Periodontal Inflamed Surface Area Is Associated With Increased Gestational Blood Pressure and Uric Acid Levels Among Pregnant Women From Rural North China

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Background: Periodontal disease has been associated with gestational complications and both conditions have a high prevalence in rural populations from developing regions. A cross-sectional study was carried out to explore the relationship between periodontal inflamed surface area (PISA), blood pressure (BP), and, serum uric acid levels (UA) in a group of rural North Chinese pregnant women in the third trimester of pregnancy.

Methods: Three hundred and thirty-five rural women aged 20–34 years, with normal body mass index (BMI) were examined in a cross-sectional study during their third trimester of gestation. Exclusion criteria were history of pregnancy complications, multiple pregnancy, smoking habits, diabetes, hypertension or any known infectious disease. Socio-demographic variables, including age and socioeconomic status (SES), systolic blood pressure (SBP) and diastolic blood pressure (DBP) readings, serum UA levels, and PISA values were recorded. A structural equation model was implemented with two constructed latent variables including "Dem" (comprising of age and SES category to represent unobserved demographic variables) and, "BP" (comprising of SBP and DBP to account for measurement error and lack of multiple BP readings). The model accounted for co-variance of BP and UA, and implemented simultaneous regressions for BP and UA as outcomes, upon Dem and PISA values as exogenous variables.

Results: The median PISA score was 1,081.7 (IQR = 835.01), reflecting high levels of periodontal inflammation in the sample. SEM showed a significant association of PISA with BP (estimate = 0.011, 95% CI = 0.009–0.012 $p < 0.001$) and UA (estimate = 0.001, 95% CI = 0.001–0.001, $p < 0.001$).

Conclusion: Higher PISA values were significantly associated with higher blood pressure and uric acid levels among rural pregnant women in a cross-sectional sample from a center in North China after accounting for a latent demographic construct derived from age and SES.

Keywords: periodontal disease, low birth weight, gestational hypertension, uric acid, periodontal inflamed surface area

INTRODUCTION

Hypertensive disorders of pregnancy affect more than 5% of women in China, with the highest incidence in North China [1]. Hypertension without the development of significant proteinuria (<0.3 g/l), after 20 weeks of gestation or during labor and/or within 48 h of delivery is termed gestational hypertension and is a risk for preeclampsia, eclampsia, and preterm low birth weight [2]. Inflammation has been implicated in the pathogenesis of preeclampsia and attributed to chronic subclinical infections and higher levels of pro-inflammatory cytokines [3]. Principally, gestational blood pressure and increased oxidative stress are interlinked [4] and both are associated with a higher risk of adverse pregnancy outcomes [5]. Chronic infections are established contributors to these, operating through increased systemic pro-inflammatory cytokine load [6]. Serum uric acid, a primary physiological antioxidant is considered as one of the primary markers of oxidative stress [7] and hyperuricemia in pregnancy is implicated both as a risk marker and contributory factor for preeclampsia [8]. In particular, increased blood pressure during the third trimester of pregnancy is linked to adverse birth outcomes [9].

Periodontal infection is a source of chronic systemic microbial load and has been associated with the incidence of preeclampsia [10] and pre-term low birth weight infants [11]. Proposed mechanisms of the periodontal infection-pregnancy outcome link include oral bacterial translocation to the uteroplacental unit, increased systemic oxidative stress and pro-inflammatory cytokine load leading to preeclampsia and premature rupture of membranes [12]. A major contributory mechanism is the systematic dissemination and placental localization of periodontal pathogens such as *Porphyromonas gingivalis* with ensuing immuno-inflammatory sequelae [9, 13]. Umbrella reviews of systematic reviews have noted that periodontal disease increases the odds of pre-eclampsia [14] and pre-term birth [15] by ~2-fold but also show that several meta-analyses have not adjusted for confounding. Heterogeneity in the strength association depends on the nature of exposure and outcome variables analyzed [16, 17]. At the same time, current evidence evaluating the efficacy of periodontal treatment in reducing adverse pregnancy outcomes is unclear and incongruent [18–22]. An umbrella review found significant effects upon subgroup analysis based on sociodemographic conditions [23], which highlights the significance of studying vulnerable populations in this context.

