Oral Inflammatory Burden and Preterm Birth

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Background: Earlier studies on the association between oral inflammation and preterm birth limited the inflammation source to periodontal disease. This might have caused an underestimation of the total inflammatory burden from the oral cavity.

Methods: We conducted a postpartum cross-sectional study of 328 Finnish women with singleton births, of whom 77 had preterm births and 251 had full-term births. Gingival bleeding on probing, probing depth, and the presence of dental calculus and mouth ulcers were recorded; the oral inflammatory burden index (OIBI) was constructed based on these clinical findings. A data-driven oral inflammation score (OIS) was also created by stochastically combining the same parameters assessed independently. We used the *t*, Mann-Whitney, and χ^2 tests for univariate analyses and multivariate logistic regression methods to examine the association between OIBI/OIS and preterm birth. The confounders adjusted for were age, smoking (past, present, and never), diabetes (type 1, type 2, and gestational), primiparity, antimicrobial treatment as a proxy for systemic infection, infertility treatment, and weight gain during pregnancy.

Results: OIBI was significantly associated with preterm birth after adjusting for confounding factors (odds ratio [OR], 1.85; 95% confidence interval [CI]: 1.10 to 3.10; $P = 0.02$). Without adjusting for weight gain, OIS was significantly associated with preterm birth (OR, 1.97; 95% CI: 1.09 to 3.57; $P = 0.03$); however, this association became non-significant after adding weight gain to the model.

Conclusion: The combined effects of multiple oral infections were significantly associated with preterm birth. *J Periodontol 2009;80:884-891.*

KEY WORDS

Infections; inflammation; preterm birth; weight gain.

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Preterm birth (PTB), defined as birth before 37 weeks of gestation, accounts for 75% of perinatal mortality and more than half of long-term morbidity.[1] A history of spontaneous preterm delivery has been identified as the most significant risk factor; other risk factors include preeclampsia, thrombophilia, low socioeconomic status, very young or old maternal age, multiparity, inadequate prenatal care, and the use of alcohol and tobacco.[1-3] Despite extensive literature on the subject and improved antenatal care, there has been no significant decrease in the incidence of PTB in developed societies.[4] This has led to the belief that other factors may contribute to PTB. Hence, the search for relevant risk factors must continue.[2]

Maternal infections may threaten the welfare of the fetus and lead to PTB through the activation of the innate immune system, leading to an increased expression of prostaglandins and inflammatory cytokines.[1] Intrauterine infections can result in spontaneous preterm delivery by stimulating uterine contractions or membrane rupture.[1] Systemic infections, such as pneumonia,[5] and genitourinary tract infections, like bacterial vaginosis, *Chlamydia trachomatis*, and syphilis, are also associated with PTB.[1,6,7]

Periodontal disease is a low-grade infection dominated by Gram-negative anaerobic and microaerophilic bacteria resulting in local and systemic inflammatory and

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immune responses.[8] Inflamed periodontal tissues serve as reservoirs for periodontal pathogens, endotoxins, and inflammatory mediators.[8] The detection of oral pathogens in amniotic fluids by polymerase chain reaction tests suggests a possible hematogenous spread of these infections.[9] Although the role of periodontal disease in PTB has been investigated extensively,[10-20] the results have been inconclusive; a number of studies[10-16] found an association, whereas other studies[17-20] did not.

Many of these studies were conducted among multiracial cohorts;[12,14,16,17,19] those of African American[10,11] ancestry consisted mainly of mothers of low socioeconomic status. These demographic factors are known to be associated with PTB.[12] We restricted the current study to a population of highly (69.5% had completed college) and moderately (22.3% had completed high school or vocational school) educated, all-white women to avoid confounding by the socioeconomic factors. Only two of the previous studies were conducted in an all-white population: one reported a significant association,[13] whereas no significant association between periodontal disease and PTB was observed in the other.[18]

These conflicting reports suggest that the impact of periodontitis on adverse birth outcomes is subtle, and precision in the measurement of the outcome and the predictor is crucial to an unbiased estimation of this relationship. Among 15 criteria for periodontitis based on probing depth (PD) and clinical loss of attachment, none has proved to be a significant predictor of adverse birth outcomes.[17] Given that these parameters include past or inactive periodontal infection and ignore other soft tissue infections, it is possible that periodontitis alone might underestimate the total inflammatory burden from the oral cavity. To overcome these deficiencies, we estimated the total oral inflammatory burden index (OIBI) from the oral cavity by using the Community Periodontal Index (CPI) of Treatment Needs,[21] a more comprehensive measure of inflammatory burden that evaluates the presence of gingivitis and potential mucositis in addition to periodontitis. To validate CPI's role as an inflammatory burden index, we also created a data-driven oral inflammation score (OIS) by mathematically combining independently collected data on gingivitis, periodontitis, and oral mucositis from this cohort.

