9	24.57 ± 2.6	NS	25 ± 2.4	24.4 ± 2.7	0.093
% of sites with:						
Plaque	80 ± 19.2	83.4 ± 20.9	NS	41.8 ± 17.4	85.3 ± 16.2	0.001
BOP	49.9 ± 16.2	55.4 ± 19.8	NS	14.9 ± 2.4	62.5 ± 14	0.001
Redness	41.2 ± 26.8	44.3 ± 30.1	NS	7.6 ± 18.8	47.7 ± 27	0.001
PD 4-6 mm	20.9 ± 17.1	23.9 ± 14.2	NS	2.9 ± 3.9	27 ± 14	0.001
CAL ≥ 3 mm	28.7 ± 16.7	24 ± 18.8	NS	6.1 ± 7.8	25.4 ± 17.2	0.001
CAL > 3 mm	7.8 ± 5.8	6.4 ± 10	NS	1.3 ± 4.3	6.38 ± 10	0.032
Mean PD (mm)	2.71 ± 0.3	2.94 ± 0.42	NS	2.1 ± 0.3	2.98 ± 0.4	0.001
Mean CAL (mm)	1.86 ± 0.62	1.75 ± 0.73	NS	1.04 ± 0.68	1.84 ± 0.67	0.001

Percentage or mean ± standard deviation. *P* values of the differences between periodontal characteristics of the treatment and control group at baseline, and between the treatment group after therapy and the control group after 28 weeks of gestation.

Table 4.

Incidence of Preterm Births (PTB), Low Birth Weight (LBW), and Preterm/Low Birth Weight (PLBW)

	Treatment Group (N = 163)		Control Group (N = 188)		
	N	%	N	%	*P* Value
Intention-to-treat analysis					
PTB	2	1.10	12	6.38	0.017
LBW	1	0.55	7	3.72	0.083
PLBW	3	1.63	19	10.11	0.001
Protocol analysis					
PTB	2	1.22	12	6.38	0.001
LBW	1	0.61	7	3.72	0.11
PLBW	3	1.84	19	10.11	0.003

Women with PLBW (N = 22) had significantly more severe and extended gingival inflammation and poorer periodontal status than women with normal birth (N = 329) (Table 6).

Table 7 shows the results of the univariate analysis for risk factors for PLBW. Risk factors that had been considered in previous studies and those for which there was some biological basis were included. In this analysis, PLBW was significantly associated with the following variables: periodontal disease (OR, 5.99; 95% CI, 1.7 to 20.6), less than 6 prenatal visits (OR, 4.98; 95% CI, 2.02 to 12.2), a previous PTB (OR, 4.07; 95% CI, 1.2 to 13.4), and low maternal weight gain (OR, 3.25; 95% CI, 1.1 to 9.06). Other variables such as urinary infections, antibiotic treatment due to urinary infections, antibiotic treatment due to periodontal disease, vaginosis, multiparity (>3 children), primiparous condition, tobacco use, history of previous abortion, and beginning prenatal care after the 20 weeks of gestation did not influence the incidence of PLBW.

In the univariate analysis presented above, variables that appear to be risk factors of PLBW may be surrogates for other factors, thereby confounding the results. To control some of these interactions, a multiple logistic regression model was constructed in which the factors discussed above were examined. The results of the multivariate logistic regression analyses are shown in Table 8. The factors significantly associated with PLBW, in order of decreasing adjusted odds ratios, were periodontal disease (OR, 4.70; 95% CI, 1.29 to 17.13), a previous PLBW (OR, 3.98, 95% CI: 1.11 to 14.21), less than 6 prenatal visits (OR, 3.70; 95% CI, 1.46 to 9.38), and low maternal weight gain (OR, 3.42, 95% CI; 1.16 to 10.03). All the other variables included in this study were not significantly related to PLBW, and showed OR lower than 1 and 95% CI that included 1. Thus, after adjusting for all the other risk factors entered into the logistic regression model, women with periodontal disease have more than 4 times greater risk to have a PLBW than periodontally healthy women.

Table 9 shows the results of the univariate analysis for risk factors associated with PTB. Three out of the 4 risk factors that were found associated with PLBW were also associated with PTB. These factors were

Table 5.

Odds Ratios for Preterm Births (PTB), Low Birth Weight (LBW), and Preterm/Low Birth Weight (PLBW) in Women With Periodontal Disease

	Odds Ratio	95% CI	*P* Value
Intention-to-treat analysis			
PTB	6.10	1.3-28.53	0.008
LBW	6.96	0.81-59.62	0.037
PLBW	6.67	1.89-23.52	0.001
Protocol analysis			
PTB	5.48	1.17-27.71	0.014
LBW	6.26	0.73-53.78	0.052
PLBW	5.49	1.65-18.22	0.001

Table 6.

