Published in final edited form as:
Am J Obstet Gynecol. 2008 February ; 198(2): 196.e1–196.e4. doi:10.1016/j.ajog.2007.09.006.

Paternal race and bacterial vaginosis during the first trimester of pregnancy

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Abstract

Objective—To determine the joint effects of maternal and paternal race on risk of bacterial vaginosis (BV) during the first trimester.

Methods—In this cohort of women with singleton gestation < 13 weeks and a race of either black or white (n=325), BV was diagnosed by vaginal pH and Gram stain

Results—BV was less common among white women than black women. Paternal race modified the effect of maternal race on BV risk. BV risk was twofold greater among both white female-black male partners and black female-white male partners. BV risk was also two-fold greater among black female-black male partners. Black race among both partners confers no additional risk than with one black partner.

Conclusions—Paternal black race is an independent risk factor for BV during pregnancy, and is as important a risk factor as maternal race. Studies of BV and adverse pregnancy outcomes should consider paternal race.

Keywords

race; bacterial vaginosis; pregnancy; paternal effect

Introduction

Bacterial vaginosis (BV) is one of the most prevalent vaginal disorders in adult women affecting 30% of reproductive age women.[1] Bacterial vaginosis is a syndrome characterized by a relative lack of lactobacillus and an increased prevalence of anaerobic bacteria, G. vaginalis, Mobiluncus spp., and M. hominis. There is a strong and consistent association of bacterial vaginosis during pregnancy with preterm birth.[2, 3] While a woman's socioeconomic and educational status characteristics and sexual and reproductive health behaviors are important contributors to risk of BV, the risk factor with the greatest magnitude of association

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Condensation: Paternal black race is an independent risk factor for BV during pregnancy, and is as important a risk factor as maternal black race.

with BV is black race. Black women have a 3-fold increased risk of BV compared with white women, and this disparity remains after controlling for most of the well-recognized risk factors.[1] The increased frequency of BV among black women has been hypothesized to be related to an increased frequency of douching, coital frequency, lower socioeconomic status, and the use of vaginal products, but accounting for these factors still does not explain completely the racial disparity.[1, 4] Furthermore, the risk of preterm birth attributable to bacterial vaginosis and vaginal inflammation is greater among African-American women than their Caucasian counterparts.[5, 6]

While maternal black race as a risk factor for preterm birth is well-established, little is known about the contribution of paternal race. The purpose of our study is to describe the contribution of paternal race and parental racial discordance to the risk of bacterial vaginosis during pregnancy.

Methods

We performed a prospective, observational cohort study of women from the general obstetrical population seeking prenatal care at the Magee-Womens Hospital prenatal clinic between April 2005 and June 2006. This study was approved by the Institutional Review Board of the University of Pittsburgh. The primary purpose of this observational cohort was to explore gene-environment interactions that contribute to a high-risk phenotype for preterm birth. This paper represents work related to an *a priori* secondary aim of this cohort study. Inclusion criteria for the cohort study were singleton intrauterine gestation prior to 13 weeks gestation and a self-reported race of either black or white. No subjects were Hispanic. Exclusion criteria included vaginal bleeding, fetal anomalies, known thrombophilias, pre-gestational diabetes mellitus, chronic hypertension requiring medication, current or planned cervical cerclage, immune compromise (HIV positive, use of systemic steroids within six months, use of post-transplant immunosuppressive medication), and autoimmune disease (inflammatory bowel disease, Systemic Lupus Erythematosus, rheumatoid arthritis, scleroderma). These exclusions were developed prior to study enrollment because they are believed to be associated with preterm delivery or an alteration in the immune status of the women which would confound the associations we proposed to examine. After provision of informed consent, all women provided demographic, medical, environmental exposures, and clinical information through standardized, closed-question, research interviews administered by research personnel. Specific open- and closed-ended questions regarding sexual practices and reproductive health behaviors (e.g. number of partners, frequency of intercourse) were used.

