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Maternal periodontitis and adverse pregnancy outcomes

Waranuch Pitiphat[1,2,3], Kaumudi J. Joshipura[1,2,4], Matthew W. Gillman[5,6], Paige L. Williams[7], Chester W. Douglass[1, 2] and Janet W. Rich-Edwards[2,5,8]

[1]Department of Oral Health Policy & Epidemiology, Harvard School of Dental Medicine, Boston, MA, USA, [2]Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA, [3]Department of Community Dentistry, Faculty of Dentistry, Khon Kaen University, Khon Kaen, Thailand, [4]Division of Dental Public Health, School of Dentistry University of Puerto Rico, San Juan, Puerto Rico, [5]Department of Ambulatory Care and Prevention, Harvard Medical School and Harvard Pilgrim Health Care, Boston, MA, USA, [6]Department of Nutrition, Harvard School of Public Health, Boston, MA, USA, [7]Department of Biostatistics, Harvard School of Public Health, Boston, MA, USA, [8]The Channing Laboratory, Harvard Medical School and Brigham and Women's Hospital, Boston, MA, USA

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Abstract – *Objectives:* Maternal periodontal diseases have been associated with increased risk of preterm birth and restricted fetal growth among relatively low socioeconomic groups. Whether the association can be generalized to middle-class populations remains uncertain. We evaluated periodontitis in relation to preterm birth (<37 weeks' gestation) and small-for-gestational-age (SGA, birth weight below the 10th percentile of birth weight for gestational age) among a group of medically insured women. *Methods:* We conducted a prospective study among participants of Project Viva, a US cohort study of pregnant women and their offspring from 1999 to 2002. Pregnancy outcomes were obtained from medical records. Self-reported periodontitis was assessed during the second trimester of pregnancy, and validated against radiographs. Logistic regression analyses were employed to evaluate the association of periodontitis with pregnancy outcomes adjusted for age, race/ethnicity, smoking status, income, frequency of dental check-ups, prepregnancy body mass index, pregnancy weight gain, gravidity, prior history of preterm birth and history of genitourinary infection. *Results:* Of the 1635 women, 72.7% were Caucasian, 65.0% had annual household income >$70 000, 3.8% reported having periodontitis, 6.4% delivered preterm, 5.4% delivered SGA babies, and 11.0% had poor pregnancy outcome (either preterm birth or SGA). The odds ratio (OR) associated with periodontitis was 1.74 (95% CI 0.65–4.66) for preterm delivery and 2.11 (95% CI 0.76–5.86) for SGA individually. When preterm delivery and/or SGA were combined, the OR was 2.26 (95% CI 1.05–4.85) relating periodontitis with poor pregnancy outcome. *Conclusion:* Within the limitations of the study, the results suggest that periodontitis is an independent risk factor for poor pregnancy outcome among middle-class women.

Key words: periodontitis; preterm birth; small for gestational age

Dr Waranuch Pitiphat, Department of Community Dentistry, Faculty of Dentistry, Khon Kaen University, Khon Kaen 40002, Thailand
Tel: +66-43-362-104
Fax: +66-43-202-862
e-mail: waranuch@post.harvard.edu

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Systemic maternal infections are hypothesized to raise the risk of placental infection, premature rupture of membranes, premature labor and preterm birth by release of inflammatory cytokines and increased prostaglandin production (1, 2). Periodontal disease is a chronic, low-grade, gram-negative anaerobic infection of periodontal tissues that is associated with an increase in the systemic levels of inflammatory cytokines (3). Periodontal organisms have been isolated from the amniotic fluid, suggesting the possibility of hematogenous spread (4, 5). Periodontal disease could potentially influence pregnancy outcomes through indirect mechanisms involving inflammatory cytokines or direct translocation of bacteria and its products to the fetoplacental unit.

Previous epidemiologic studies have reported positive associations between periodontal disease and adverse pregnancy outcomes including preterm low birth weight (6, 7), low birth weight (7, 8), preterm birth (9), fetal growth restriction (10), and pre-eclampsia (11). Small intervention studies suggest a reduction in the risks of preterm birth (12) and preterm low birth weight (13) after mechanical periodontal therapy during pregnancy. Most of the studies with positive findings were conducted among minorities and women of lower socioeconomic position, while a recent study conducted

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among predominantly white women reported no association between either preterm birth or low birth weight and periodontal disease (14). Hence, additional studies are needed to clarify whether periodontal disease is independently associated with adverse pregnancy outcomes among non-low-income or other populations. To address this issue, we prospectively evaluated periodontitis in relation to preterm birth and small-for-gestational-age (SGA) birth in a group of medically insured women enrolled in Project Viva.

