

Periodontal Disease Early in Pregnancy Is Associated With Maternal Systemic Inflammation Among African American Women

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Background: Maternal periodontal disease is a chronic oral infection with local and systemic inflammatory responses and may be associated with adverse pregnancy outcomes. This study determined whether maternal periodontal disease in early pregnancy is associated with elevated serum C-reactive protein (CRP) levels and whether maternal race influences the relationship between maternal periodontal disease and systemic inflammatory responses.

Methods: A secondary analysis of prospectively collected data from the Oral Conditions and Pregnancy study was conducted. Healthy women at <26 weeks of gestation underwent an oral health examination and had blood collected. Periodontal disease was categorized by clinical criteria, and maternal serum was analyzed for CRP levels using highly sensitive enzyme-linked immunosorbent assay kits. An elevated CRP level was defined as >75th percentile. Demographic and medical data were obtained from the women's charts. Chi-square and multivariable logistic regression models were used to determine maternal factors associated with an elevated CRP. An adjusted odds ratio (OR) for elevated CRP levels was calculated and stratified by race and periodontal disease category.

Results: The median (interquartile) CRP level was 4.8 (0.6 to 15.7) $\mu\text{g/ml}$, and an elevated CRP level (>75th percentile) was 15.7 $\mu\text{g/ml}$. African American race and moderate/severe periodontal disease were significantly associated with elevated CRP levels. When stratified by race, moderate/severe periodontal disease remained associated with an elevated CRP level among African American women (adjusted OR: 4.0; 95% confidence interval [CI]: 1.2 to 8.5) but not among white women (adjusted OR: 0.9; 95% CI: 0.2 to 3.6) after adjusting for age, smoking, parity, marital status, insurance status, and weight.

Conclusion: Among African American women, moderate/severe periodontal disease is associated with elevated CRP levels early in pregnancy. *J Periodontol* 2008;79:1127-1132.

KEY WORDS

African American; C-reactive protein; periodontitis; pregnancy.

Gingivitis and periodontitis are two periodontal conditions of 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%.¹ Periodontitis is a more severe condition affecting 5% to 20% of pregnant women, and results in the destruction of tooth-supporting structures.^{2,3} Among non-pregnant and pregnant individuals, periodontal disease is more common among African Americans; when present, it is likely to be more severe than in whites.⁴ The reasons for the racial disparity in the prevalence and severity of periodontal disease remain unclear and may be due to racial differences in the oral microflora, inflammatory responses to oral pathogens, and cultural, environmental, and socioeconomic conditions.⁵ Studies indicate that different racial groups possess differing patterns of bacterial colonization^{6,7} as well as genetic polymorphisms that predispose to proinflammatory cytokine responses.⁸

Recent evidence suggests that maternal periodontal disease is associated with adverse pregnancy

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outcomes including early pregnancy loss, preterm birth, low birth weight, and preeclampsia.^{9,10} However, interventions to improve periodontal health during pregnancy and reduce these adverse pregnancy outcomes have produced disparate results.¹¹⁻¹⁶ The underlying mechanism is unknown, but it has been hypothesized that systemic inflammatory responses may be involved.¹⁷ Individuals with periodontal disease also have a moderate systemic inflammatory response as evidenced by elevations in serum acute-phase reactants such as fibrinogen and C-reactive protein (CRP).^{17,18} CRP is believed to be a highly sensitive, albeit non-specific, marker of inflammatory status and may reflect infectious burden. CRP is higher among pregnant women compared to non-pregnant women¹⁹ and is higher among women with periodontal disease compared to periodontally healthy women.²⁰ A study²¹ suggested that African American women have higher CRP levels compared to white women. We hypothesize that exposure to oral pathogens leads to elevated inflammatory responses in early pregnancy and that maternal race influences this response. In this study, we investigated the relationships among maternal periodontal disease, maternal systemic inflammation, and maternal race.

