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The Interaction Effect of Bacterial Vaginosis and Periodontal Disease on the risk of Preterm Delivery

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Abstract

Objective—To determine if coexistence of periodontal disease (PD) and bacterial vaginosis (BV) is synergistic on the risk of spontaneous preterm delivery (sPTD).

Study Design—Secondary analysis of a prospective cohort study. Women were screened 6–20 weeks gestation for PD and BV. Groups were defined by presence of BV and stratified on PD. The primary outcome was sPTD <37 weeks gestation. Univariable, stratified and multivariable analyses were performed to estimate the main and interaction effects of BV and PD on sPTD.

Results—Of 1453 women screened, 792 (54.5%) were diagnosed with BV. Neither women with BV in the first trimester nor PD were at higher risk of sPTD (risk ratio (RR) for BV 1.1, 95% confidence interval (CI) 0.8–1.5, RR for PD 0.9, 95% CI 0.7–1.3). The interaction between BV and PD did not statistically significantly impact the odds of sPTD.

Conclusions—Coexistence of PD and BV did not have a synergistic effect on sPTD.

Keywords

bacterial vaginosis; periodontal disease; preterm delivery

Introduction

Both bacterial vaginosis (BV) and periodontal disease have been independently associated with an increased risk of preterm delivery.^{1–5} Interestingly, similar microbes are responsible for bacterial vaginosis and periodontal disease; both have been associated with *Fusobacterium sp* and *Prevotella sp*.⁶ Additionally, women are frequently affected by both bacterial vaginosis and periodontal disease; spread of bacteria from one location to the other may occur through hematogenous dissemination or spread through the gastrointestinal system.⁶ Women with periodontal disease may have higher associated vaginal bacterial counts.⁶ An increased bacterial load in bacterial vaginosis may increase the risk of preterm

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delivery.⁷ Consequently, a synergistic effect of periodontal disease and BV on preterm delivery may be expected.

The mechanism behind the association of BV and periodontal disease with preterm delivery may be an inflammatory response leading to preterm labor.^{8,9} The severity and chronicity of periodontal disease has been linked with genetic variations in cytokine expression,¹⁰ and genetic polymorphisms have been linked to the carriage of vaginal bacteria¹¹ as well as the risk of preterm birth in the presence of bacterial vaginosis.^{12,13} The genetic polymorphisms in the inflammatory response linked with BV and periodontal disease are also associated with preterm delivery, suggesting a common mechanism for BV and periodontal disease to cause preterm delivery. Alternatively, BV and periodontal disease may simply represent clinical markers of genetic polymorphisms linked to preterm delivery rather than causative agents of preterm delivery.

Therefore, we sought to determine whether the coexistence of bacterial vaginosis and periodontal disease was synergistic on the risk of spontaneous preterm delivery.

Materials and Methods

This is a secondary analysis of a multicenter prospective cohort study, the Periodontal Infection and Prematurity Study (PIPS). The cohort has been described in detail previously,^{14,15} a brief description follows. Institutional review board approval was obtained from all participating sites. Women at three prenatal clinics in Philadelphia were screened between 6–20 weeks gestation for periodontal disease by a trained nurse; women with periodontal disease were enrolled in a randomized control trial of treatment while women without periodontal disease were followed as a comparison group. Periodontal disease was defined as periodontal attachment loss greater than or equal to 3-mm on 3 or more teeth. Recruitment occurred from October 2004 to October 2007. Each study nurse was retrained and observed once or twice annually for the duration of the study. Women who received periodontal treatment during pregnancy, used antibiotic or antimicrobial mouthwash within 2 weeks, had a multiple gestation, or known mitral valve prolapse were excluded from the original study.

Women with periodontal disease were asked to complete a baseline interview and provide consent for enrollment into the randomized portion of the trial. Randomization took place at the subsequent visit. Women without documented periodontal disease were also asked to complete a baseline interview and provide consent for the follow-up study. All data were collected by a structured interview at enrollment and a standardized chart review by trained research nurses at the end of the follow up period. Data collected included delivery outcomes, prior obstetric history, maternal race, age, education, obesity, medical complications, tobacco and drug use. Women were screened for BV at enrollment; BV was defined as a Nugent score greater than or equal to 7 on a vaginal swab Gram-stain.¹⁶ Nugent scores were determined after the completion of the study and were not available to the providers. Treatment of BV as part of routine care was at the discretion of the provider.