Methods

Project Viva

Project Viva is a prospective cohort study of prenatal diet, pregnancy outcomes, and offspring health. Women attending their first prenatal visit at one of eight Harvard Vanguard Medical Associates centers in Eastern Massachusetts were approached to participate in the study. Women were ineligible if they had a multiple gestation, could not answer questions in English, intended to move away before delivery, or had gestational age greater than 22 completed weeks at the first prenatal visit. Details of recruitment and data collection are available elsewhere (15). We enrolled 2670 consenting women (64% of those eligible) between April 22, 1999 and July 31, 2002, of whom 329 subsequently became ineligible because of multiple gestations ($n = 19$), transfer of obstetric care to a nonstudy site ($n = 115$), or because they were no longer pregnant ($n = 195$). Of the 2341 remaining participants, 195 (8%) withdrew and 18 (<1%) were lost to follow-up, leaving 2128 who delivered a live infant. The Institutional Review Boards of the participating institutions approved the research protocol. All procedures were in accordance with the ethical standards for human experimentation established by the Declaration of Helsinki (16).

Subject characteristics

In the present study, we included women with live births who also completed a dental questionnaire in the second trimester of pregnancy. Periodontitis was determined by a question 'Have you ever been told by a dentist or dental hygienist that you have periodontal disease (gum disease with bone loss)?' Of the 1666 responders, 62 (3.7%) reported yes, 1573 (94.4%) no, and 31 (1.9%) did not know. We limited our analysis to the 1635 women who reported their periodontal status. Of these women, 72.7% were white, 12.7% black, 5.5% Asian, 5.5% Hispanic and 3.6% other race/ethnicity, closely reflecting the profile of the US population (17).

Validation of self-reported periodontitis.

Among the 1666 women who responded to the dental questionnaire, 1501 (90.1%) reported having dental radiographs taken within the past 5 years. There were 1429 women who both had dental radiographs and continued to participate in Project Viva 8 months after delivery. We wrote to these women requesting dental radiographs or contact information of their dentist who might have the radiographs. After obtaining written consent, we contacted the dentist to send us bitewing radiographs taken before the date of delivery. We were able to obtain radiographs for 354 participants (80.6% of the 439 women who provided consent). Prevalence of self-reported periodontitis in this subgroup (3.7%) was similar to the prevalence in the whole population with self-report (3.7%), although the subgroup had a higher proportion of whites and women with higher SES (data not shown).

We evaluated the validity of self-reported periodontitis using radiographs as a standard. Women who reported periodontitis had significantly higher mean radiographic alveolar bone loss (1.54 ± 0.54 mm, SD) than those who did not (0.70 ± 0.33 mm, Wilcoxon test $P < 0.001$). Self-report had a sensitivity of 18.4%, a specificity of 98.7%, positive predictive value of 69.2%, and negative predictive value of 88.1% against radiographically diagnosed periodontitis (at least one site with bone loss ≥3 mm). In a recent systematic review of validation of self-reported periodontal disease, Blicher et al. (18) considered a measure to have good validity when the sum of either sensitivity plus specificity or positive plus negative predictive values was 120% or above. In this case, the sum of positive plus negative predictive values was 157.3% and the sum of sensitivity and specificity 117.1% which seems reasonably valid. As shown in our earlier manuscript (19), most of the misclassification is likely to be among people with mild disease, which has a smaller impact on the observed association than misclassification of the extremes. Importantly, there is no reason to believe that the misclassification is different among women with and without adverse pregnancy outcomes; hence, the random misclassification is likely to result in an underestimate of the association.

We reviewed hospital records for birth weight and delivery information. Gestational age was determined by recalled last menstrual period. If it differed from the second trimester ultrasound estimate by 10 days or more, the ultrasound estimate was used. We defined preterm birth as birth prior to 37 completed weeks of gestation. SGA was defined as birth weight below the 10th percentile of birth weight for gestational age using a continuous measure based on the US national reference population (20). Poor pregnancy outcome was defined as the presence of either preterm birth or SGA. Birth weight data were missing for three participants.

