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Periodontal Disease, Oxidative Stress, and Risk for Preeclampsia

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Abstract

Background—Maternal periodontal infection is associated with an increased risk for preeclampsia. Periodontal infection is also associatedwith increased oxidative stress. Our objective was to determine the relationship among maternal periodontal disease, maternal oxidative stress, and the development of preeclampsia.

Methods—A secondary analysis of prospectively collected data from the Oral Conditions and Pregnancy Study was performed. A cohort of healthy women enrolled at <26 weeks of gestation underwent an oral examination, serum sampling, and delivery follow-up. Aperiodontal infection was categorized by clinical parameters as healthy or mild or moderate/severe periodontal infection. Preeclampsia was defined by the American Congress of Obstetricians and Gynecologists criteria as blood pressure >140/90 mmHg and ≥1+ proteinuria on a catheterized specimen. Maternal blood was assayed for 8-isoprostane concentrations using an enzyme-linked immunosorbent assay and stratified as elevated (≥75th percentile) or not elevated (<75th percentile). Odds ratios (ORs) for preeclampsia were calculated and stratified by periodontal disease and the level of 8-isoprostane concentration.

Results—A total of 34 (4.3%) of 791 women developed preeclampsia. Women with an 8-isoprostane concentration ≥75th percentile at enrollment were more likely to develop preeclampsia compared to women with an 8-isoprostane concentration <75th percentile (38.2% versus 24.4%, respectively; $P = 0.07$; OR: 1.91; 95% confidence interval [CI]: 0.94 to 3.90). Among women with moderate/severe periodontal disease, an elevated 8-isoprostane concentration (≥75th percentile) did not significantly increase the likelihood for preeclampsia (adjusted OR: 2.08; 95% CI: 0.65 to 6.60).

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The authors report conflicts of interest related to this study.

Conclusions—Women with oxidative stress early in pregnancy, as measured by an 8-isoprostane concentration ≥75th percentile, were at an increased risk for developing preeclampsia. The presence of periodontal disease did not appear to modify this risk.

Keywords

Inflammation; oral health; oxidative stress; periodontal diseases; pre-eclampsia; pregnancy

Oxidative stress occurs through the generation of reactive oxygen species and free radicals in excess of the available antioxidant buffering capacity.[1] When an excess production of reactive oxygen species is formed, oxidative stress ensues. 8-Isoprostane prostaglandin (8-*iso* $PGF_{2\alpha}$), a member of the isoprostane family, has been advocated as the "gold standard" for measurement of in vivo "whole body" oxidative stress.[2,3] 8-*iso* $PGF_{2\alpha}$ is predominately generated by the cyclooxygenase independent free-radical attack on arachidonic acid in cell membranes.

Proteins, lipids, and DNA are susceptible to oxidative stress, resulting in a wide variety of chronic diseases and acute pathologic processes. Oxidative stress plays an important role in the pathogenesis of periodontal disease and its complications.[4,5] Periodontal disease is a common oral infection, with a prevalence ranging from 10% to 60%.[6] Gingivitis and periodontitis are two periodontal conditions of noteworthy significance during pregnancy. Gingivitis is an infectious and inflammatory condition of the superficial gingival tissues, with prevalence estimates during pregnancy ranging from 30% to 100%.[7] Periodontal disease is a more severe condition, affecting 5% to 20% of pregnant women, and results in destruction of tooth-supporting structures.[8]

Individuals with periodontal disease display high levels of local and systemic biomarkers of oxidative stress.[9] Among pregnant women, oxidative stress is one of the pathologic processes associated with preeclampsia. Preeclampsia is characterized by the overproduction of lipid peroxides and impaired antioxidant defense in the blood and placentas of women with preeclampsia.[10,11] Women destined to develop preeclampsia have increased systemic concentrations of 8-*iso* $PGF_{2\alpha}$ early in pregnancy prior to the clinical manifestation of the disease.[12]

It was reported[13] that women with moderate/severe periodontal disease at delivery or disease progression during pregnancy are at an increased risk for preeclampsia. Several other investigators[14–17] reported this finding; however, the underlying mechanism of this association is unknown but may be mediated, in part, by maternal systemic inflammatory responses.