Periodontal Characteristics of Women With Normal Birth (NB) and Women With Preterm/Low Birth Weight (PLBW)

Characteristic	NB (N = 329)	PLBW (N = 22)	*P* Value
N teeth	24.7 ± 2.6	25.5 ± 2.4	0.17
% of bleeding sites	35.6 ± 25.4	52 ± 23.5	0.003
% of units with redness	26.1 ± 30.7	44 ± 37	0.036
Mean PD (mm)	2.53 ± 0.56	2.88 ± 0.51	0.006
% PD 4-6 mm	13.6 ± 14.6	21.8 ± 17.8	0.045
Mean attachment level (mm)	1.39 ± 0.78	1.81 ± 0.81	0.029
% attachment level ≥3 mm	15 ± 17	24 ± 17	0.028
% surfaces with plaque	63 ± 28	80 ± 26	0.007

periodontal disease, less than 6 prenatal visits, and a previous PTB. None of the other factors reached a significant level of association with PTB.

Figure 2 shows the probability of PLBW in association with the combination of the 4 significant risk factors identified in the present study. The combination of 2, 3, or 4 of the risk factors substantially increased the probabilities of PLBW. Periodontal disease combined with any of the other 3 factors increased the probability of PLBW in higher proportion than any other possible combination of these factors. A woman with periodontal disease, a previous PLBW, low weight gain, and less than 6 prenatal visits increased the probability of having another PLBW to 70.4%.

DISCUSSION

The method used in the present study attempted to control several of the known risk factors of PLBW. Women aged from 18 to 35 years were selected because maternal age under 18 and over 35 years has been found a risk factor for PLBW.[3] Only patients with a singleton gestation were included because the relationship between multiple gestation and preterm labor is well established.[3] Women were randomly assigned to each group equalizing periodontal disease as the relevant variable. As the study sample was obtained from a homogeneous population in relation to age and other demographic characteristics, it was assumed that the distribution of other variables would be similar in both groups of women. The only 2 significant differences in both groups at baseline were the mean age of women (28 versus 27) and the percentage of single women. Both factors were significantly higher in the treatment group. The difference of one year in the age of women is irrelevant since women in both groups were in the range of age in which this factor is not related to PLBW and there were no differences in the distribution of women by age in either group (Table 2). Unmarried women have been generally found to be at a higher rate of preterm birth than married women after adjusting for other related factors,[3] but in the present study, marital status was not found to be related to PLBW. Although proper random assignment prevents selection bias, it does not always guarantee that the groups are totally equivalent at baseline. Any differences in some baseline characteristics, as occurred in the present study, may be the result of chance rather than bias.[32] Women in the present study had free access to prenatal care services to reduce the risk of adverse birth outcomes. A relationship between the use of prenatal care and birth outcomes has been shown[33-35] and the beneficial effects of prenatal care are strongest among socially disadvantaged women.[35-37] Adequate utilization of this care has been associated with improved birth weights and a lower risk of preterm delivery.[38,39] In the present study, it was possible to control many of the known risk factors for PLBW, if the patients adequately used the prenatal care offered. Women with less than 6 prenatal visits or those who showed low weight gain during pregnancy inadequately utilized the prenatal care available and were at a higher risk of a PLBW.

After evaluating the relationship between many potential factors and PLBW in the present study, 4 significant associations were found: periodontal disease, previous PLBW, less than 6 prenatal visits, and low maternal weight gain. Of these, periodontal disease showed the strongest association in the univariate analysis and, after adjustment for confounding variables, showed an odds ratio of 4.70 (95% confidence

Table 7.