MATERIALS AND METHODS

We performed a secondary analysis of data from the Oral Conditions and Pregnancy study (OCAP). 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, Durham, North Carolina, from December 1997 through July 2001. The study design, procedures for subject enrollment, inclusion and exclusion criteria, clinical measurements, data collection methods, medical record abstraction, and biologic sampling methods were described previously.^{22,23} 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. 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 through subject interviews and questionnaires at the first visit and were reviewed by a physician at the first prenatal visit. Race was determined by self report. All women underwent periodontal examinations and maternal serum specimen collection at enrollment. Periodontal disease status

was defined as healthy, mild, or moderate/severe, based on clinical criteria.²⁴

CRP determination was performed with a commercially available highly sensitive enzyme-linked immunosorbent assay (ELISA).[§] The range of this assay is 0.5 to 50 $\mu\text{g/ml}$ with inter- and intra-assay variabilities of 3% and 15%, respectively.²⁵ For this analysis, serum quartile levels of CRP $\geq 75\%$, which correspond to a level $>15.7 \mu\text{g/ml}$, were defined as elevated.²⁶ Subsequent to this analysis, these numbers were validated by Belo et al.²⁶

Statistical analysis was performed with a statistical program.^{||} CRP levels were examined as continuous and ordinal values. Because our interquartile range (IQR) for serum CRP values included the traditional clinical cut-off of 10 $\mu\text{g/ml}$, we defined elevated CRP values as >75th percentile ($>15.7 \mu\text{g/ml}$) for our cohort of pregnant women. Bivariate analysis was performed to determine associations between maternal demographic characteristics and CRP using the χ^2 test. These variables, which were statistically significant, along with smoking history, were included in a multivariable logistic regression model. Crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for elevated CRP were determined and stratified by periodontal disease and race. African American and white races were selected because they accounted for >95% of our cohort.

RESULTS

A total of 775 women had complete data and serum specimens available for this analysis. Demographic, medical, and obstetric data of the women who made up the cohort for this analysis are shown in Table 1. Although the cohort was distributed equally between African American and white women, African American women were significantly more likely to weigh more, to smoke, and to have experienced a prior preterm delivery and were less likely to be married or privately insured (Table 2).

The median gestational age at the time of enrollment was 14 weeks (range, 4 to 26 weeks). Median CRP value at the time of enrollment for all women was 4.8 $\mu\text{g/l}$ (IQR: 0.63 to 15.7 $\mu\text{g/l}$). African American women had significantly higher median CRP values at enrollment than white women (7.68 $\mu\text{g/ml}$ versus 2.59 $\mu\text{g/ml}$; $P < 0.001$). Moderate/severe periodontal disease was observed in 114 of 775 (15%) women in the study cohort. There was a significantly higher prevalence of moderate/severe periodontal disease in African American women than in white women (27% versus 5%; $P < 0.001$).

§ VIRGO C-Reactive Protein Kit, Hemagen Diagnostics, Waltham, MA.
|| SAS version 9.1.3, SAS Institute, Cary, NC.

Table 1.
Demographic, Medical, and Obstetric Data for the Cohort

Subject Characteristics	Entire Cohort (N = 775)
Maternal age (years; mean \pm SD)	28 \pm 6.5
Maternal weight at enrollment (pounds; mean \pm SD)	162 \pm 44.7
Maternal race (n [%])	
White	374 (48)
African American	360 (46)
Other (Asian, Hispanic, Native American)	41 (6)
Periodontal disease status (n [%])	
Healthy	211 (27)
Mild	450 (58)
Moderate/severe	114 (15)
CRP (μ g/ml; mean \pm SD)	12.6 \pm 17.1
CRP (μ g/ml; median [IQR])	4.8 (0.63 to 15.7)
CRP >75th percentile (n [%])	194 (25)
Married (n [%])	394 (51)
Privately insured (n [%])	358 (46)
Eligible for WIC/food stamps (n [%])	171 (22)
Primigravida (n [%])	308 (40)
Multiparous with previous preterm delivery (n [%])	133 (28)
Sexually transmitted infection (n [%])	97 (13)
Smoking during current pregnancy (n [%])	132 (17)
Alcohol use during current pregnancy (n [%])	122 (16)

African American race, maternal age, weight at enrollment, unmarried status, eligibility for a special supplemental nutritional program for women, infants, and children (WIC)/food stamps, lack of private insurance, previous preterm delivery, and moderate/severe periodontal disease were all significantly associated with elevated serum CRP levels ($P \leq 0.03$ for all parameters). Using multivariable logistic regression, moderate/severe periodontal disease (OR: 2.3; 95% CI: 1.3 to 4.4) and African American race (OR: 1.8; 95% CI: 1.1 to 2.9) were the strongest predictors of elevated CRP levels. Although smoking status was not associated with elevated CRP levels, it was included in the regression analysis because of its known association with periodontal disease.