MATERIALS AND METHODS

Ethics Approval

The study was approved by the Ethics Committee of the Helsinki University Central Hospital (HUCH; HUS 107/E6/2000, 25.10.2000) and the Institutional Review Board (TYH 3245 10.2.2003, T1020Y0003 1.12.2006). The study was conducted according to the principles of the Declaration of Helsinki.[22]

Evolvement of the Final Cohort

A total of 482 women aged 18 to 44 years who had given birth at the Department of Gynecology and Obstetrics, HUCH, between September 2002 and May 2004 participated in the study. The study nurse randomly recruited subjects postpartum in the labor ward, and those who agreed to participate provided written consent. Primary exclusion criteria were illicit drug abuse and infection with hepatitis B, hepatitis C, or human immunodeficiency virus. We restricted the current analysis to singleton births, thus removing 25 mothers who delivered twins, and four women dropped out for personal reasons. In addition, we excluded 125 women whom we were unable to examine within 2 days postpartum. Thus, the final study group consisted of 328 women (Fig. 1).

Assessment of the Outcome

We defined the study outcome of PTB as a birth before 259 days of gestation (37 weeks), consistent with the recommendations of the World Health Organization (WHO) and the International Federation of Gynecology and Obstetrics.[23] Gestational age was determined based on the date of the last menstrual period and was confirmed by ultrasound examination between 11 and 14 weeks of gestation. Among the 328 singleton births, 77 were PTB, a proportion that is higher than the average for Finland. This high PTB rate might be explained by the fact that the accrual lasted almost 2 years, and the Department of Gynecology and Obstetrics, HUCH, is a tertiary referral center; hence, it is more likely to receive women experiencing or anticipating complications during pregnancy. The catchment area of the Department of Gynecology and Obstetrics has a population of 1.5 million and, for certain diseases, pregnant women from all over Finland are referred to HUCH.

Clinical Examination and Assessment of the Predictor

Mothers were subjected to a clinical examination by two dentists within 2 days postpartum in a specially equipped dental office at the hospital. The examining

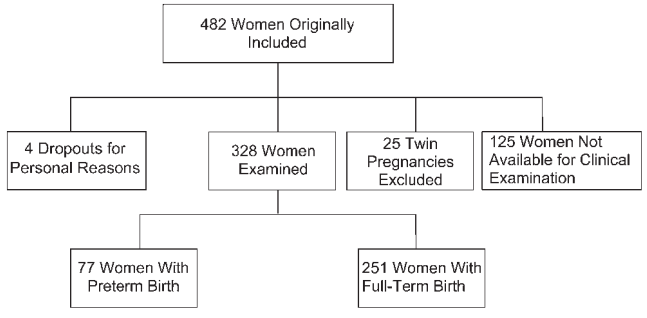

Figure 1.
Study cohort development.

dentists were masked to the pregnancy outcome of the mother. The examiners were not calibrated, but they were employees of the City of Helsinki Health Department, where regular diagnostic meetings served as calibration sessions according to the WHO principles of oral diagnosis. PD was measured using a calibrated probe at six sites per tooth on all teeth. Gingival bleeding on probing (BOP) and visible dental plaque were recorded at four sites per tooth on all teeth (plaque index). OIBI was calculated using mean values of the WHO CPI of Treatment Needs in all jaw sextants. The CPI incorporated gingivitis measured by gingival BOP (CPI 1), gingival irritation caused by supragingival calculus (CPI 2), and moderate (CPI 3) to severe periodontitis (CPI 4) as measured by the probing depth. Thus, OIBI reflects the severity and the extent of potential inflammatory burden from the oral cavity. It was not possible to take dental x-rays of the patients at the Department of Gynecology and Obstetrics; thus, potential periapical lesions were not diagnosed and included in the OIBI. To validate the function of CPI as an OIBI, we created a current data-based OIS by stochastically summing gingivitis assessed by gingival bleeding, periodontitis defined by more than one site with PD ≥4 mm, and oral mucositis assessed by the presence of open sores on the oral mucosa.