We hypothesized that chronic exposure to the oral pathogens of periodontal infection leads to maternal systemic oxidative stress and preeclampsia, and oxidative stress may be one possible explanatory variable in this relationship. In this study, we investigate the relationship among maternal periodontal disease, maternal systemic oxidative stress, and the risk for preeclampsia.

MATERIALS AND METHODS

We performed a secondary analysis of data from the Oral Conditions and Pregnancy (OCAP) study.[18] The OCAP study was a prospective cohort study of maternal periodontal disease and obstetric outcomes performed at the Center for Oral and Systemic Disease, School of Dentistry, University of North Carolina in collaboration with Duke University Medical Center from December 1997 through July 2001. The study design, procedures for patient enrollment, inclusion and exclusion criteria, clinical measurements, data collection methods, medical record abstraction, and biologic sampling methods were previously described.[18] The Duke University Medical Center and the University of North Carolina Institutional Review Boards granted approval to conduct the study, and written informed consent was obtained from all study participants. Over a 42-month period, eligible healthy women with a singleton pregnancy were enrolled at <26 weeks of gestation. Women were excluded from the study if they were <18 years of age without a legal guardian, at >26 weeks of gestation, had a multifetal gestation, chronic hypertension, pregestational diabetes, cardiac valvular disease, history of fenfluramine-phentermine use (unless a normal echocardiogram was documented), a medical condition that required antibiotics for prophylaxis during dental treatment, human immunodeficiency virus, or delivery was planned at another medical center. Gestational age was calculated by the date of the last menstrual period and was confirmed by a first-or second-trimester ultrasound examination. Demographic information, health behavior, and medical history data were obtained by a patient interview and questionnaire at the first visit and were reviewed by a physician at the first prenatal visit. Race was determined by a self-report. Details on the course of the pregnancy, labor, delivery, and the newborn were abstracted from the medical record and entered into the OCAP study database.[§]

Oral health examinations and maternal blood were collected at enrollment and at delivery. The periodontal disease status of patients was defined as healthy, mild, or moderate/severe based on clinical criteria.[19] A healthy periodontal disease status was defined as no sites with pockets ≥4 mm and no sites with bleeding pockets >3 mm. Mild periodontal disease was defined as <15 sites with the presence of one or more pockets ≥4 mm or one or more pockets with bleeding. Moderate/severe periodontal disease was considered present if ≥15 sites demonstrated a probing depth ≥4 mm. Preeclampsia was categorized as two episodes of blood pressure >140/90 mmHg and ≥1+ proteinuria on a catheterized urine specimen.

The 8-isoprostane quantification was performed with a commercially available ultrasensitive enzyme-linked immunoassay[‖] at a single laboratory at the Center for Oral and Systemic Disease, School of Dentistry, University of North Carolina. The lower limit of detection of this assay was 0.022 pg/ml with an inter- and intraassay variability of 5.4% and 10.4%, respectively. For this analysis, plasma quartile concentrations of 8-isoprostane ≥75th percentile, which corresponds to a concentration >81,870 pg/ml, were defined as elevated. 8-isoprostane concentrations were determined to be low at <75th percentile or elevated at ≥75th percentile and were examined as a categoric variable.

[§]Microsoft Access, 1997 SR2, Microsoft, Redmond, WA.
[‖]Assay Designs: Direct 8-iso-PGF2alpha kit, Biomol, Hamburg, Germany.

A bivariate analysis was performed on a priori candidate confounders to determine the association between an elevated maternal plasma 8-isoprostane concentration and the development of preeclampsia using the χ^2 or Student *t* test. Variables were considered confounders if they changed the association between periodontal disease and preeclampsia by ≥5%. All confounding variables were included in a multivariable logistic regression model. The smoking history of patients was also included in the model. Odds ratios (ORs) and 95% confidence intervals (CIs) for a risk of preeclampsia were determined by stratifying periodontal disease as healthy/mild, moderate/severe, or absent and 8-isoprostane concentrations ≥75th and <75th percentile. All analyses were performed using a statistical program.[¶]

RESULTS

A total of 1,020 women aged 19 to 38 years were enrolled in the OCAP study and considered for analysis. Of these women, 791 (78%) had an oral health examination and 8-isoprostane results. No significant differences were found in age, race, parity, marital status, gestational age, tobacco use, insurance status, periodontal disease, and preeclampsia between women with and without plasma 8-isoprostane results (data not shown).

