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Higher Risk of Preterm Birth and Low Birth Weight in Women with Periodontal Disease

ABSTRACT

Pregnant women with periodontal disease (PD) may be at increased risk for having preterm low-birth-weight (PLBW) children. We investigated whether the maintenance of the mothers' periodontal health after 28 weeks' gestation reduces the risk of PLBW. Of the 639 women studied, 406 had gingivitis and received treatment before 28 weeks' gestation, and 233 had PD and were treated after delivery. Data about previous and current pregnancies and known risk factors were obtained from patients' medical records. Primary outcomes were delivery before 37 weeks' gestation or an infant with birth weight below 2500 g. The incidence of PLBW was 2.5% in periodontally healthy women, and 8.6% in women with PD ($p = 0.0004$, relative risk = 3.5, 95% CI, 1.7 to 7.3). Risk factors significantly associated with PLBW were previous PLBW, PD, fewer than 6 pre-natal visits, and low maternal weight gain. PD was associated with both preterm birth and low birth weight, independent of other risk factors.

KEY WORDS: preterm birth, low birthweight, periodontal disease/adverse effects, pregnancy, risk factors.

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INTRODUCTION

Low birth weight (LBW), a major determinant of neonatal infant morbidity and mortality (Kramer, 1987), has been treated as a single entity in most studies, although it can result from either preterm birth (PTB) or intra-uterine growth restriction, or both. A case-control study found that periodontal infection may be a potential independent risk factor for preterm low birth weight (PLBW) (Offenbacher *et al*., 1996), and two prospective studies showed an association between preterm birth and periodontal infection (Jeffcoat *et al*., 2001; Mitchell-Lewis *et al*., 2001).

Periodontal diseases are a group of infectious diseases caused by predominantly Gram-negative, anaerobic, and microaerophilic bacteria that colonize the subgingival area. Inflamed periodontal tissues produce significant amounts of pro-inflammatory cytokines, mainly interleukin 1 beta (IL-1β), IL-6, prostaglandin E_2, and tumor necrosis factor alpha (TNF-α), which may have systemic effects on the host.

We undertook a concurrent cohort study with intervention to determine the association between periodontal disease and preterm low birth weight. Two groups of pregnant women were used: a group of women with gingivitis or mild periodontitis who received periodontal treatment before 28 weeks' gestation, and a group of women with periodontal disease who received no periodontal treatment during pregnancy. For the objective of the current study, to determine the relationship between periodontal disease and adverse delivery outcomes, women with gingivitis or mild periodontitis treated before 28 weeks' gestation were periodontally healthy and without periodontal infection, and were used as a comparison group.

The null hypothesis tested was that there are no significant differences in the incidence of preterm low birth weight in women with periodontal disease compared with that of periodontally healthy women.

MATERIALS & METHODS

Patient Population

The study population consisted of pregnant women of low socio-economic status who received uniform pre-natal care in a public health clinic in Santiago, Chile, and delivered at El Salvador Hospital between April, 1998, and December, 2000. Routine pre-natal care included screening for pregnancy complications, nutritional advice, stress reduction, education about the symptoms of preterm labor, correction of identified risk factors, and referral to the high-risk obstetric clinic when appropriate.

Selection of Subjects

Criteria for inclusion were: women aged 18 to 35, with singleton gestation, before 21 weeks' gestation. Exclusion criteria included: fewer than 18 teeth, indication of prophylactic antibiotics for invasive procedures, or diabetes.

Potential participants were identified by the midwives who attended the pre-natal care clinics. A total of 945 women who gave verbal consent to a dental examination were referred to the investigators. All of these women received a clinical oral examination, the patient records were thoroughly examined, relevant data were extracted, and eligibility for the study was determined. Of the 945 women, 45 were ineligible because they declared intention to deliver at a hospital different from that of the study, and 19 refused to participate. In total, 881 women were selected.

Measurement of Periodontal Status

A clinical periodontal examination was performed on all the women by two calibrated examiners using a calibrated periodontal probe (University of North Carolina No. 15 probe; Hu-Friedy, Chicago, IL, USA). Both of the examiners are periodontologists (authors NJL and PS). The following variables were determined: oral hygiene status, gingival inflammation, probing depth, and clinical attachment level measurements. Oral hygiene status was assessed as the percentage of surfaces demonstrating plaque. Probing depth and attachment level measurements were performed at six sites on each tooth. Gingival bleeding was assessed on the sites at which probing depth was measured. Gingival redness was determined on two gingival units *per* tooth.

Dental examinations and periodontal treatment were performed in a dental clinic located in the pre-natal care center.