The presence of moderate/severe periodontal disease was associated with a higher median CRP level compared to periodontal healthy or mild disease (10.5 μ g/ml versus 3.0 μ g/ml versus 4.9 μ g/ml; $P < 0.0001$). Significantly more women with moderate/severe periodontal disease had serum CRP levels >75th percentile than women with periodontal healthy or mild disease (42.5% versus 14.9% versus 25.6%; $P < 0.001$). However, when stratified by race, moderate/severe periodontal disease remained associated with an elevated CRP among African Americans (adjusted OR: 4.0; 95% CI: 1.2 to 8.5) but not among white women (adjusted OR: 0.9; 95% CI: 0.2 to 3.6) after adjusting for age, smoking, prior preterm delivery, marital status, insurance status, and weight (Table 3).

DISCUSSION

In this study, we found that maternal periodontal disease was associated with maternal inflammation, as measured by CRP, among African American women but not white women. The reasons for this finding are unclear but may be explained by racial differences in oral microbiology, maternal genetic predisposition to proinflammatory responses to microbial challenges, or maternal behavioral differences that predispose to oral infection and subsequent inflammation. Alternatively, biologic differences such as genetic polymorphisms or hyperinflammatory genotypes may influence one's susceptibility to oral pathogens or inflammatory responses.²⁷ Social, cultural, and environmental factors may also play a role in oral health. African Americans and persons of low socioeconomic status have worse oral health measures than non-Hispanic white persons and those of high socioeconomic status.²⁸ Compared to their African American counterparts with high socioeconomic status, African Americans with low socioeconomic status have more negative attitudes toward dental care, worse dental health, and are less likely to receive preventive dental care.²⁸ As measured by marital status, insurance status, and enrollment in WIC/food stamps, the African American women in our cohort seemed to have a markedly lower socioeconomic status compared to the white women. Our data suggest that maternal serum CRP may serve as an additional marker for social disadvantage.

Our results are consistent with previous studies^{14,20,29} reporting that elevated levels of CRP during pregnancy are related to periodontal disease. Pitiphat et al.²⁰ found 65% higher elevated median CRP levels among pregnant women with periodontitis compared to periodontally healthy women (2.23 μ g/ml versus 1.46 μ g/ml). However, this study differed from ours with respect to the racial characteristics. More than 80% of the population studied was white, whereas only 5% of the population was African American. Herrera et al.²⁹ also reported increasing median levels of

Table 2.
Demographic, Medical, and Obstetric Data by Maternal Race

Subject Characteristics	African American (n = 360)	White (n = 374)	P Value*
Maternal age (years; mean \pm SD)	25.6 \pm 5.9	30.3 \pm 6.3	NS
Maternal weight at enrollment (pounds; mean \pm SD)	167.3 \pm 43	150.9 \pm 38	0.009
CRP ($\mu\text{g/ml}$; mean \pm SD)	17.3 \pm 19.3	8.0 \pm 13	<0.001
CRP ($\mu\text{g/ml}$; median [IQR])	7.68 (1.88 to 31.7)	2.59 (0.16 to 9.95)	<0.001
CRP >75th percentile (n [%])	126 (35)	57 (15)	<0.001
Periodontal disease status (n [%])			
Healthy	40 (11)	162 (43)	NS
Mild	235 (62)	191 (51)	NS
Moderate/severe	85 (27)	21 (5)	<0.001
Married (n [%])	81 (23)	278 (74)	<0.001
Privately insured (n [%])	70 (19)	264 (71)	<0.001
Eligible for WIC/food stamps (n [%])	129 (36)	38 (10)	<0.001
Primigravida (n [%])	117 (33)	175 (47)	<0.001
Multiparous with previous preterm delivery (n [%])	79 (22)	47 (13)	<0.001
Sexually transmitted infection (n [%])	69 (19)	27 (7)	<0.001
Smoking during current pregnancy (n [%])	74 (21)	57 (15)	NS
Alcohol use during current pregnancy (n [%])	48 (13)	73 (20)	0.02

NS = not statistically significant.

* χ^2 test.

Table 3.
Periodontal Disease Status, Maternal Race, and CRP \geq 75th Percentile

Periodontal Disease/Race*	White	African American
	Adjusted OR (95% CI) [†]	
Healthy	1.0 (reference)	0.7 (0.2 to 2.2)
Mild	1.1 (0.5 to 1.9)	2.9 (1.1 to 3.8)
Moderate/severe	0.9 (0.2 to 3.6)	4.0 (1.2 to 8.5)

* Based on 734 women of African American and white race.

[†] Adjusted for age, smoking, prior preterm delivery, marital status, insurance status, and weight.