Maternal Characteristics

In addition to the clinical dental examination, the participants completed a questionnaire reporting important health- and lifestyle-related behaviors. Smoking was recorded as past, current, or never. The frequency of alcohol consumption during pregnancy was recorded and classified into five categories: daily, less than once a day, less than once a week, less than once a month, or not at all. Data on demographic factors, prenatal care, and medical and obstetric history were obtained from medical records. Body mass index and weight gain between the first and third trimesters were calculated from anthropometric measurements. The number of previous pregnancies, including spontaneous miscarriages, PTB, and stillbirths, as well as information on complications, such as infections and preeclampsia, were recorded. Antecubital venous blood samples and salivary samples were taken and analyzed in the hospital laboratory with routine methods. The results of these analyses will be reported separately. In the present article, C-reactive protein (CRP) values and salivary elastase values were only used for validation of the method (see later discussion).

Statistical Analyses

We conducted all univariate analyses with a statistical program.** The *t* test and non-parametric tests were used to compare baseline distributions of continuous variables after testing for normality, whereas categoric data were tested using the χ^2 test.

The multivariate analyses were conducted, by the logistic regression method, using statistical software.†† OIBI, calculated as the mean CPI of all six sextants, was the predictor, and PTB (yes/no) was the outcome. OIBI based on CPI was intended for the assessment of periodontal condition rather than the assessment of inflammation. Thus, we validated OIBI against a conceptual model using actual inflammation variables, such as periodontitis, gingivitis, and mucositis. These variables were in the model and were weighted by their statistical importance and summed to create a single-score OIS in the same manner as the Asymptotic Dental Score.[24] We also validated OIBI against CRP, quantified from serum samples collected during the first antenatal clinic visit, as a systemic marker of inflammation and against elastase as a local inflammation marker. We considered the women who attained the top 25th percentile of the inflammation score (OIS) as "women with high inflammatory potential." Then, we compared the probability of their having preterm birth to the same probability in women who were in the lower three quartiles of the inflammatory score using the logistic regression analyses.

We adjusted both of the multivariate models for maternal age and weight gain as continuous variables and for smoking as a three-category variable; all types of diabetes, antimicrobial treatment, infertility treatment, and primiparity were treated as dichotomous variables. Alcohol consumption and education level were not found to be significant confounders in this cohort and were omitted in the interest of retaining power.

RESULTS

Table 1 gives baseline data of the preterm and full-term mothers. No significant differences in the demographic data were found between the two groups. Women with PTBs experienced significantly less weight gain (11.7 ± 4.9 kg versus 13.9 ± 5.1 kg; $P < 0.01$), were more likely to be primigravid (64.9% versus 45.4%; $P < 0.01$), and more frequently had a history of fertility treatment (7.8% versus 2.4%; $P < 0.05$) than the women who delivered a full-term baby. Only one woman in each group had previous preterm delivery. No difference was observed between the groups in terms of maternal preeclampsia or infections, but women with PTBs received significantly more medications overall (49.4% versus 25.1%; $P < 0.001$) and antimicrobial drugs, in particular (24.3% versus 8.5%; $P < 0.01$), than those with a full-term delivery. Women who delivered preterm babies were also hospitalized more often because of preterm contractions (10.4% versus 2.0%; $P < 0.01$).

** Statistical Package for Social Sciences for Unix, SPSS, Chicago, IL.
†† SAS version 9.1, SAS Institute, Cary, NC.

Table 1.

General Characteristics of the Cohort (N = 328)