Criteria for Periodontal Diagnosis

The presence of 4 or more teeth showing one or more sites with probing depth 4 mm or higher, and with clinical attachment loss 3 mm or higher at the same site, was diagnosed as periodontal disease. These criteria were selected for the clinical definition of patients who positively and unequivocally exhibited periodontal disease.

All of the women who did not fulfill all of the criteria for periodontal disease showed gingival redness and bleeding on probing at more than 25% of sites and were diagnosed as having gingivitis or mild periodontitis.

Of the 881 women who were selected to participate in the study, 263 had periodontal disease, and 618 had gingivitis or mild periodontitis. Of these women, 159 refused to receive periodontal treatment during pregnancy, but they accepted a new periodontal examination between 28 and 30 weeks' gestation. The results of the analyses of women with untreated gingivitis will be reported in the near future. An informed written consent was obtained from each volunteer, and the study protocol was approved by the institutional review board.

Periodontal Intervention

Four hundred and fifty-nine women with gingivitis received treatment which consisted of plaque control instructions and supra- and subgingival scaling. Subgingival scaling was performed for some women under local anesthesia when necessary. A 0.12% chlorhexidine solution for use as a mouthrinse once a day was given to each woman. The treatment was finished for all women before 28 weeks of gestation, and maintenance treatment was given every 2-3 weeks until delivery.

Two hundred and sixty-three women with periodontal disease received no periodontal treatment during pregnancy, and they were monitored every 4-6 weeks during the gestational period so that any worsening of their periodontal status could be detected. All of the women with periodontal disease were treated after delivery.

Caries lesions were treated, and teeth indicated for extraction were extracted from all patients. A new periodontal examination was performed between 28 and 30 weeks' gestation.

Recording of Maternal Characteristics

Demographic factors and detailed data about previous and the current pregnancies, as well as information on known risk and obstetric factors, were obtained from the patients' medical records and from interviews during the pre-natal visits.

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 weight range for her weight-to-height proportion. According to the weight gain, women were assigned to one of the following categories: underweight, normal weight, overweight, or obese.

Pre-natal care was categorized as that starting before 12 weeks' gestation, between 13 and 20 weeks' gestation, or after 20 weeks' gestation. The number of pre-natal visits and the onset of pre-natal care were used for assessment of the adequacy of pre-natal care. Cigarette smoking and the number of alcoholic drinks consumed *per* week were recorded. Smoking more than 5 cigarettes *per* day was considered tobacco abuse. According to the protocol of the pre-natal care program, women with urinary infections or with asymptomatic bacteriuria were treated with oral nitrofurantoin for 10 days. Women with vaginosis were treated with locally applied antibiotics according to the results of the microbiological culture.

Definition of Pregnancy Outcomes

Primary outcomes measured were preterm birth and low birth weight. Preterm birth was defined as delivery at fewer than 37 completed weeks' gestation, and low birth weight as delivery of an infant with a birth weight under 2500 g (World Health Organization, 1984). Estimation of gestational age was based on the date of the last menstrual period, ultrasound examinations, sequential physical examinations, and post-natal examination. The records of women who delivered an infant before 37 completed weeks' gestation, or an infant with a birth weight under 2500 g, were reviewed by an obstetrician (author JG) before a final gestational age assignment was made. The obstetrician had no knowledge of the mother's periodontal data.

For the analyses of data, women were grouped according to pregnancy outcomes into: a preterm-birth group (PTB) if they delivered before 37 weeks of gestation, a low-birth-weight group (LBW) if they delivered a baby with a birth weight under 2500 g, and a preterm/low-birth-weight group (PLBW) if they delivered either a preterm or a low-birth-weight baby.

Statistical Analysis

Analyses included descriptive statistics and univariate/multivariate logistic regression analyses. Categorical variables were compared by the chi-square test or Fisher's exact test and continuous variables by the Student's *t* test. Univariate and multivariate logistic regression analyses were constructed for preterm birth, low birth weight, and for preterm low birth weight, starting with all variables included in the univariate analyses.

Unadjusted and adjusted risk ratios were calculated with 95% confidence intervals. Statistical analysis was performed with the SAS system (version 6.12, Cary, NC, USA). Statistical significance was defined as $P < 0.05$.