CRP in women with periodontitis. In this case-control study, women with mild periodontitis had median CRP levels of 4.98 $\mu\text{g/ml}$, whereas women with moderate/severe periodontitis had median CRP levels of 8.16 $\mu\text{g/ml}$. This population of women is similar to our cohort of women with respect to very low socioeconomic status; however, <30% of the women were African American.

The recent development of highly sensitive CRP assays by nephelometry, which have decreased the discriminatory range for serum CRP values from 10 to <1 $\mu\text{g/ml}$, has allowed investigators to further explore the role of subclinical and low-grade inflammation in predicting and diagnosing pathology characterized by inflammation. The ELISA method used in this study had detection limits that approximate those levels (0.5 $\mu\text{g/ml}$). CRP is one of the most studied and validated measures of vascular inflammation.¹² The usefulness of measuring serum CRP as a biomarker of cardiovascular risk has been well described.^{21,30} Non-pregnant individuals with serum CRP levels >3 $\mu\text{g/ml}$ are considered to be at high risk for future cardiovascular disease and events.³¹

Limited information is available on normal values of CRP in pregnancy. Early studies,³²⁻³⁴ using older assays with less sensitivity and narrower discriminatory ranges over broad ranges of gestational ages, reported varying results regarding CRP levels in healthy pregnant women. This has limited the usefulness of CRP to screen or predict disease among pregnant women. Serum CRP levels are higher among pregnant women compared to non-pregnant women,

confirming that pregnancy is associated with a low-grade maternal inflammatory response.²⁶ Median CRP levels may fluctuate during pregnancy but are $\sim 3 \mu\text{g/ml}$ throughout all trimesters of pregnancy. In a recent longitudinal study using the highly sensitive immunoassay for CRP, Belo et al.¹⁹ reported longitudinal data on CRP fluctuation on a small number of women during normal pregnancy. Compared to non-pregnant women, CRP levels were significantly higher in pregnant women. CRP levels remained fairly constant throughout gestation, with a median CRP level $\sim 3 \mu\text{g/ml}$; no values were $>15 \mu\text{g/ml}$.

The limitations of our study warrant discussion. This is a secondary analysis of data collected for the OCAP study in which CRP levels were measured in 76% of the women enrolled. This raises the concern for potential bias. However, maternal demographic characteristics and oral health status were similar among women with and without serum available for CRP testing (data not shown). In addition, although our cohort was evenly divided between African American and white women, significant differences existed in the sociodemographic characteristics of these two groups. If the racial groups had been better matched for socioeconomic characteristics, we may not have observed these racial differences in CRP. However, in our multivariable logistic model, elevations in serum CRP among women with periodontal disease persisted among African Americans, even after adjusting for possible confounding.

CRP is a non-specific marker of inflammation and is known to be elevated in persons with periodontal disease.^{17,18} It is possible that our subject population had elevated CRP levels for reasons that we were unable to account for or evaluate. We did not assess the presence or absence of dental caries and recognize that our cohort of women could have periapical inflammation in teeth with advanced caries that would have contributed to oral inflammation. It is also plausible that maternal periodontal disease is acting as a surrogate for some other maternal factor. The overall amount of periodontal disease in this pregnant population was not as severe or extensive as reported in other studies^{17,18} that examined the relationship between periodontal disease and CRP levels in older subjects with more periodontal disease.

CONCLUSIONS

As measured by CRP, African American women with moderate/severe periodontal disease evoke a high systemic inflammatory response early in pregnancy. Uncovering racial differences in maternal serum CRP levels and periodontal disease does not explain why these disparities exist, and the impact of these differences on adverse pregnancy outcomes is unknown. In addition, the role of maternal inflammation in re-

sponse to periodontal infection in mediating adverse pregnancy outcomes remains to be explored, although Ruma et al.³⁵ demonstrated that the relationship between maternal periodontal disease and pre-eclampsia may be partially explained by maternal inflammation. Further research is needed to determine whether the treatment of periodontal disease decreases the burden of maternal systemic inflammation and impacts pregnancy outcomes. Because the implementation of dental services to underserved pregnant women with limited access to care is a daunting task, it may be possible to tailor preventive dental care to those women in greatest need and/or who are most likely to benefit. Understanding that African American women are at greater risk for moderate/severe periodontal disease compared to white women, which is associated with a significant inflammatory burden and potential adverse pregnancy outcomes, justifies further research in this at-risk population.

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