Periodontal disease can be highly prevalent among pre-conception women in some regions of China [24], compounded by low levels of oral health awareness and utilization of dental services in rural areas [25]. Periodontal disease has been reported to have a high prevalence among rural pregnant women in China [26]. Therefore, its potential impact on pregnancy-related variables and outcomes in rural Chinese populations needs greater investigation. In addition, a large-scale retrospective study showed an increased risk of hypertension was associated with periodontal disease in the Chinese population [27], further highlighting the necessity of investigating periodontal disease as an exposure in the context of gestational blood pressure in

Chinese populations. Higher prevalence of both periodontitis [24, 25] and hypertensive disorders during pregnancy [1] in populations in underserved regions of North China begets further investigations into their association.

Traditional measures of periodontal disease and disease categories pose limitations in assessing the burden of active inflammation which is responsible for its systemic sequelae, and therefore, the Periodontal Inflamed Surfaced Area (PISA) index was developed [28], representing the net probing depth of bleeding on probing positive sites for an individual. PISA values comprise a continuous quantitative variable that prevents the loss of information inherent to the categorization of periodontal disease categories [29]. Moreover, different case-definition criteria applied for periodontal diagnosis in pregnant women yield widely variable disease estimates, and PISA may be a more suitable measure of inflammatory burden [30]. Furthermore, periodontal inflammation as measured by PISA values has been associated with high blood pressure in a large-scale study of over 8,000 subjects [31].

The present cross-sectional study aimed to explore the association of periodontal inflammatory burden assessed using PISA values with prenatal gestational blood pressure and serum uric acid levels in a sample of rural-living North Chinese women in the third trimester of pregnancy.

MATERIALS AND METHODS

Ethical approval and sample size estimation: The study protocol was approved by the Medical Ethics Committee of Changzhi Medical College. All study procedures were compliant with the Declaration of Helsinki. Sample size estimation was performed using the "epi.sssimpleestb" function from the epidemilogical R packge "EpiR" (https://cran.r-project.org/web/packages/epiR/index.html). Data for the estimated prevalence of gestational hypertension in North China (7.44%) [1] was used to estimate the sample size, assuming a population of 1,000 suitable pregnant women would visit the sampling center during the data collection period. At a confidence interval of 95% and margin of error 20%, the target sample size was determined as 352. However, 335 subjects finally participated in the study as 17 recruited subjects were unable or unwilling to complete the study procedures.

Study Participants

A group of 335 eligible subjects in week 28 or beyond of pregnancy were recruited consecutively during their routine prenatal visit at The Heping Affiliated Hospital of Changzhi Medical College, Changzhi City, Shanxi Province, China, from January to April 2021. The inclusion criteria were; pregnant women aged between 18 and 34 years in the third trimester, Body Mass Index (BMI) of 18.5–24.9, presence of at least 20 teeth, with no history of periodontal or dental treatment in the past 1 year. Exclusion criteria were smoking or smoking habits, previous history of preterm delivery, previously diagnosed gestational hypertensive disorders, or other pregnancy complications, known systemic conditions or diseases such as

chronic hypertension, diabetes, renal disease, polyhydramnios or known congenital malformation in fetus, infections during pregnancy such as bacterial vaginosis and chorioamnionitis, other bacterial or viral illnesses, or antibiotic use during pregnancy. All subjects provided written and oral informed consent before any study procedure. Oral health counseling was provided to all screened subjects by a dental professional irrespective of their study participation. Appropriate referral for dental or medical management was also provided when deemed necessary based on the clinical findings.

Data Collection

Medical records were the source of demographic variables; age, socioeconomic level (SES), scored as high, medium or low, where to assess SES, monthly family income was noted and grouped into; low (<2,000 RMB per month), moderate (2,000–6,000 RMB per month) or High (6,000 RMB per month) (32), and retrospective medical data. The mean of three consecutive readings of blood pressure (SBP and DBP) was calculated and serum uric acid level (UA) was measured. A full mouth periodontal examination was performed by a trained single examiner (W.S) and included the recording of pocket probing depth (PPD), clinical attachment loss (CAL) and bleeding on probing (BOP) at 6 sites per tooth, by using a UNC-15 periodontal probe. PPD and CAL were measured as the linear distance in millimeters and rounded to the nearest millimeter, where PPD was the distance from the gingival margin to the base of the pocket and CAL was measured as the linear distance from the cementoenamel junction to the base of the pocket. Bleeding on probing (BOP) was recorded as a dichotomous variable representing presence of absence of bleeding. PISA values were calculated for each subject as described earlier (28) using an excel spreadsheet. In brief, the mean CAL and gingival recession for each tooth were recorded and were used to determine the periodontal epithelial surface area (PESA) score per tooth, representing the surface area in mm2 enveloped by pocket epithelium. Next, the PESA for score multiplied by the number of BOP positive sites around that tooth indicated the PISA score for that tooth, and the sum of these determined the full-mouth PISA score.