We obtained information on demographics, medical and reproductive history, smoking, prepregnancy weight, and physical activity from the interview at the first prenatal visit and an accompanying self-administered questionnaire (15). Each participant described her race/ethnicity as one of the following: Hispanic or Latina, White or Caucasian, Black or African American, Asian or Pacific Islander, American Indian or Alaskan Native, or other race/ethnicity. Average alcohol intake during pregnancy was determined in grams per day from a self-administered food frequency questionnaire at first trimester. Prepregnancy body mass index (BMI) was computed by dividing self-reported prepregnancy weight in kilograms by height in meters squared. Pregnancy weight gain was defined as the last weight in the medical record (within 1 month before delivery) minus the participant's self-reported prepregnancy weight. We estimated the weekly rate of weight gain by dividing pregnancy weight gain by length of gestation in weeks at last weight taken. Individuals with a diagnosis of a genitourinary infection in current pregnancy were identified according to ICD-9 codes from the automated medical record system. These infections included infection of the kidney, urethra, urinary tract, pelvic organs and genital organs, as well as sexually transmitted diseases.

Statistical analyses

We compared the characteristics of women with adverse pregnancy outcomes with those who delivered normal babies. Risks of preterm, SGA, and poor pregnancy outcome were estimated using logistic regression analysis. In the multivariable models, we adjusted for maternal age (continuous), race/ethnicity (white race versus other), smoking in the 3 months before the woman learned she was pregnant (yes/no), annual household income (≤$40 000, $40 001–70 000 versus >$70 000), prepregnancy BMI (continuous), weekly weight gain during pregnancy (continuous), having dental check-up at least once per year (yes/no), gravidity (first versus later pregnancy), prior history of preterm birth (yes/no), and presence of genitourinary infection (yes/no). We classified race/ethnicity as white and other, because the number of subjects from non-white groups was small. Other variables considered as potential confounders included employment status (yes/no), completion of college education (yes/no) and alcohol intake (continuous), which we omitted from the final models because each variable changed the estimated odds ratio (OR) associated with periodontitis less than 10%. To examine periodontitis–adverse pregnancy outcome association among different race/ethnicity and socioeconomic groups, we repeated the analyses in subgroups of race and income. All analyses were performed using Statistical Analytical Systems 8.1 (SAS Institute, Cary, NC, USA).

Results

The majority of the 1635 women in this study were white (72.7%), college graduates (71.1%), married (86.3%), currently employed (85.8%) and had annual household income more than $70 000 (65.0%). Women who reported having periodontitis were older, less likely to be married and to have completed college education, and more likely to be black, have regular dental check-ups, have had at least one previous pregnancy, have had previous history of preterm birth, and smoke (Table 1). One hundred and five (6.4%) women had preterm birth, 88 (5.4%) had SGA babies, and 180 (11.0%) had poor pregnancy outcome (preterm or SGA). Women with and without adverse pregnancy outcomes were similar with respect to education, employment status, and alcohol consumption. Women with adverse pregnancy outcomes were more likely to be black, had history of preterm birth, had genitourinary infections during pregnancy, smoked, and gained less weight during pregnancy (Table 2). They were also more likely to report history of periodontitis when compared with women with normal pregnancy (preterm birth, 4.8% versus 3.7%; SGA, 5.7% versus 3.7%; poor pregnancy outcome, 5.6% versus 3.6%).

In age-adjusted analyses, women who reported periodontitis had no increased risk of having preterm birth (OR = 1.39; 95% CI 0.54–3.59) or

Table 1. Characteristics of subjects according to self-reported periodontitis (data from 1635 participants in Project Viva)

Characteristics	Periodontitis		*P*-value
	Yes (n = 62)	No (n = 1573)	
Age (years)	35.2 ± 3.9	32.2 ± 4.8	<0.001
Race/ethnicity (%)			
White	61.3	73.1	0.02
Black	24.2	12.3	
Other race	14.5	14.7	
Married (%)	77.4	86.6	0.04
Completed college education (%)	59.7	71.6	0.04
Annual household income (%)			
≤$40 000	15.4	11.8	0.72
$40 001–70 000	21.2	23.2	
>$70 000	63.5	65.1	
Employed (%)	91.5	85.6	0.20
Had dental check-up at least once per year (%)	96.8	81.8	<0.01
Primigravida (%)	21.0	33.2	0.04
Previous history of preterm birth (%)	4.9	3.9	0.67
Genitourinary infection during pregnancy (%)	17.7	17.3	0.95
Smoking in the 3 months before pregnancy (%)	12.1	10.5	0.71
Alcohol consumption during first trimester (g/day)	1.7 ± 3.1	2.2 ± 3.1	0.21
Prepregnancy body mass index (kg/m^2)	24.8 ± 5.4	24.5 ± 5.2	0.67
Pregnancy weight gain (kg/week)	0.38 ± 0.14	0.40 ± 0.14	0.51
Preterm birth (%)	8.1	6.4	0.59
Small-for-gestational-age (%)	8.1	5.3	0.34
Poor pregnancy outcome (%)	16.1	10.8	0.19