Maternal demographic characteristics and obstetric data are illustrated in Table 1. Thirty-four women (4.3%) developed preeclampsia. Women with preeclampsia were similar to those without preeclampsia, except for mean gestational age at delivery. Oxidative stress and periodontal disease status are shown in Table 2. The mean ± SD and median (inter-quartile range [IQR]) values of 8-isoprostane concentrations for women with preeclampsia tended to be higher than those without preeclampsia. Women with an 8-isoprostane concentration ≥75th percentile at enrollment were more likely to develop preeclampsia compared to women with an 8-isoprostane concentration <75th percentile, but this was not statistically significant (38.2% versus 24.4%, respectively; $P = 0.07$; OR: 1.91; 95% CI: 0.94 to 3.90).

Adjusted ORs for preeclampsia among women with an 8-isoprostane concentration ≥75th percentile, a periodontal disease state, and the combination of both exposures are illustrated in Table 3. Among women with periodontal disease, the presence of 8-isoprostane ≥75th percentile did not significantly increase the odds for the development of preeclampsia.

DISCUSSION

Moderate/severe periodontal infection at delivery and periodontal disease progression were reported to be associated with an increased risk for preeclampsia.[19] In addition, it was suggested that maternal systemic inflammation may play a role in this process.[17] The results of the present analysis, after adjustment for potential confounders, do not suggest that the relationship between periodontal disease and preeclampsia, as measured by maternal plasma 8-isoprostane concentrations early in pregnancy, may be mediated by maternal oxidative

[¶]Statistical Analytical Systems 9.1, SAS Institute, Cary, NC.

stress. This is the first report, to our knowledge, that hypothesizes that periodontal disease and preeclampsia may be linked through maternal systemic oxidative stress responses.

Pregnancy, per se, is a state of oxidative stress arising from the increased metabolic activity in placental mitochondria and the reduced scavenging power of antioxidants.[20] Consistent with previous reports, [12,21,22] we found elevated plasma levels of 8 isoprostane in patients with preeclampsia. Isoprostanes are a specific marker of oxidative damage to lipids from endogenous lipid peroxidation. They are prostaglandin-like compounds derived by autooxidation of the arachidonic acid moiety.[23]

Chappell et al.[12] conducted a longitudinal study of biochemical markers in women at risk for preeclampsia and found a trend toward elevated plasma concentrations of 8-isoprostane in preeclamptic women (increase: 51%; 95% CI: 0.99 to 2.31; $P = 0.055$). In a prospective observational study, Rogers et al.[24] found that women who developed gestational hypertension/preeclampsia had significantly higher concentrations of 8-isoprostane between 24 to 32 weeks than normotensive women (764.6 ± 517.1 versus 191.9 ± 173.7, respectively; $P < 0.001$). Chappell et al.[25] conducted a clinical trial of supplementation with vitamins C and E in gravid women at a high risk for preeclampsia. When Chappell et al.[25] compared baseline concentrations of isoprostane in high-risk women to those in low-risk control subjects before random assignment of antioxidant supplements or placebo, isoprostane concentrations at baseline in the high-risk group were 40% higher than those in the low-risk group. During the remainder of the gestation, isoprostane concentrations remained elevated in high-risk women on the placebo but fell to the levels of the low-risk women in those assigned to antioxidant supplements.