Table 1. Characteristics of Women

Characteristic	Periodontally Healthy	With Periodontal Disease	P Value
Mean age	24.1 ± 4.6[a]	27.1 ± 4.3	< 0.0001
Parity	0.6 ± 0.9	1.2 ± 1.2	< 0.0001
Percentage of women:			
single	27.6	19.6	0.24
primiparous	50.0	24.5	< 0.0001
< 12 yrs educ.	32.0	39.0	0.088
previous preterm low birth weight	3.5	6.4	0.08
with previous abortion	6.7	13.7	0.003
who smoked	15.0	21.4	0.038
with urinary infection	12.6	15.0	0.38
with vaginosis	17.7	20.6	0.37
underweight	14.8	11.1	0.19
of normal weight	31.7	22.7	0.01
overweight	29.8	23.6	0.11
obese	24.1	42.5	0.0001
with fewer than 6 pre-natal visits	7.4	12.0	0.050
Mean number of pre-natal visits	8.8 ± 1.9	8.1 ± 2.2	< 0.0001
Infant mean weight	3364 ± 468	3297 ± 502	0.36
Onset of pre-natal care:			
before 12 wks' gestation	38.0	29.6	0.033
between 13 and 20 wks' gestation	37.7	46.4	0.031
after 20 wks' gestation	24.4	24.0	0.92
Mean wks of gestational period	39.3 ± 1.0	39.1 ± 1.9	0.10

[a] Mean ± standard deviation.

Table 2. Periodontal Characteristics of Patients

Characteristic	Periodontally Healthy	With Periodontal Disease	P Value
Number of teeth	25.6 ± 2.2[a]	24.6 ± 2.8	0.001
Percentage of sites with:			
plaque	33.0 ± 18.7	83.8 ± 15.0	< 0.0001
bleeding on probing	13.9 ± 8.1	52.6 ± 18.8	< 0.0001
gingival redness	2.4 ± 3.6	42.2 ± 29.0	< 0.0001
probing depth ≥ 4 mm	1.2 ± 1.4	25.5 ± 15.6	< 0.0001
attachment level sites > 3 mm	0.3 ± 0.2	8.1 ± 11.7	< 0.0001
attachment level sites ≥ 3 mm	1.1 ± 0.7	27.7 ± 20.6	< 0.0001
Mean probing depth (mm)	2.0 ± 0.5	3.0 ± 0.5	< 0.0001
Mean attachment level (mm)	0.8 ± 0.6	1.9 ± 0.8	< 0.0001

[a] Percentage or mean ± standard deviation.

RESULTS

Of the 722 women enrolled in the study, 83 (11.5%) were excluded for various reasons. Of these, 53 (11.5%) were in the group of periodontally healthy women and 30 (11.2%) in the group with periodontal disease. Of the excluded women, 60 were lost to follow-up, 14 had a spontaneous abortion, and nine had medically indicated preterm delivery due to pre-eclampsia, gestational diabetes, or polyhydroamnios. There were 639 women who finished. Of these, 406 were in the group of periodontally healthy women and 233 in the group with periodontal disease.

The mean age of the women was 25 (SD ± 4.5), 24.4% were single, 35.5% had fewer than 12 years of education, 40.8% were primiparous, and 18.3% were smokers. Alcohol consumption, as a variable, was eliminated from the analyses, since no woman declared drinking more than 2 drinks *per* week.

The total incidence of PLBW was 4.7% (30/639). Of these, 18 were preterm births and 12 were low-birth-weight infants. The incidence of PLBW was 2.5% (10/406) in periodontally healthy women and 8.6% (20/233) (P = 0.001) in women with periodontal disease. The relative risk for a woman with periodontal disease having a PLBW was 3.5 (95% confidence interval 1.7 to 7.3; P = 0.004).

The total incidence of preterm birth was 2.8% (18/639). The incidence was 1.5% (6/406) in periodontally healthy women and 5.2% (12/233) (P = 0.014) in women with periodontal disease. The relative risk for a woman with periodontal disease having a preterm birth was 3.5 (95% confidence interval 1.3 to 9.2; P = 0.006).

The total incidence of low birth weight was 1.9% (12/639). It was 1.0% (4/406) in periodontally healthy women and 3.4% (8/233) (P = 0.024) in women with periodontal disease. The relative risk for a woman with periodontal disease of having a low-birth-weight infant was 3.5 (95% confidence interval 1.06 to 11.4; P = 0.028).

Table 1 shows the distribution of maternal characteristics in both groups of women. The group with periodontal disease had a significantly higher mean age, mean number of children, a higher ratio of previous abortion, of women who were smokers, obese, who had fewer than 6 pre-natal visits, and who began the pre-natal control between 13 and 20 weeks of gestation.

The periodontal characteristics of women with periodontal disease showed that they had moderate to severe periodontal disease, while those of women who were treated were compatible with a healthy gingival and a healthy periodontal status (Table 2). No woman with periodontal disease showed a clinical worsening of her periodontitis during the gestational period.