The primary exposure of interest was BV at the time of enrollment. The primary outcome was spontaneous preterm delivery less than 37 weeks. The secondary outcomes were spontaneous preterm delivery less than 35 weeks, any preterm delivery prior to 37 weeks, and any preterm delivery prior to 35 weeks. Baseline characteristics of the study groups were compared between subjects who had BV at enrollment and those who did not have BV at enrollment using the Students t-test for continuous variables and χ^2 test for categorical variables. The presence of BV at enrollment and periodontal disease, along with other maternal characteristics, were individually evaluated for association with spontaneous

preterm delivery in a univariate analysis. The population was then stratified by periodontal disease and relative risks (RR) for spontaneous preterm delivery were estimated. Multivariable logistic regression models were then fit for the association between BV and spontaneous preterm delivery, controlling for potential confounding factors identified in the univariate analysis. Non-significant variables were removed in a backwards stepwise fashion. To further evaluate for synergist interaction between BV and PD on the risk for spontaneous preterm delivery, an interaction variable was added to the base model. The two models (with and without the interaction variable) were compared using the likelihood ratio test. Treatment of periodontal disease in the randomized control trial did not impact the risk of spontaneous preterm delivery;¹⁴ therefore, treatment group allocation was not included in the model. All statistical analyses were performed using STATA version 10.0, Special Edition (College Station, TX).

Results

In the original PIPS trial, 5,085 women were assessed for eligibility. Of these, 1722 women were assessed for bacterial vaginosis at enrollment, 1453 had complete delivery information available. Figure 1 demonstrates the occurrence of BV and periodontal disease in the subjects. Approximately 10% of subjects in each group (BV with or without PD) experienced a spontaneous preterm delivery prior to 37 weeks. Table 1 describes the baseline characteristics of the 1453 subjects included in the study groups based on the presence or absence of bacterial vaginosis at enrollment. The study groups were similar with respect to maternal age, gravidity, gestational age at enrollment, the presence of periodontal disease and history of a spontaneous preterm delivery. Women with BV were equally likely to be randomized to receive treatment for PD. Women with BV were slightly more likely to be Black.

Univariate analysis demonstrated that having BV at enrollment was not associated with an increased risk of spontaneous preterm delivery less than 37 weeks (risk ratio (RR) 1.1, 95% confidence interval (CI) 0.8–1.5) or less than 35 weeks (RR 1.0, 95% CI 0.6–1.6). No association between periodontal disease and preterm delivery was noted (for <37 weeks RR 0.9, 95% CI 0.7–1.3, for <35 weeks RR 0.9, 95% CI 0.6–1.4).

To evaluate for a possible synergistic effect modification of periodontal disease on the association between BV and PTD, the population was first stratified by periodontal disease (Table 2). The incidence and RR of PTD was calculated for BV in both the PD and no PD strata. The difference in the risk of spontaneous preterm delivery between the two groups when stratified by PD was not statistically significant, thereby indicating no evidence of synergism. Subjects with both BV & PD were stratified by whether or not the PD was treated; no difference in the risk of preterm delivery less than 37 or 35 weeks was noted in either group (Table 2).

To further evaluate for synergism, a base logistic regression model was created for the association of preterm delivery and BV adjusting for potential confounders. Confounders included in the final model were BV, PD, black race and history of spontaneous preterm delivery. After adjusting for black race and history of spontaneous preterm delivery, neither BV nor PD were associated with spontaneous preterm delivery <37 weeks (AOR for BV 1.0, 95% CI 0.9–1.1, AOR for PD 1.0, 95% CI 0.7–1.4) (Table 3). The interaction term did not have a statistically significant effect on the risk of preterm delivery (AOR 1.0, 95% CI 0.8–1.3). The base model was then compared to a second model containing the interaction term (BV*PD). PD did not display a significant effect modification on the association between BV and preterm delivery <37 weeks when the two models were compared using the likelihood ratio test ($p=0.68$). Similar results were obtained for preterm delivery <35 weeks.

Results were similar when considering any (spontaneous or iatrogenic) preterm delivery less than 37 and less than 35 weeks (data available upon request).

Discussion

In this prospective cohort study, periodontal disease and bacterial vaginosis did not have a synergistic effect on preterm delivery. Neither bacterial vaginosis diagnosed at enrollment nor periodontal disease was associated with an increased risk of preterm delivery less than 35 or 37 weeks.

The majority of prior studies have investigated periodontal disease and bacterial vaginosis independently as risk factors for preterm delivery.^{1,3-5,15,17,18} Although many studies have suggested a link between periodontal disease and preterm delivery and bacterial vaginosis and preterm delivery, treatment studies of low-risk patients have not demonstrated any risk reduction in preterm birth with treatment of either.^{14,17,19} These findings, in combination with our finding that the presence of both periodontal disease and BV is not synergistic, suggest that perhaps BV and periodontal disease are clinical markers for a genetic susceptibility or other environmental factors rather than causative agents. It is possible that the polymorphisms in the inflammatory pathway that make subjects more likely to have BV or periodontal disease also place them at higher risk for preterm delivery.