Unadjusted Odds Ratios for Preterm/Low Birth Weight Risk Factors

Risk Factor	Normal Birth (N = 329) N	%	PLBW (N = 22) N	%	Odds Ratio	*P* Value	95% CI
Periodontal disease							
Yes	169	89.9	19	10.1	5.99	0.001	1.7-20.6
No	160	98.2	3	1.8			
Less than 6 prenatal visits							
Yes	55	83.3	11	16.6	4.98	0.001	2.02-12.2
No	274	96.1	11	3.8			
Previous PLBW							
Yes	17	80.9	4	19	4.07	0.034	1.2-13.4
No	312	94.5	18	5.4			
Low maternal weight gain							
Yes	34	85	6	15	3.25	0.028	1.1-9.06
No	295	84.7	16	15.3			
Urinary infections							
Yes	54	93.1	4	6.9	1.13	0.77	0.36-3.47
No	275	93.8	18	6.1			
Antibiotic therapy due to urinary infection							
Yes	50	92.5	4	7.4	1.24	0.75	0.40-3.81
No	279	93.9	18	6			
Vaginosis							
Yes	70	95.8	3	4.1	0.58	0.58	0.16-2.03
No	259	93.1	19	6.8			
Primiparous							
Yes	78	95.1	4	4.8	0.71	0.55	0.23-2.17
No	251	93.3	18	6.6			
Onset of prenatal care after 20 weeks gestation							
Yes	146	95.4	7	4.5	0.58	0.25	0.22-1.5
No	183	92.4	15	7.5			
Tobacco use							
Yes	83	96.5	3	3.4	0.46	0.22	0.13-1.62
No	246	92.8	19	7.1			
Previous abortion							
Yes	45	93.7	3	6.3	0.99	0.99	0.28-3.5
No	284	93.7	19	6.3			

interval 1.29 to 17.13, Table 8) which suggests that it is an independent risk factor for PLBW. Although the estimates of odds ratios for the 4 risk factors associated with PLBW are high and statistically significant, the associated confidence intervals are rather wide, indicating some imprecision in these estimates. The wide confidence intervals are probably a consequence of the small frequencies of these 4 variables in the PLBW cells of the model (Table 7) and to the size of the sample used. The study aimed to achieve a sample size of 280 women in each group. After 160 deliveries had occurred in each group of women, an interim analysis was performed as previously planned, which revealed that the difference in PLBW rates between the groups reached a P value <0.05. For ethical reasons, it was decided to cease enrollment and stop the clinical trial.

Eighteen women in the treatment group withdrew from periodontal therapy because they felt uncomfortable during the treatment appointments. Data from the dental public services in Chile show that 12% of pregnant women usually abandon dental treatments during pregnancy.[40] Therefore, our 18 patients prob-

Table 8.

Multivariate Logistic Regression Model for Preterm/Low Birth Weight (PLBW)

Risk Factor	Parameter Estimate	Standard Error	Adjusted Odds Ratio	95% CI	*P* Value
Periodontal disease	1.5483	0.6595	4.70	1.29-17.13	0.018
Previous PLBW	1.3830	0.6486	3.98	1.11-14.21	0.033
Less than 6 prenatal visits	1.3097	0.4741	3.70	1.46-9.38	0.005
Low maternal weight gain	1.2310	0.5484	3.42	1.16-10.03	0.024

Table 9.

Unadjusted Odds Ratios for Preterm Birth Risk Factors

	Normal Birth (N = 329)		Preterm Birth (N = 22)				
Risk Factor	N	%	N	%	Odds Ratio	*P* Value	95% CI
Previous PLBW							
Yes	18	85.7	3	14.3	5.33	0.036	1.34-21.0
No	320	97	10	3			
Periodontal disease							
Yes	177	94.2	11	5.8	5.0	0.022	1.09-22.9
No	161	98.7	2	1.3			
Less than 6 prenatal visits							
Yes	55	83.4	11	16.6	4.98	0.005	2.02-12.28
No	274	96.2	11	3.8			
Urinary infections							
Yes	55	94.8	3	5.2	1.54	0.45	0.41-5.79
No	283	96.6	10	3.4			
Antibiotic therapy							
Yes	51	94.5	3	5.6	1.68	0.43	0.44-6.34
No	287	96.6	10	3.4			
Vaginosis							
Yes	73	100	0	0.0	1.05	0.079	1.02-1.07
No	265	93.1	19	6.9			
Primiparous							
Yes	81	98.8	1	1.2	0.26	0.31	0.03-2.06
No	257	95.5	12	4.5			
Tobacco use							
Yes	84	97.7	2	3.3	0.55	0.74	0.11-2.53
No	254	95.8	11	4.2			
Previous abortion							
Yes	46	95.8	2	4.2	1.15	0.69	0.24-5.35
No	292	96.3	11	3.7			

ably represent the proportion of Chilean pregnant women who abandon dental treatment in routine practice and is not an effect of treatment bias.