Data Analysis

All data analysis was performed in the R statistical environment. Prior to modeling, variable distribution was examined for normality using the Shapiro Wilk test. Structural equation modeling (SEM) was applied using the "lavaan" package (v 0.5-9) (33) using a maximum likelihood estimator. SEM is a multivariate modeling technique that allows simultaneous modeling of observed and unobserved or latent variables, and these variables can account for measurement error and observed covariation (34, 35). In the SEM model, UA, SBP, DBP were utilized as observed endogenous or dependent variables, and, age, SES and PISA were modeled as observed exogenous or independent variables. Two latent variables were created, including, "BP" as a combination of endogenous variables SBP and DBP, and "Dem" as a combination of exogenous variables

TABLE 1 | Descriptive statistics.

Parameter	Range	Median (interquartile range)
Age (years)	18–34	24 (6)
PISA value (mm^2)	0.0–2,472.6	1,081.7(835.01)
SBP (mm of Hg)	110–160	120 (5)
DBP (mm of Hg)	70–100	70 (10)
UA (mg/dl)	3.1–5.0	3.7 (0.6)
	Frequency	
SES	Low = 119 (35.5%), Medium = 216 (64.5%)	

PISA, Periodontal Inflamed Surface Area; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; UA, Serum Uric Acid; SES, Socioeconomic status.

age and SES. The co-variance of BP with UA was modeled to account for residual correlation. Two simultaneous regressions were modeled for BP and UA, using Dem and PISA values as predictors. Model fit was estimated as acceptable where Tucker-Lewis Index (TLI) > 0.90 (36) and normed Chi-square value <5 (37).

RESULTS

Descriptive data pertaining to the cross-sectional sample are presented in **Table 1**. The median age of the cohort was 24 (IQR = 6) years. The distribution of SES showed that 119 (35.5%) were in low SES and 216 (64.5%) were in the medium SES category. The mean PISA score was 1,081.7 (IQR = 835.01). The median SBP was 120 (IQR = 5) and DBP was 70 (IQR = 10), while median UA was 3.7 mg/dl (IQR = 0.6). Based on SBP and DBP reading cut-offs for gestational hypertension (1, 2), 11.3% women satisfied the criteria and were referred for additional investigations. However, it was recognized that single day BP readings were not sufficient for definitive diagnosis; hence this grouping was not utilized for data analysis. Significant correlations between the observed variables are summarized in a correlation matrix plot presented in **Figure 1**. Significant and strong correlations ($r > 0.6$, $p < 0.001$, all) were noted between the three endogenous dependent variables DBP, SBP, and UA. Among the exogenous variables, age was significantly but weakly correlated with DBP ($r = 0.14$, $p = 0.01$), lower SES was weakly correlated with SBP ($r = 0.24$, $p < 0.001$), DBP ($r = 0.24$, $p < 0.001$) and UA ($r = 0.23$, $p < 0.001$). PISA score was moderately correlated with DBP ($r = 0.58$, $p < 0.001$) and strongly correlated with SBP ($r = 0.66$, $p < 0.001$) and UA ($r = 0.72$, $p < 0.001$). Very weak but significant correlations were noted for lower SES with Age ($r = 0.13$, $p = 0.02$) and PISA score ($r = 0.12$, $p = 0.03$). The SEM model outcomes are summarized in **Table 2**. The latent variable BP was highly significantly predicted by PISA (estimate = 0.011, 95% CI = 0.009–0.012, $p < 0.001$) and also significantly predicted by Dem (estimate = 3.37, 95% CI = 0.41–6.83, $p = 0.03$). UA was also significantly predicted by PISA (estimate = 0.001, 95% CI = 0.001–0.001, $p < 0.001$) and also significantly predicted by Dem (estimate = 0.15, 95%ci = 0.13–0.29, $p = 0.04$).
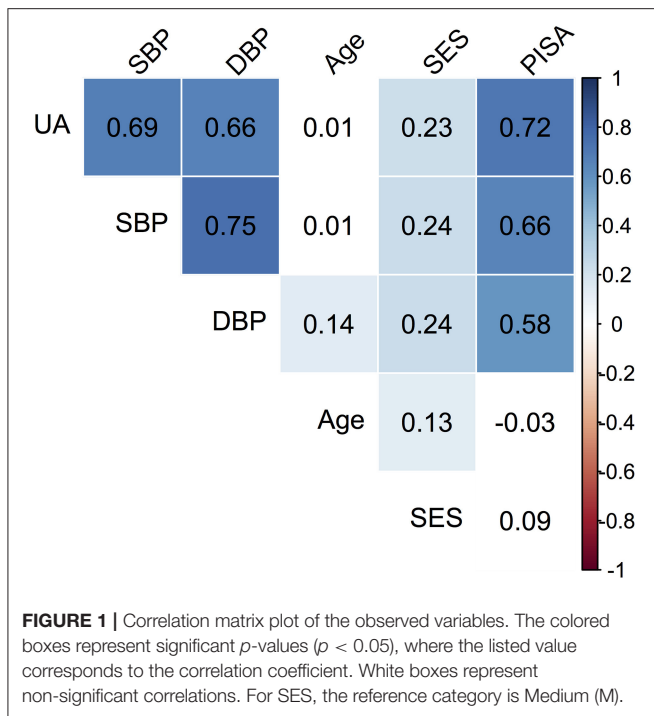
FIGURE 1 | Correlation matrix plot of the observed variables. The colored boxes represent significant p-values (p < 0.05), where the listed value corresponds to the correlation coefficient. White boxes represent non-significant correlations. For SES, the reference category is Medium (M).