Continuous variables presented as mean ± standard deviation.

SGA (OR = 2.23; 95% CI 0.85–5.84) (Table 3). These associations remained non-significant after adjustment for smoking, race/ethnicity, income, prepregnancy BMI, weekly weight gain, primigravida, history of preterm birth, dental check-up at least once per year and presence of genitourinary infection. However, there was a significant association between periodontitis and poor pregnancy outcome (age-adjusted OR = 2.20; 95% CI 1.07–4.50); this association remained essentially unchanged after further adjustment for other potential confounders (OR = 2.26; 95% CI 1.05–4.85 for poor pregnancy outcome).

Among whites, women reporting periodontitis were three times more likely to have poor pregnancy outcome when compared with those who did not report periodontitis (multivariable adjusted OR = 3.24; 95% CI 1.28–8.20). The association was considerably lower (multivariable adjusted OR = 1.33; 95% CI 0.34–5.13) among women of other racial/ethnic groups. Similarly, we found a strong association between periodontitis and poor pregnancy outcome among women with household incomes >$70 000 per annum (multivariable adjusted OR = 3.51; 95% CI 1.42–8.66), but not among women with lower household income (multivariable adjusted OR = 0.89; 95% CI 0.19–4.27). The stratified analyses with preterm birth and SGA as separate outcomes also yielded similar results, but with wider confidence intervals. The limited sample size of subgroups made it impossible to examine strata of race/ethnicity and income together.

Discussion

In this prospective study, maternal periodontitis was associated with a two-fold increased risk of poor pregnancy outcome (either preterm birth or SGA birth). The association was similar but with wider confidence intervals for preterm birth or SGA considered separately owing to relatively small numbers of outcomes. We adjusted for major potential confounders including maternal age, race/ethnicity, smoking status, income, frequency of dental check-ups, gravidity, history of preterm birth, prepregnancy BMI, pregnancy weight gain, and presence of genitourinary infection. As inflammatory cytokines are on the common hypothesized pathway between periodontitis and both preterm birth and SGA, it is reasonable to combine them into a single outcome in this analysis. The use of combined outcome, such as preterm birth and/or

Table 2. Characteristics of the participants according to pregnancy outcomes (data from 1635 participants in Project Viva)