At a first trimester study visit (median gestation 6.5 weeks), in accordance with a standardized protocol, a pelvic examination was performed using a clean, non-lubricated speculum. Two Dacron swabs were placed in the cervix and left there for 10 seconds to achieve saturation. These swabs were placed in a plastic tube containing 400 ml of Purified Bovine Serum (final dilution of 1:5), and stored at −80°C until assay. Two vaginal swabs were also collected for culture and identification of vaginal flora. Bacterial vaginosis was diagnosed by vaginal pH ≥ 4.7 and a score of 7 through 10 from a Gram-stained vaginal smear interpreted using the Nugent method.[7] The identification of *T. vaginalis* was by culture using Diamonds media, incubated at 37° C in 5% CO_2 for up to 5 days. Each day, microscopic identification by direct observation of motile forms was performed. If the culture media was negative for five days, the results were considered negative. *C. trachomatis* and *N. gonorrhoeae* were identified from cervical swabs using nucleic acid amplification tests and culture, respectively. All women who tested positive for *T. vaginalis*, *C. trachomatis*, or *N. gonorrhoeae* were excluded from this analysis.

With respect to race/ethnicity ascertainment, subjects responded to several questions regarding their own race as well as that of their parents. Additionally, we queried the subjects regarding

the race/ethnicity of the father of the current pregnancy. Maternal and paternal race were categorized as white, black, and other (Chinese, Japanese, Indian, American Indian, Eskimo, Aleutian). Maternal and paternal ethnicity was classified as persons reporting themselves to be Hispanic or non-Hispanic.. For these analyses, only non-Hispanic black and non-Hispanic white subjects were considered.

Among 526 eligible women meeting inclusion and exclusion criteria, a total of 410 women were enrolled in the cohort during the study period. For these analyses, 6 women were excluded for an uninterpretable vaginal Gram stain, 52 women were excluded for positivity for *T. vaginalis*, *C. trachomatis*, or *N. gonorrhoea*, and 27 women were excluded for uncertainty of the identity and/or race of the father of the pregnancy. Thus, the cohort for this analysis consists of 325 women.

Descriptive statistics, univariable and multivariable regression were performed using Stata 9 (College Station, TX). Multivariable log-binomial regression was used to assess the joint contribution of maternal and paternal race on risk of BV. Log-binomial regression was used because BV was common (35.7%) and odds ratios from logistic regression would have overestimated relative risks. Multiplicative interaction between maternal and paternal race was assessed using a likelihood ratio test (α=0.05). Indicator variables for maternal and paternal race were included in the model, as well as a maternal race-by-paternal race interaction term. Relative risks were generated after exponentiating the linear combination of the main effects and interaction terms, with white female/white male as the common referent. Candidate confounders of the relation between maternal and paternal race/ethnicity and bacterial vaginosis were years of mother's education, marital status, employment status, smoking during pregnancy, gestational age at study enrollment, parity, number of sexual partners in the 3 months and 12 months prior to pregnancy, frequency of vaginal intercourse in the 3 months and 12 months prior to pregnancy, and frequency of vaginal intercourse since pregnancy. To determine which covariates should be entered into the multivariable model, we used directed acyclic graphs [8], theory-based causal diagrams that rely on the investigators' *a priori* subject-matter knowledge of the causal relationships of variables to one another. Covariates were defined as confounders if their removal from the model changed the odds ratio of the primary exposure by $\geq$ 10%. Gestational age at enrollment, parity, cigarette smoking, and marital status were identified as confounders and were included in the final model.

Results

Of these 325 women, 164 (50.5%) were white and 161 (49.5%) were black. With respect to the distribution of couple race, most couples were female black/male black (46%) or female white/male white (40%), with smaller proportions female white/male black (11%) and female black/male white (4%) (Table I). White female/white male couples were most likely to be married and smokers. There were no significant differences in other characteristics by couple race. Bacterial vaginosis was less common among white women [n=43 (26.2%)] than black women [(n=73 (45.3%)] (p = 0.001, χ^2 test). When stratified by couple race, bacterial vaginosis was least common among white female/white male couples and most common among racially discordant couples (Table II). The effect of maternal race varied by paternal race. Compared with white females whose partners were also white race, white women with black partners had a two-fold increased risk of bacterial vaginosis (RR: 2.2 (95% CI: 1.4, 3.5)) after adjustment for gestational age at enrollment, parity, cigarette smoking, and marital status. Compared with the same referent, black females incurred twice the risk of bacterial vaginosis regardless of if their partners were white (RR: 2.1 (95% CI: 1.1, 4.2)) or black (RR: 2.0 (95% CI: 1.4, 2.8)), independent of confounders. This interaction between maternal and paternal race was statistically significant (p=0.02, likelihood ratio test). If there had been no interaction, we would have expected a RR of approximately 4.6 for black females with black male partners (i.e., 2.2

[RR for white women-black partner] × 2.1 [RR for black women-white partner]). Instead, we observed a RR that was significantly less than would be expected with no interaction. The addition of other covariates into the final model had no meaningful effect on the results (data not shown).