Women with PLBW had significantly more severe and extended gingival inflammation and poorer periodontal status than women with normal parturition.

In the univariate analysis for PLBW, a significant association was found with a previous PLBW, fewer than 6 pre-natal visits, periodontal disease, a previous abortion, and low maternal weight gain (Table 3). Maternal overweight showed a significant negative association with PLBW. No significant association was found between the other variables studied (parity, single status, fewer than 12 years of education, primiparous, cigarette smoking, urinary infection, vaginosis, mean number of pre-natal visits) and PLBW.

In the univariate analysis for preterm birth, significant associations with a previous PLBW (risk ratio 9.06, 95% confidence interval 3.5 to 23.5; P = < 0.0001) and periodontal disease (risk ratio 3.5, 95% confidence interval 1.3 to 9.1; P = 0.006) were found. Periodontal disease was the only risk factor significantly associated with LBW in the univariate analysis (risk ratio 3.5, 95% confidence interval 1.06 to 11.4; P = 0.028).

Table 4 shows the results of multivariate logistic regression analyses for PLBW and for PTB. In order of decreasing risk ratios, the risk factors associated with PLBW were: a previous PLBW, fewer than 6 pre-natal visits, periodontal disease, and low maternal weight gain. Except for low maternal weight gain that did not reach the significant level, the other factors associated with PLBW were also associated with PTB.

The risk factors for LBW were periodontal disease (adjusted risk ratio 3.6, 95% confidence interval 1.07 to 12.2; P = 0.028), and onset of pre-natal care after 20 weeks of gestation (adjusted risk ratio 3.3, 95% confidence interval 1.03 to 10.3; P = 0.034).

Table 3. Unadjusted Risk Ratios for Risk Factors Associated with Preterm Birth/Low Birth Weight

Risk Factor	Preterm Low Birth Weight	Normal Birth	Risk Ratio	95% Confidence Interval	P Value
Previous PLBW					
Yes	6 (20.6)	23 (79.3)			
No	24 (3.9)	586 (96.0)	5.3	2.3-11.9	< 0.0001
Fewer than 6 pre-natal visits					
Yes	10 (17.8)	46 (82.1)			
No	20 (3.4)	563 (96.5)	5.2	2.6-10.6	< 0.0001
Periodontal disease					
Yes	20 (8.5)	213 (91.4)			
No	10 (2.4)	396 (97.5)	3.5	1.7-7.3	0.0004
Previous abortion					
Yes	6 (10.1)	53 (89.9)			
No	24 (4.1)	556 (95.8)	2.5	1.0-5.8	0.036
Low maternal weight gain					
Yes	8 (9.3)	78 (90.7)			
No	22 (4.0)	531 (96.0)	2.3	1.1-5.1	0.029
Overweight					
Yes	3 (1.7)	171 (98.2)			
No	27 (5.8)	438 (94.2)	0.3	0.1-1.0	0.029

Table 4. Adjusted Risk Ratios, 95% Confidence Intervals (CI), and P Values for Risk Factors Associated with Preterm Birth/Low Birth Weight (PLBW) and with Preterm Birth (PTB)

Risk Factor	Risk Ratio for PLBW	95% CI	P Value	Risk Ratio for PTB	95% CI	P Value
Previous PLBW	4.8	1.6-14.0	0.0004	7.5	2.2-24.8	0.001
Fewer than 6 pre-natal visits	4.7	1.9-11.1	< 0.0001	7.5	2.6-20.6	0.0001
Periodontal disease	3.5	1.5- 7.9	0.003	2.9	1.0- 8.1	0.045
Low maternal weight gain	2.6	1.1- 6.5	0.030	-	-	-

DISCUSSION

Patients in our study were relatively homogeneous, based on social and demographic factors reported as related to PLBW. The distribution of several known risk factors for PLBW was similar in both groups (Table 2). However, there were significant differences between the groups in the distribution of other variables which may also be associated with PLBW. Nevertheless, none of these variables whose distribution was different between the groups resulted in being a risk factor for PTB or LBW. To control the effect of maternal age as a risk factor for PTB and LBW (Wen *et al*., 1990; Carmichael and Abrams, 1997), we included in the study only women aged 18 to 35.

The definition of preterm birth used in our study includes births that followed spontaneous labor or spontaneous rupture of membranes, because there is considerable evidence that the risk factors for both are similar, and the distinction is artificial (Guinn *et al*., 1995). Since the determinants of PTB and intra-uterine growth restriction appear to differ (Kramer, 1987), we analyzed our data evaluating the risk factors for the two components of low birth weight together, and for each of the components individually, to determine which risk factors affect PTB and which LBW. Relatively few significant associations were found. The risk factors that showed significant association with PLBW were a previous PLBW, periodontal disease, fewer than 6 pre-natal visits, and low maternal weight gain.