It has been recommended that the principle of intention-to-treat analysis be applied in reporting randomized controlled clinical trial results.[41,42] The intention-to-treat analysis was designed to compare patients in the groups to which they were originally randomly assigned in controlled trials. This is usually interpreted as including all patients, regardless of whether they actually satisfied the entry criteria, the treatment was actually received, and subsequent withdrawal or deviation from the protocol. However, there is no consensus about the validity of excluding specific cases within each of these categories from an intention-to-treat analysis.[43] Some authors have postulated that treatment effectiveness may be overestimated if an intention-to-treat analysis is not done.[44] However, in the current study, after including the 18 women who withdrew from periodontal treatment in the intention-to-treat analysis to determine the odds ratios for PTB, LBW, and PLBW, it was found that all the OR were higher than those obtained from the protocol analysis (Table 5). Thus, the effect of periodontal treatment to reduce PTB and PLBW appears overestimated when applying the intention-to-treat analysis. The inclusion of the 18 patients who withdrew from treatment in the intention-to-treat analysis assumes that they were periodontally healthy at the time of the delivery, or at least that the portion of periodontal treatment they had received had reduced the periodontal infection to a level that did not influence the pregnancy outcome. Since we could not assess the periodontal status of these patients before delivery, and it has been shown that the periodontal status of patients who do not comply with plaque control during treatment may deteriorate,[45,46] we preferred not to include these 18 women in the multivariate logistic regression analyses.

The results of the present study agree with those of a concurrent cohort study[18] that included 406 pregnant women with gingivitis or mild periodontitis who received treatment before 28 weeks

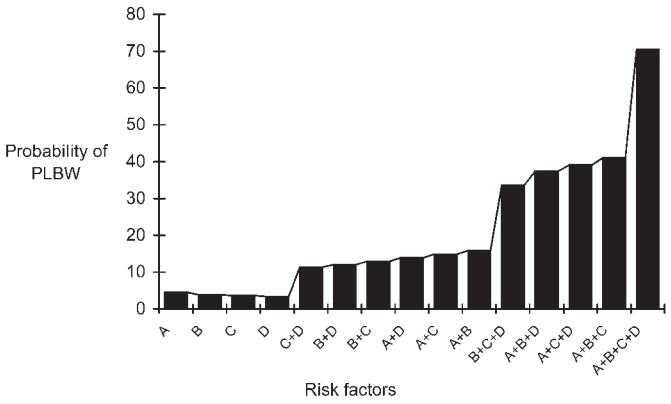

Figure 2.
Probability of PLBW in association with the combination of the 4 risk factors of PLBW. A: periodontal disease; B: a previous PLBW; C: low maternal weight gain; D: less than 6 prenatal visits.

of gestation and 233 women with periodontitis who were treated after delivery. In that study, the adjusted 3.5 risk ratio for women with periodontal disease to have a PLBW was lower than the OR of 4.7 found in the present study.

The other factors in the present analysis that were significantly associated with PLBW are consistent with the results of other studies.[18,33,38,47-50] Urinary infections and vaginosis are well known risk factors of PLBW.[6-10] There was a significant proportion of women in the present study who presented urinary infections and/or vaginosis, but no association was found between these variables and PLBW probably due to the adequate treatment of these infections. Since there is no data about the effect of oral nitrofurantoin on the progression of periodontal disease, the possible influence of this antibiotic on periodontal disease in the control group was investigated. No differences were found in the patients in the control group who received nitrofurantoin when we compared their periodontal characteristics at baseline with those after 28 weeks of gestation, and with those of the patients in the control group who did not receive nitrofurantoin (data not shown). Additionally, the logistic regression analyses detected no relationship between nitrofurantoin therapy and PLBW.

There is convincing evidence that maternal smoking is associated with LBW and with a moderately increased risk for PTB.[51,52] In the present study, the proportion of smokers was similar in both groups, and smoking did not show an association with PLBW. A dose-response relationship between smoking and LBW has been found, with birth weight impairments increasing with the number of cigarettes smoked.[3,53] In a study by Cnattingius et al.,[54] the odds ratio for preterm delivery among women who smoked 1 to 9 cigarettes per day and those who smoked ≥10 cigarettes per day as compared with non-smokers was 1.4 and 1.6, respectively. Of the 351 women in the present study, 126 women smoked ≥1 cigarettes per day. Of these, 107 (87.7%) smoked ≥5 cigarettes per day. As the percentage of women who smoked <4 cigarettes per day was low (12%) and considering that the risk of PTB has been found to increase with an increasing number of cigarettes smoked, we decided to use the case-definition of non-smoker as one who smoked <5 cigarettes per day. Thus, the result of the relationship between smoking and PLBW in the current study may have some limitations. Additionally, data about tobacco use in the present study were recorded at the time the women entered the study, and we did not verify if smoking continued during pregnancy. Prenatal care given to women in the present study involved health education and strong anti-smoking counseling to reduce or eliminate smoking during pregnancy. Therefore, a large percentage of smokers probably quit smoking, and this may explain the lack of association between PLBW and smoking.