Characteristics	Preterm birth			Small-for-gestational-age			Poor pregnancy outcome (preterm birth and/or small-for-gestational-age)		
	Case (n = 105)	Non-case (n = 1530)	P-value	Case (n = 88)	Non-case (n = 1544)	P-value	Case (n = 180)	Non-case (n = 1452)	P-value
Age (years)	31.8 ± 4.8	32.3 ± 4.8	0.27	31.0 ± 5.7	32.4 ± 4.7	0.02	31.6 ± 5.2	32.4 ± 4.7	0.03
Race/ethnicity (%)									
White	60.6	73.5	0.01	55.2	73.6	<0.001	59.0	74.3	<0.001
Black	20.2	12.2		18.4	12.4		19.1	12.0	
Other race	19.2	14.3		26.4	14.0		21.9	13.8	
Married	83.7	86.5	0.42	81.6	86.5	0.20	82.6	86.7	0.13
Completed college education (%)	68.3	71.3	0.51	69.0	71.2	0.65	68.0	71.5	0.33
Annual household income (%)									
≤$40 000	12.6	11.9	0.46	13.6	11.8	0.72	13.3	11.8	0.36
$40 001–70 000	17.9	23.4		19.8	23.3		18.8	23.7	
>$70 000	69.5	64.7		66.7	64.8		67.9	64.6	
Employed (%)	83.0	86.0	0.41	81.0	86.0	0.21	83.9	86.0	0.47
Primigravida (%)	36.2	32.5	0.43	40.9	32.3	0.07	38.3	32.0	0.09
Previous history of preterm birth (%)	9.7	3.5	<0.01	6.9	3.7	0.14	8.5	3.3	<0.001
Genitourinary infection during pregnancy (%)	22.9	17.1	0.13	22.7	17.2	0.18	22.2	16.7	0.07
Smoking in the 3 months before learned pregnancy (%)	15.8	10.2	0.08	18.1	10.2	0.02	16.4	9.9	<0.01
Alcohol consumption during first trimester (g/day)	2.2 ± 3.4	2.2 ± 3.0	0.99	2.0 ± 2.7	2.2 ± 3.1	0.65	2.1 ± 3.1	2.2 ± 3.1	0.67
Prepregnancy body mass index (kg/m^2)	25.0 ± 6.3	24.5 ± 5.1	0.48	23.0 ± 4.3	24.7 ± 5.2	0.001	24.1 ± 5.6	24.6 ± 5.2	0.22
Pregnancy weight gain (kg/week)	0.37 ± 0.13	0.40 ± 0.14	0.03	0.37 ± 0.13	0.40 ± 0.14	0.03	0.37 ± 0.12	0.41 ± 0.14	0.001
Self-reported periodontitis (%)	4.8	3.7	0.59	5.7	3.7	0.38	5.6	3.6	0.19
Pregnancy outcome									
Gestational age (weeks)	35.1 ± 1.8	39.9 ± 1.2	<0.001	38.8 ± 1.9	39.6 ± 1.7	<0.001	36.9 ± 2.7	39.9 ± 1.1	<0.001
Birth weight (g)	2526 ± 585	3559 ± 481	<0.001	2547 ± 362	3547 ± 509	<0.001	2580 ± 474	3606 ± 444	<0.001

Continuous variables presented as mean ± standard deviation.

Table 3. Logistic regression analysis relating self-reported periodontitis with adverse pregnancy outcomes

Odds ratio (95% confidence interval)	Preterm birth	Small-for-gestational-age	Poor pregnancy outcome (preterm birth and/or small-for-gestational-age)
Age adjusted	1.39 (0.54–3.59)	2.23 (0.85–5.84)	2.20 (1.07–4.50)
Age and smoking adjusted	1.75 (0.67–4.57)	2.32 (0.88–6.12)	2.28 (1.10–4.70)
Multivariable adjusted[a]	1.74 (0.65–4.66)	2.11 (0.76–5.86)	2.26 (1.05–4.85)

[a]Adjusted for age (years), race/ethnicity (white race versus other), smoking in the 3 months before pregnancy (yes, no), annual household income (≤$40 000, $40 001–70 000 versus >$70 000), prepregnancy BMI (kg/m^2), weekly weight gain (kg), primigravida (yes, no), history of preterm birth (yes, no), dental check-up at least once per year (yes, no) and presence of genitourinary infection (yes, no).

low birth weight, is common in studies investigating the association between periodontal disease and adverse pregnancy outcomes (7, 13, 21).

To our knowledge, this is the first US study conducted among predominantly white, non-low-income women. Most previous studies have been conducted mostly among poor, minority, young, and unmarried women (6, 9, 10, 21, 22) In two previous studies, cases of preterm and low birth weight were, respectively, 7.5 and 3.3 times more likely to have periodontal disease when compared with controls (6, 8). However, there was no association between periodontal disease and preterm low birth weight in a predominantly Bangladeshi population residing in East London (22), and in a German Caucasian population (23). A limitation of these studies was that periodontal health was measured after delivery. Our results are consistent with those of two previous prospective studies. In a study of 1313 predominantly black (83%) women, those with generalized periodontitis (>90% sites with attachment loss ≥3 mm) were at increased risk of delivering before 37 weeks' gestation (RR = 4.45; 95% CI 2.16–9.18) (9). In another prospective study of 639 poor Chilean women, those with periodontal disease had a higher risk of preterm or low birth weight (RR = 3.5; 95% CI 1.5–7.9) (7). In another study conducted among predominantly white (62%) women in the UK, there was no association between the severity of periodontal disease and either preterm birth or low birth weight. However, there appeared to be an association between poor periodontal health and late miscarriage (14).