TABLE 2 | Structural relationships and variances in the SEM[a] analysis.

Structural relationship	Estimate	95% CI	P-value
PISA ➔ BP[b]	0.011	0.009–0.012	<0.0001***
Dem[c] ➔ BP[b]	3.59	0.44–6.73	0.03*
PISA ➔ UA	0.001	0.001–0.001	<0.0001***
Dem[c] ➔ UA	0.15	0.13–0.28	0.04*
Variances			
SBP	18.45	12.78–24.13	<0.0001***
DBP	15.48	11.97–18.99	<0.0001***
UA	0.09	0.07–0.12	<0.0001***
Age	14.45	12.12–16.78	<0.0001***
SES*	0.14	0.05–0.24	0.003
BP	24.56	12.50–36.62	<0.0001***
Dem	0.70	−0.34–1.74	0.19

***p < 0.0001, *p < 0.05.
[a]Model fit indices: TLI = 0.96, normed Chi-square = 3.40.
[b]"BP" indicates a latent BP variable constructed from SBP and DBP.
[c]"Dem" indicates a latent Demographic variable constructed from Age and SES.
PISA, Periodontal Inflamed Surface Area; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; UA, Serum Uric Acid; SES, Socioeconomic status.

DISCUSSION

This cross-sectional study explored the association of gestational blood pressure and UA, a marker of oxidative stress with periodontal inflammatory burden among pregnant women at a rural center in North China, using structural equation modeling. While the present study, identified the nature of the association between periodontal inflammation, BP and a marker of oxidative stress among rural women using a cross-sectional design, epidemiological studies have linked periodontal disease with a higher risk of pregnancy complications (10, 11, 14, 15, 17, 19) including preeclampsia and preterm low birth weight deliveries (38, 39). The type of periodontal disease case-definition may influence the outcome of an association of periodontal disease with pregnancy complications as noted by Papapanou and Ide (40), who also found that case-control and cross-sectional studies provided a higher estimate of the association as compared to prospective studies. Therefore, a strength of the current study is the utilization of PISA as an exposure variable indicating the inflammatory burden arising from periodontal disease. The median PISA score was 1,081.7 (IQR = 835.01), reflecting high levels of active periodontal inflammation in this sample, largely in agreement with previous findings of a very high prevalence of periodontal disease among rural Chinese pregnant women (41). Of note, A PISA value $\geq$ 130.33 mm^2 has been found to indicate periodontitis at very high sensitivity and specificity (42). Another strength of the present study is the use of SEM, a multivariate technique incorporating observed variables and latent constructs that allows for simultaneous modeling of multiple relationships and accounts for covariance between variables. Here, BP was modeled as a latent variable, as a trait derived from SBP and DBP (43), which can account for measurement errors inherent to the lack of longitudinal data, circadian pattern, and their correlation. Differences in circadian amplitudes of BP have been found to predict gestational complication even when BP readings were within physiological limits (44). In addition, 24-h BP during the third trimester has shown superior prediction of pregnancy complications than in-office BP readings, plausibly owing to the phenomenon of white coat hypertension (45). The restricted inclusion criteria were chosen to avoid the confounding effects of obesity, advanced age and other known systemic conditions. Age and income are established co-factors in the multi-factorial nature of gestational complications (46, 47) and were recorded. However, a number of confounding variables including the quality and regularity of prenatal care and diet that can influence gestational health. Considering these and other such variables were not assessed directly, a latent variable "dem" was constructed using maternal age and SES, as both of these factors are contributory to antenatal care utilization patterns, dietary variables, and pregnancy outcomes (48–50).