One prospective cohort study examined women for both periodontal disease and bacterial vaginosis prior to pregnancy.²⁰ In this study of 130 women, periodontal disease and bacterial vaginosis were both independently associated with adverse pregnancy outcomes (miscarriage and preterm birth). Only 5 women had both periodontal disease and bacterial vaginosis, and three of them developed an adverse pregnancy outcome. However, whether this outcome was miscarriage or preterm birth was not specified and conclusions from these findings are limited by the fact that only 5 women in the study had both infections.

Our study has several strengths. First, all women were screened prospectively at less than 20 weeks gestation for both periodontal disease and bacterial vaginosis, using standardized and objective definitions of both, thus allowing all women included in the study to be assessed equally for the exposures of interest and limiting misclassification. Additionally, a significant number of included subjects (n=546) had both periodontal disease and bacterial vaginosis, allowing us to investigate the association between preterm delivery and the coexistence of periodontal disease and bacterial vaginosis. The multicenter design provided a heterogeneous population, making the findings generalizable. Finally, a large amount of clinical information was gathered on all participants, allowing important confounders to be investigated.

Some important limitations should be noted. Not all patients agreed to participate in the study or returned to follow up appointments after consenting to participate, leading to a potential selection bias in participants. In comparing women who did not return for follow up and participants, the two groups were similar with respect to nearly all baseline demographic characteristics, suggesting that any selection bias would have been minimal. It is also possible that despite our best efforts to measure important confounding factors, some exposure was either unknown or immeasurable, making it impossible to consider in our logistic regression models. Periodontal disease was considered only as a dichotomous variable; it is possible that severity of periodontal disease impacts the associated risk of preterm birth. However, this is difficult to measure as a standardized definition of periodontal disease severity does not exist. Finally, treatment of BV was at the discretion of providers. This could have altered the results by impacting the time of exposure to BV; however, treatment of BV has not been demonstrated to impact the risk of spontaneous

preterm delivery in randomized control trials and we therefore do not expect that this impacted our findings.¹⁷

In conclusion, our study did not demonstrate evidence of a synergistic interaction of the coexistence of bacterial vaginosis and periodontal disease on preterm birth. Absence of synergism suggests that rather than being causative agents of preterm delivery, BV and periodontal disease may be epidemiologic markers of susceptibility to preterm delivery. Whether they represent a genetic susceptibility to these infectious agents and preterm delivery or other unidentified environmental risk factors remains to be determined.

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Figure 1.
Flow chart of subjects through study

Table 1

Characteristics of the Study Groups

	Bacterial Vaginosis (n=792)	No Bacterial Vaginosis (n=661)	p
Maternal age (yrs)	23.5 ± 5.2	23.7 ± 5.5	0.23
Gravidity (mean)	3.0 ± 2.0	3.0 ± 2.0	0.78
Gestational Age at Enrollment/Initial Screen	13.1 ± 3.6	13.2 ± 3.6	0.23
Black Race	681 (86.2%)	535 (81.3%)	<0.01
Prior Spontaneous Preterm Delivery	69 (8.7%)	49 (7.4%)	0.37
Periodontal Disease	546 (68.9%)	432 (65.3%)	0.15
Assigned to Receive Treatment for PD	204 (25.8%)	143 (21.6%)	0.12

Table 2

Risk of preterm delivery stratified by the presence or absence of periodontal disease

	Delivery <37 wks	Delivery <35 wks
BV	1.1 (0.8–1.5)	1.0 (0.6–1.6)
BV, No Periodontal Disease	1.0 (0.6–1.7)	0.8 (0.4–1.7)
BV, Periodontal Disease All	1.2 (0.8–1.7)	1.2 (0.7–2.0)
BV, Periodontal Disease Treated	1.1 (0.6–2.0)	1.8 (0.6–4.9)
BV Periodontal Disease, Not Treated	1.2 (0.6–2.1)	0.7 (0.3–1.8)

Data presented as RR (95% CI)

Table 3

Effect modification of PD and BV on PTD

	aOR (95% CI) No interaction variable	aOR (95% CI) Interaction variable
	Preterm Delivery <37 weeks	
BV	1.0 (0.9–1.1)	1.0 (0.8–1.1)
PD	1.0 (0.7–1.4)	0.9 (0.6–1.4)
	LR test p=0.82	
	Preterm Delivery <35 weeks	
BV	1.0 (0.8–1.1)	0.8 (0.4–1.9)
PD	0.9 (0.5–1.4)	0.8 (0.4–1.5)
	LR test p=0.72	

Model also adjusted for black race and history of spontaneous preterm delivery