Our study population was a general population sample with race/ethnicity profile similar to that of the US population. However, they represented a relatively high socioeconomic status group. The low prevalence of periodontitis, preterm birth, and SGA in this cohort limits the precision of effect estimates. Future prospective studies in a population with low risk of periodontitis and adverse pregnancy outcomes should enroll a larger sample size. We classified race/ethnicity as white and other, because the number of subjects from non-white groups was small. This may lead to incomplete control of confounding by race.

Our measure of periodontitis is based on a self-report and may not be indicative of active infection and inflammation during their pregnancy, but rather a measure of cumulative disease over the lifetime. Other cumulative measure of periodontitis such as clinical attachment loss has been associated with adverse pregnancy outcomes in previous studies (6, 9). The use of self-reported periodontitis may have resulted in random misclassification, possibly leading to an underestimation of the size of the association between periodontitis and poor pregnancy outcomes. The ORs for preterm birth or low birth weight related to clinically measured periodontitis ranged from three to eight in case-control studies (6, 8) and from three to seven in cohort studies (7, 9), when compared with ORs between two and three in our study using self-report. Based on the sensitivity and specificity of the self-reported periodontal measure, we calculated, using the formula from Flegal et al. (24), that in the absence of misclassification, our estimated OR of 2.26 would correspond to a true OR of 5.07.

In this study, we found a stronger association between periodontitis and poor pregnancy outcome among whites and in the higher income group. It is important to note that there were only a small number of non-whites and low-income women in this study, only a small number of individuals had poor pregnancy outcomes, and understanding mechanistic differences between different racial/ethnic or socioeconomic groups was not the primary hypothesis to be tested. Therefore, it is possible that the weaker associations of periodontitis with adverse pregnancy

outcomes among non-whites and in the lower income group may be due to insufficient statistical power or chance, especially as previous studies have found strong associations in these groups. Another explanation may be that white and high-income women are groups generally thought to be at less risk of early onset of chronic periodontal disease. The fact that they had disease with bone loss in their early thirties suggest that they might have a different form of more aggressive disease, or a disease mediated through a unique genetic susceptibility, when compared with women from groups with higher risk for periodontal disease (e.g. blacks, low-income or older individuals). For example, the interleukin-1 polymorphism, found in about 30% of Caucasians (25), is associated with increased risk and severity of periodontitis (26, 27). It is also associated with hyperinflammation and higher circulating C-reactive protein (CRP) (28). We did not assess this polymorphism but it is plausible that if it were present, white women with periodontitis may have more severe disease and higher circulating CRP levels.

The association between maternal periodontitis and adverse pregnancy outcomes is biologically plausible. Periodontitis induces the release of inflammatory cytokines such as interleukins and tumor necrotic factor-alpha. Circulating cytokines may stimulate Prostaglandin E_2 production, resulting in preterm labor, cervical ripening and premature rupture of membranes and ultimately preterm delivery (2). CRP is associated with periodontal disease among adults (29), as well as with preterm birth (30) and restricted fetal growth (31). In our population, women with periodontitis measured by radiographic bone loss had higher plasma CRP levels during early pregnancy than women without periodontitis (32). CRP can amplify the inflammatory response through complement activation, tissue damage and inducing cytokine release in monocytes (33) and may thus mediate the relation between periodontitis and adverse pregnancy outcomes. In addition, inflammatory cytokines and CRP released in periodontitis may also induce endothelial dysfunction of the placental blood vessels (34) limiting nutrients to the developing fetus resulting in restricted fetal growth (35, 36). Previous animal experiments (37, 38) and human studies (10) provide evidence to support this association.

While the relation between periodontal disease and adverse pregnancy outcomes presents a potentially modifiable cause of adverse pregnancy outcomes, it is possible that maternal periodontitis may only be a surrogate for other factor(s) predisposing to adverse pregnancy outcomes, such as genetic factors; the observed association may not thus be causal. Further research is needed to evaluate if periodontal treatment could eventually decrease the risk of adverse pregnancy outcomes. Recent pilot intervention studies provided preliminary evidence that scaling and root planing therapy of periodontal disease may reduce the risk of preterm low birth weight (12, 13). If larger randomized controlled trials show that treatment of periodontal infections could prevent the occurrence of adverse pregnancy outcomes, then periodontal therapy should be considered as a necessary part of prenatal care.

In summary, the results suggest that periodontitis is an independent risk factor for poor pregnancy outcome among middle-class women. These findings, however, should be interpreted with caution given the limitations of the small sample size and indirect measure of periodontitis. Future studies with a larger sample size are needed to examine the association in more detail.

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