Several limitations of our study merit discussion. A few investigators failed to find an association between periodontal disease and preeclampsia.[26,27] Some investigators[28–30] failed to find a relationship between elevated 8-isoprostane concentrations and preeclampsia. Plausible explanations for these different findings include population and demographic differences. Our study population included a significant number of African American women who are known to have worse periodontal disease than their white counterparts and have higher concentrations of systemic inflammation.[31] Our study also reported a 4% rate of preeclampsia, which likely allowed for an improved assessment of the association between preeclampsia and inflammatory oral health conditions compared to other populations that reported a lower preeclampsia rate.[30]

Additionally, one inherent difficulty in our analysis was the relatively infrequent events of preeclampsia with and without moderate to severe periodontal diseases, thus yielding small numbers of events for statistical analysis even from this large cohort of women. It is possible that significant results could be obtained with a larger cohort by combining these results with future studies in a meta-analysis.

8-isoprostane is a highly sensitive marker for systemic oxidative stress. It is influenced by many factors other than periodontal infection, including smoking, dyslipidemia, diabetes, hyperhomocysteinemia, obesity, diet, and oral antioxidant consumption.[32] The OCAP study does not provide specific details on dietary habits or the use of over-the-counter vitamin

supplementation, thus we were limited in the ability to account for these variables in our analysis. There is also limited longitudinal data to characterize 8-isoprostane concentrations during pregnancy. We chose to use the 75th percentile as a cutoff point to represent those women whom we felt were in the highest risk category.

CONCLUSIONS

In conclusion, women with oxidative stress early in pregnancy, as measured in this study by an 8-isoprostane concentration ≥75th percentile, had an increased risk for the development of preeclampsia. Periodontal disease does not appear to significantly modify this risk. Future research is needed to gather longitudinal data on biomarkers of oxidative stress and to determine whether the treatment of maternal periodontal disease decreases maternal oxidative stress during pregnancy.

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Table 1

Demographic and Obstetric Characteristics of the Study Population*

Characteristic	Non-Preeclamptic (n = 757)	Preeclamptic (n = 34)	*P* Value†
Maternal age (years; mean ± SD)	28.2 ± 6.5	26.3 ± 6.1	0.10
Race: African American (n [%])	347 (46)	20 (59)	0.14
Weight (lb; mean ± SD)	162.3 ± 45	160.1 ± 50	0.78
Unmarried (n [%])	372 (49)	17 (50)	0.92
No insurance (n [%])	402 (53)	23 (68)	0.10
WIC (n [%])	165 (22)	7 (21)	0.87
Smoking during pregnancy (n [%])	131 (17)	4 (11.8)	0.40
Nulliparous (n [%])	297 (39)	16 (47)	0.36
Gestational age (weeks; mean ± SD) at delivery	38.5 ± 2.5	35.5 ± 3.2	<0.0001
Gestational age (weeks; mean ± SD) at blood draw	14.9 ± 4.9	14.6 ± 4.3	0.68

WIC = Special Supplemental Nutrition Program for Women, Infants, and Children.

*Data based on 791 women at enrollment.

†χ^2 or Student *t* test.

Table 2

Oxidative Stress and Periodontal Disease Status Among the Study Population

Oxidative Stress/Periodontal Status	Non-Preeclamptic (n = 757)	Preeclamptic (n = 34)	*P* Value
8-Isoprostane (pg/ml; median [IQR])	1,637 (16 to 81,430)	15,834 (448 to 1,000,500)	0.08
8-Isoprostane (pg/ml; mean ± SD)	191,891 ± 393,742	356,261 ± 569,666	0.11
8-Isoprostane ≥75th percentile (n [%])	185 (24)	13 (38)	0.07
Moderate/severe periodontal disease (n [%])	108 (14)	6 (18)	0.58
8-Isoprostane ≥75th percentile and periodontal disease (n [%])	46/50 (92)	4/50 (8)	0.18

Table 3

Periodontal Disease, Percentile of 8-Isoprostane Concentration, and Risk for Preeclampsia

Periodontal Status/8-Isoprostane Percentile	Adjusted OR (95% CI)*
Healthy/mild/<75	1.0 (referent)
Healthy/mild/≥75	1.69 (0.74 to 3.84)
Moderate/severe/<75	0.80 (0.18 to 3.59)
Moderate/severe/≥75	2.08 (0.65 to 6.60)

*Adjusted for African American race and smoking status.