Parameter	Preterm (n = 77)	Full-Term (n = 251)	*P* Value
Age (years; mean ± SD)	30.9 ± 5.4	31.2 ± 4.9	0.45
Body mass index (kg/m^2; mean ± SD)	23.5 ± 4.6	23.4 ± 4.1	0.91
Maternal weight gain (kg; mean ± SD)	11.7 ± 4.9	13.9 ± 5.1	<0.01
Smoking (n [%])			
During pregnancy	11 (14.3)	25 (10.0)	0.30
Before pregnancy	7 (9.1)	42 (16.7)	0.14
Not at all	59 (76.6)	184 (73.3)	0.66
Alcohol consumption during pregnancy (n [%])			
Less than once a week	7 (9.1)	17 (6.8)	0.46
Less than once a month	9 (11.7)	55 (21.9)	0.05
Not at all	61 (79.2)	179 (71.3)	0.19
Education ≥college (n [%])	53 (68.8)	175 (69.7)	0.89
Primiparity (n [%])	50 (64.9)	114 (45.4)	<0.01
Previous PTB (n [%])			
0	76 (98.7)	250 (99.6)	0.99
≥1	1 (1.3)	1 (0.4)	
Infertility treatment (n [%])	6 (7.8)	6 (2.4)	<0.05
Maternal diseases (n [%])			
Asthma	7 (9.6)	10 (4.0)	0.08
Diabetes (type 1, type 2, or gestational)	15 (19.5)	36 (14.3)	0.27
Medication (n [%])			
All medication	38 (49.4)	63 (25.1)	<0.001
Antimicrobial drugs	18 (24.3)	20 (8.5)	<0.01
Preeclampsia (n [%])	8 (10.4)	22 (8.8)	0.66
Hospitalization due to preterm contractions (n [%])	8 (10.4)	5 (2.0)	<0.01
Infection (n [%])			
All infections	11 (14.3)	24 (9.6)	0.29
Gynecologic infection	6 (7.8)	14 (5.6)	0.59
Teeth (n; mean ± SD)	28.9 ± 2.7	28.7 ± 1.7	0.75
Probing depth (n; mean ± SD)			
4 to 5.5 mm	1.7 ± 5.4	1.8 ± 5.1	0.91
≥6 mm	0.09 ± 0.79	0.03 ± 0.24	0.50
Gingival bleeding surfaces (n [%])			
Quartile 1 (<10)	11 (14.7)	62 (25.5)	0.05
Quartile 2 (10 to <22)	27 (36.0)	64 (26.3)	0.11
Quartile 3 (22 to <33)	18 (24.0)	50 (20.6)	0.53
Quartile 4 (33)	19 (25.3)	67 (27.6)	0.70
Plaque-covered surfaces (n; mean ± SD)	20.4 ± 20.0	18.2 ± 18.1	0.35
Oral inflammatory burden (mean ± SD)			
CPI-based OIBI	1.62 ± 0.55	1.33 ± 0.66	0.0004
Data-driven OIS	5.47 ± 2.86	4.35 ± 2.25	0.003

Because of missing values, not all categories have N = 328.

No significant differences were found in any individual periodontal data between preterm and full-term mothers; however, OIBI values were significantly higher in the women with preterm babies compared to those with full-term delivery (1.62 ± 0.55 versus 1.33 ± 0.66; $P = 0.0004$), as were OIS values (5.47 ± 2.86 versus 4.35 ± 2.25; $P = 0.003$). In addition, women who had delivered preterm babies had more extensive signs of oral infection as assessed using data from all six jaw sextants with CPI ≥1 (68.8% versus 51.0%; $P < 0.01$).

Although OIBI was based on CPI, which is not a precise measure of periodontitis,[25] it demonstrated satisfactory ability in assessing total oral inflammation as evidenced by significant correlation with markers for systemic and local inflammation. When we validated CPI against CRP and elastase, the Spearman correlation coefficients were 0.22 ($P = 0.0002$) and 0.21 ($P = 0.0001$), respectively. It also demonstrated a significant correlation to the data-driven inflammation score ($r = 0.8$; $P < 0.0001$). The median CRP value was 2.0 mg/l (interquartile range: 0.8 to 4.3 mg/l) among the preterm mothers and 2.1 mg/l (interquartile range: 1.05 to 4.3 mg/l) in the full-term group. Median salivary elastase values were 0.0005 optical density per hour at a wavelength of 450 nm (ΔOD_{450}/hour) (interquartile range: 0.0003 to 0.0008 ΔOD_{450}/hour) and 0.0005 ΔOD_{450}/hour (interquartile range: 0.0003 to 0.0019 ΔOD_{450}/hour), respectively. Detailed hematologic and biochemical data will be reported separately.