Twenty-nine women in the treatment group were given metronidazole and amoxicillin because of severe periodontitis. It is possible that this antibiotic therapy may have controlled or eliminated other infections which may have also been a risk factor for PLBW. However, the univariate regression analyses did not show a relationship between PLBW and antibiotic treatment for periodontal disease.

The association between a previous PLBW and the current PLBW, with an odds ratio of 3.98, was the strongest risk factor found after periodontal disease, even though the prevalence of a previous PLBW was rather low (7.80%) in the multiparous women. Several other studies have found that a history of PLBW is a significant risk factor for PTB in subsequent pregnancies with adjusted odds ratios ranging between 2.45 to 6.2.[3,18,47-50] It is not known why a woman with a previous PLBW has a higher risk to have a subsequent one. It is possible that in women with a positive history of PLBW, the cause of the subsequent PLBW may be the same factor that caused the previous PLBW. Kramer[53] stated that only 25% to 30% of cases of PTB can be explained by identified risk factors. Until recently, there was no awareness that periodontal disease could be a risk factor for PLBW. However, according to the results of the present study, periodontal disease may be one of the unidentified risk factors in women with a history of previous PLBW.

The mechanisms by which periodontal disease might cause PLBW are still not known, but there is evidence that this association has biologically feasible bases. The role of prostaglandins (PG) in human labor has been well documented.[21] Increased amniotic fluid concentrations of PG, including PGE_2, have been shown in term and preterm labor,[55] and the stimulatory effect

of PGE_2 on myometrial contractility is also well known. There is also experimental evidence that interleukin-1β (IL-1β) might be involved in infection-induced preterm labor by interfering with the normal regulation of EP_1 receptor levels and with the promotion of increased PGE_2 production in amnion tissue.[56] Gingival crevicular fluid increases considerably in inflamed periodontal tissues and contains high levels of inflammatory mediators. It has been shown that increased levels of PGE_2 and IL-1β in gingival crevicular fluid in patients with periodontal disease were highly correlated with the levels of intra-amniotic PGE_2 and IL-1β.[23] Additionally, in a pregnant hamster model, subcutaneous infection with *Porphyromonas gingivalis,* a common periodontal pathogen, induced elevations in intra-amniotic PGE_2 and tumor necrosis factor-α and result in fetal growth restriction.[57] Recently, a prospective follow-up study among predominantly African-American primiparous women[58] found that the second trimester levels of serum antibody against *P. gingivalis* were related to LBW. These studies provided evidence that periodontal disease can produce an unfavorable change in the fetal environment and may be a sufficiently infectious challenge to produce PLBW.

The main characteristics of the current study can be summarized as follows: 1) periodontal disease was diagnosed before the third trimester of pregnancy, establishing that the exposure variable was present before the occurrence of outcomes. 2) The treatment and control groups were similar with respect to the risk factors for PLBW and were also comparable in the extent and severity of periodontal disease at baseline. 3) Periodontal therapy administered to the treatment group significantly changed the periodontal characteristics to the level of periodontal health. Thus, for the objective of the current study, to determine the association between periodontal disease and PLBW, women in the treatment group were periodontally healthy and without periodontal infection. 4) The periodontal characteristics of women in the control group did not change significantly during pregnancy, thus an effect of the passage of time, as a confounder factor in women in the control group, did not exist. 5) Women with PLBW exhibited significantly more severe periodontal disease than women with normal births, which may suggest a dose-response relationship.

The present study analyzed risk factor data for PLBW prospectively collected, fulfilling several of the criteria needed to assess the causal contribution of associated factors. To our knowledge, this represents the first effort to examine the relationship between periodontal disease and PLBW using a randomized controlled clinical trial. Additional studies using similar methodology in other populations are needed to corroborate these results.

CONCLUSIONS

Results of the present study showed that: 1) periodontal disease is an independent risk factor for PLBW and affords more than a 4-fold increase in the risk of PLBW; 2) other risk factors significantly associated with such deliveries in the population studied were a history of PLBW, less than 6 prenatal visits, and low maternal weight gain; and 3) periodontal therapy significantly reduces the rate of PLBW in women with periodontal disease.

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