In the model, after accounting for the effects of latent demographic variables, higher gestational blood pressure was significantly associated with higher PISA values, in agreement with the results of Pietropaoli et al. (31) in the general population. Serum UA was also significantly associated with PISA score. Chronic infection and cytokine load have both been associated with increased xanthine oxidase activity (51) which is an important mediator of endogenous UA production. UA being a major plasma antioxidant and marker of systemic oxidative stress has been investigated with regards to periodontal disease and better periodontal status has been associated with higher levels of serum uric acid in healthy subjects (52). UA in pregnancy is considered an important risk marker of fetal risk in women with gestational hypertension (53)

and may have a causal role in its etiology (54). These findings suggest a contributory role of periodontal inflammatory burden to systemic oxidative stress and hypertension occurring during pregnancy.

The major limitations of the current study include the cross-sectional design that precludes causal inferences, the small sample size, and possible effects of unaddressed predictors such as nutritional status, lifestyle-related risk factors, genotype, the possibility of occult infection, level of antenatal care level, physical activity, weight gain, sleep, psychological status, among others (16, 55–60). To compensate in part, a SEM model was thus designed to construct and model unobserved or latent dimensions and has been previously applied in periodontal research (61–65). Furthermore, this study design fails to address the possible syndemic nature of the association between periodontal inflammation and systemic state, whereby vulnerable subsets may be affected by both periodontal and other inflammatory conditions (66). Importantly, as this cross-sectional sample consisted of pregnant women classified previously as medically healthy and within a narrow age range and excluded advanced maternal age which is an independent risk factor for gestational hypertension (67), broader conclusions regarding the general populace in this region are precluded. As all subjects were recruited from those seeking care at a single tertiary center located in rural North China, selection bias may be applicable, as those reporting to small primary health care centers or those not seeking any antenatal care were not included. Thus, the present findings may be considered as the basis for further research using more robust study designs. In particular, future interventional studies investigating the effects of periodontal therapy on BP and UA are warranted in light of the present findings. Future studies should focus on shared risk factors (55–60), specific vulnerable subgroups (23) and optimal timing of intervention (68). A previous study has noted those receiving prophylactic treatment had a 7.6% incidence of low birth weight as compared to 10.1% among those not receiving any treatment (18). Considering that unexplained perinatal mortality has been linked with periodontal disease (69) and has a high prevalence in developing regions with low oral health awareness and accessibility, this preliminary data highlights that further research is essential to estimate the risk burden attributable to periodontal inflammation in mediating pregnancy complications in specific demographics. Such data would enable tailored public health measures to direct resource allocation within specific high-risk groups.

CONCLUSION

A cross-sectional study using an SEM modeling approach showed that higher periodontal inflamed surface area was associated with increased gestational blood pressure and serum uric acid in a sample of rural North Chinese pregnant women. The quantum of risk imposed by periodontal inflammation and its clinical significance in this demographic warrants investigation in more appropriately designed large-scale, longitudinal studies.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Medical Ethics Committee of Changzhi Medical College, City of Changzhi, Shanxi Province, China (No. RT2021001). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SH conceptualized the research idea, carried out data analysis, and led the paper writing. FY and HJ performed the data analysis. WS and HM were responsible for study design and data collection. SL, JZ, and HX initiated the idea of the study, supervised the project, and edited the manuscript. All authors contributed to the article and approved the submitted version.

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