Table 2 shows the results of the multivariate regression model for PTB. The OIBI was significantly associated with PTB in this study population (odds ratio [OR] = 1.85; 95% confidence interval [CI]: 1.10 to 3.10; $P = 0.02$). The other significant covariates were primiparity (OR = 3.72; 95% CI: 1.84 to 7.52; $P = 0.0003$), history of antimicrobial treatment (OR = 4.37; 95% CI: 1.93 to 9.90; $P = 0.0004$), and weight gain (OR = 0.90; 95% CI: 0.85 to 0.97; $P = 0.002$). Each kilogram of maternal weight gain was associated with 10% lower odds of a PTB. Without adjusting for weight gain, OIS was also significantly associated with PTB (OR = 1.97; 95% CI: 1.09 to 3.57; $P = 0.03$). However, when weight gain was added to the final model, OIS lost its significance (OR = 1.62; 95% CI: 0.83 to 3.16; $P = 0.16$).

DISCUSSION

Our results suggest that oral inflammation may be associated with PTB. Unlike previous studies that examined only periodontitis, our assessment of the oral inflammation burden also takes into account other infections, i.e., gingivitis and mucositis. CPI-based OIBI remained significant even after controlling for all other covariates. The data-driven OIS was highly significant when weight gain was not part of the model. The small sample size of our study also explains why OIS failed to achieve significance because 327 women had CPI data, but only 271 women had data on three independent infections. However, the parallels between OIBI and OIS were evident (Table 2).

Several studies,[17,18] including our own earlier data,[26] did not find any association between periodontal health, as assessed by PD, and PTB. Given that gingival bleeding is common during pregnancy, and increased prostaglandin and interleukin-1β levels in gingival crevicular fluid were shown to be associated with PTB,[18,27] it is reasonable to include gingivitis as a potential source of infection adding to the oral inflammatory burden. Additionally, we included mucosal irritation from calculus deposits in the assessment of the total oral inflammatory burden. This comprehensive assessment of potential oral inflammation seemed to be significantly associated with PTB.

Some of the earlier studies[17,28] were conducted among populations with poor oral health and incomplete dentitions. A majority of the women in our study had complete dentitions, with a mean of 28.7 ± 2.0 teeth. There was no history of tooth loss due to poor oral health in our cohort; further, only five women had PD ≥6 mm, and 75% of the women did not have even one site with PD ≥4 mm. This indicates that the load of inflammatory mediators and bacterial products attributable to periodontitis alone was relatively low in this cohort. Nevertheless, 77 women in our cohort experienced PTB, and we hypothesized that inflammatory mediators coming from multiple oral infections could be responsible for PTB.

In the present study, the definition of PTB was birth at or before 258 gestational days of pregnancy, and the definition of full-term birth was birth after 258 gestational days of pregnancy. We also compared mean oral inflammatory burden in women who had delivered before 224 days of gestation (32 weeks). These women (although the number was only four) demonstrated extremely high OIBI compared to those who delivered after 32 weeks of gestation (9.7 ± 1.5 versus 4.6 ± 2.4). However, OIBI for women who gave birth at ≤35 weeks of gestation (5.4 ± 3.1) versus those who gave birth after 35 weeks of gestation (4.5 ± 2.3) did not differ much from women who gave birth at or before 37 weeks of gestation (5.5 ± 2.8) versus those who gave birth after 37 weeks of gestation (4.3 ± 2.2).

Several studies showed associations between periodontal disease and PTB among women from multiracial backgrounds[12,14,16,18,19] and low socioeconomic status.[12,28] Two studies[16,18] conducted among white middle-class women, similar to our cohort, reported similar point estimates, although these were not significant. Results of a study[18] on oral inflammation and PTB among German white women with middle or high

Table 2.

Multivariate Regression Models for the OR for PTB

	CPI-Based OIBI (n = 327)			Data-Driven OIS (n = 271)		
Variables	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Main predictor	1.85	1.10 to 3.10	0.02*	1.62	0.83 to 3.16	0.16
Age (per year >18 years)	1.00	0.94 to 1.07	0.97	0.99	0.93 to 1.06	0.87
Smoking status						
Never	1.00			1.00		
Current	0.85	0.29 to 2.47	0.77	0.95	0.33 to 2.71	0.92
Past	0.69	0.25 to 1.90	0.48	0.75	0.28 to 2.02	0.57
Primiparity						
No	1.00			1.00		
Yes	3.72	1.84 to 7.52	0.0003*	3.47	1.71 to 7.02	0.0005*
Diabetes†						
No	1.00			1.00		
Yes	1.73	0.76 to 3.91	0.19	1.79	0.80 to 4.03	0.16
Antimicrobial Tx						
No	1.00			1.00		
Yes	4.37	1.93 to 9.90	0.0004*	4.42	1.95 to 10.01	0.0004*
Infertility Tx						
No	1.00			1.00		
Yes	2.45	0.51 to 11.78	0.26	2.96	0.60 to 14.48	0.18
Weight gain‡ (per kilogram gained)	0.90	0.85 to 0.97	0.002*	0.91	0.85 to 0.97	0.003*

n = number of women included in the analysis; Tx = treatment.
* Significant at the α level of 0.05.
† Includes type 1, type 2, and gestational diabetes.
‡ Weight gain between first and third trimesters.