The factors exhibiting the largest risk ratios for PLBW and for PTB were a previous PLBW and fewer than 6 pre-natal visits. However, periodontal disease was the only risk factor associated with both PTB and LBW. The relationship between periodontal disease and PTB, and periodontal disease and LBW, was consistently maintained without substantial changes

after adjustment for other risk factors and covariates in the logistic regression models constructed. These observations strongly suggest that periodontal disease is an independent risk factor for both PTB and LBW.

The risk factors associated with PTB and LBW in our study are in concordance with those reported in several other studies. A previous history of PLBW is one of the most important risk factors for a subsequent PTB (Guick *et al.,* 1984; Hediger *et al.,* 1989; Wen *et al.,* 1990; de Hass *et al*., 1991; Berkowitz and Papiernik, 1993), and low maternal weight gain has also been shown to increase the risk of PTB in several studies (Kramer, 1987; Abrams *et al.*, 1989; Hediger *et al*., 1989; Carmichael and Abrams, 1997).

Low maternal weight gain and inadequate pre-natal care are risk factors considered weakly associated with PTB in retrospective studies (Abrams *et al.*, 1989; Carmichael and Abrams, 1997). However, in our study, fewer than 6 pre-natal visits showed adjusted risk ratio values that were consistently associated with PLBW and with PTB.

Inadequate pre-natal care is often cited as a risk factor for poor pregnancy outcomes in low socio-economic status and poorly educated women (Sokol *et al*., 1980; United States General Accounting Office, 1987). Several studies have shown that adequate utilization of pre-natal care is associated with improved birth weights and lower risk of PTB (Quick *et al*., 1981; Greenberg, 1983; Donaldson and Billy, 1984). The women in our study had free access to a well-designed pre-natal care program to control many of the known risk factors for PLBW. Free provision of pre-natal care is advisable as an effective means of reducing preterm births based on the observation that PTB is less likely among women who seek pre-natal care early or have more pre-natal visits. The results of our study agree with those of studies showing that making more pre-natal care available to women does not reduce preterm births (Fink *et al.,* 1992; Fiscella, 1995).

Urinary infections and vaginosis are well-known risk factors for PLBW (Romero and Mazor, 1988; Holst *et al.,* 1994; Paige *et al.,* 1998). However, these factors were not associated with PLBW in our study, probably because the antibiotic therapy given to the women could either eliminate these infections or modify their effects on the pregnancy outcome. Cigarette smoking has been related to PTB and LBW (Shiono *et al.,* 1986; Kierse, 1989), but this factor was not associated with any of the pregnancy outcomes in our study, probably due to the low proportion of women who smoked.

Periodontal disease has been only recently identified as a potential risk factor for PLBW (Offenbacher *et al.,* 1996), and it might be one of the factors associated with some of the approximately 50% of preterm births that occur in women without established risk factors (Kramer, 1987).

The mechanisms by which periodontal disease may cause preterm LBW or PTB have still not been elucidated, but there is evidence that this association has biologically feasible bases. It has been suggested (Offenbacher *et al.,* 1996) that the effect of periodontal disease on PLBW could result from stimulation of fetal membranes on prostaglandin synthesis by cytokines produced by inflamed gingival tissues, or through the effect of endotoxin derived from periodontal infection. Endotoxin can stimulate prostaglandin production by macrophage amnion (Romero *et al.,* 1988) and decidua *in vitro* (Romero *et al.,* 1989). In animal models, it has been shown that endotoxin produces fetal growth retardation (Beckman *et al.,* 1993; Offenbacher *et al.,* 1998). On the other hand, peripheral monocytes obtained from some patients with periodontal disease showed enhanced release of inflammatory mediators such as PGE_2, IL-β, and TNF-α, when challenged with bacterial endotoxin (Shapira *et al.,* 1994; Salvi *et al.,* 1997). Endotoxin derived from periodontal pathogens in women with periodontal disease might signal preterm labor through primed monocyte-macrophage activation in peripheral blood and decidua.

The results of our study, in which all evaluations were conducted before the babies were born, show that periodontal disease is an independent risk factor for PLBW and affords more than a three-fold increase in the risk for PTB and for LBW. These adverse pregnancy outcomes are frequently associated with potentially correctable lifestyles, or with infectious diseases that, like periodontal disease, can be eliminated prior to or during pregnancy.

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