socioeconomic status failed to reach significance (OR = 1.12; 95% CI: 0.46 to 3.11). This is expected from a small study with a sample size <100 and in which periodontitis was the only predictor. The other study,[16] conducted among predominantly white, middle-class American women, used a questionnaire to assess oral inflammation. Considering the low sensitivity of the questionnaire, we are not certain if the predictor was actually periodontitis.[29]

The strength of our study lies in the fact that our results were finely adjusted for the most important confounders. Additionally, this study was conducted among women with homogenous ethnicity and high socioeconomic status, thus avoiding additional confounding by racial and socioeconomic status; however, this racial and social homogeneity may limit the generalizability of our results to other populations. Only one woman in each group reported experiencing previous PTB, which was a significant risk factor in other studies. The definitive medical cause for PTB in our cohort remained uncertain: 10.4% of the women had preeclampsia, 10.4% were hospitalized due to preterm contractions, 7.8% had gynecologic infection, 5.2% had hepatogestosis, and 3.9% had placental inadequacy. The limitations of the current study include the study design and the small sample size. The dental examination was done within 2 days postpartum, and the cross-sectional design may be considered a weakness of our study. However, several previous studies[8,12,18] examining the association between periodontal disease and PTB/preterm low birth weight performed the dental examination within 1 to 3 days postpartum.

The prevalence of PTB was relatively high in this study group. However, the accrual lasted >1 year, and the Department of Gynecology and Obstetrics of our hospital is a tertiary referral center. In addition, pregnant women throughout Finland are referred to HUCH for certain diseases. However, it is possible that there might have been selection bias, due to the timing of the dental examination, such that women with PTBs might have been more willing to participate in the study.

It was not possible to take dental x-rays of the patients at the Department of Gynecology and Obstetrics; hence, potential periapical lesions were not diagnosed

and included in the OIBI. This can be considered a weakness of the study. However, no participant reported any toothache; thus, it is unlikely that many patients had periapical lesions.

It was suggested that infection may contribute to up to 50% of PTBs.[2,30,31] Infections from remote sites, such as oral infections, may also influence cytokine- and hormone-regulated inflammation and biomechanisms leading to PTB.[32] Antibiotic treatment of bacterial vaginosis significantly reduced miscarriage and PTB in a randomized controlled trial,[33] giving further support to the infection theory.

Periodontal treatment intervention studies[11,34] showed that scaling and root planing might reduce PTB. However, a more recent randomized trial by Michalowicz et al.[20] did not find any improvement in birth outcomes for mothers who received non-surgical periodontal treatment between the first and third trimesters compared to those treated after delivery. The self-reported use of illicit drugs was higher in the treatment group, but weight gain was not assessed. Because illicit drug use may be associated with less food intake and subsequent inadequate weight gain, this might have biased their results. The non-surgical periodontal treatment might have been provided too late into the pregnancy and left other potential inflammatory sources untreated. We must also keep in mind that any randomized trial results investigating the benefit of periodontal treatment on PTB will likely be attenuated. Because of ethical considerations, the control group would have a current standard-of-care intervention, thus minimizing the contrast between the two groups. In the real world, many expectant mothers do not receive any oral care during or before pregnancy. Thus, the results of Jeffcoat et al.[11] are closer to the true periodontal treatment effect that might occur. However, future randomized trials rendering the best possible treatment for all possible inflammatory diseases of the oral cavity well before pregnancy may show better pregnancy outcomes.

CONCLUSIONS

The results of this study are consistent with the hypothesis that oral inflammatory burden may be associated with PTB. Although further research is needed to elucidate the mechanisms of this relationship, our study reinforces the consensus[35] that recommends preventive oral care for women who are pregnant or planning a pregnancy.

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