Comment

In this prospective, observational cohort of gravidas, we have uniquely demonstrated that paternal black race is a risk factor for bacterial vaginosis. The contribution of paternal black race to risk of BV is independent of maternal race as well as other potential confounders. Importantly, paternal race was a significant modifier of the effect of maternal race on risk of bacterial vaginosis. Racially discordant couples had the same elevation in risk as black female/black male couples, which suggests that paternal black race is as important a contributor to BV in pregnancy as maternal black race.

The magnitude of the risk of BV associated with female black race in our cohort is similar to that reported in the literature. Allsworth and Peipert reported that among non-pregnant women aged 14–49 in the National Health and Nutrition Examination Survey, the adjusted odds ratio for BV for female black race was 2.66(95% confidence interval 2.18–3.25).[1] In a cohort of nearly 14,000 pregnant women from the Vaginal Infections and Prematurity study, the adjusted odds ratio for BV for female black race was 2.9 (95% confidence interval 2.5–3.4).[9]

The emphasis of decades of work on the epidemiology and etiology of disruption of vaginal flora leading to bacterial vaginosis during pregnancy has focused on maternal demographic factors and behaviors such as douching, coital frequency, and the use of vaginal products.[4] In general, the contribution of male factors to BV is poorly understood. Male circumcision is not thought to be associated with BV among non-pregnant women.[10] Less frequent condom use is, however, a risk factor for BV among non-pregnant women.[11] Factors such as condom use, circumcision status, and penile or seminal microbiologic and immunological milieu might be important in disruption of vaginal flora during pregnancy. Furthermore, any or all of these factors may differ by a man's race or ethnicity. Ongoing work is needed to explore these risk factors for BV in pregnant and non-pregnant women.

The notion of a male role in BV suggests that there may be, in part, a sexually transmitted component to this disruption of vaginal flora. To date, the issue of whether BV is a sexually transmitted or sexually associated condition is controversial. Certainly, BV shares several epidemiologic risk factors and contributing behaviors with sexually transmitted infections.[12, 13] Still, epidemiologic data suggest that BV has a 15% prevalence among women who have never had sexual intercourse.[1] Our finding of a male contribution to BV certainly does not settle this issue, but lends support to some sexual contribution. The importance of our data lies not in their ability to inform directly patient care or counseling, but in raising hypotheses regarding underlying biological mechanisms. Furthermore, the notion of paternal contribution to BV has not previously been considered in studies of disease-BV association or in treatment trials aimed at normalizing vaginal flora or avoiding related complications, such as preterm birth. Failure to account for paternal race may misrepresent the relation between a woman's race and her risk of BV as well as the risk of downstream consequences.

The validity of our findings is supported by our systematic protocol for ascertaining maternal and paternal race, the strict microbiologic characterization of BV, and our consideration of a broad range of covariates. Despite our relatively small number of racially-discordant couples, we detected statistically significant effects in univariate and multivariable analyses. Further subgroup analyses are unfortunately limited by sample size. While self-reported race is a reliable and valid assessment tool[14], the reliability of maternal report of paternal race is

unknown. We are also limited by the unavailability of any additional paternal demographic, clinical, or biological data. Thus our notions of possible explanations underlying these findings are largely speculative and require rigorous hypothesis-testing in valid model systems. Observational and interventional trials of BV in pregnancy could provide insight into this phenomenon further by including data on paternal race and behavioral characteristics, and may potentially explore paternal microbiologic and immunologic factors as well.

Although our findings need to be confirmed in other populations and datasets, our findings suggest that future studies of the epidemiology and biology of bacterial vaginosis and its associated adverse pregnancy outcomes must consider paternal contribution.

Acknowledgments

HNS and MAK were supported by 1R01HD41663-01A1 and1R01 HD052732-01

LMB was supported by K01 MH074092

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Table I

Clinical and demographic descriptors of cohort, stratified by couple race

	Female white/Male white n=129	Female white/Male black n=35	Female black/Male white n=12	Female black/Male black n=149	p
Maternal age, yrs Median (range)	25 (18–41)	23 (18–34)	23 (18–34)	25 (17–42)	0.23*
Gestational age at enrollment, wks Median (range)	8.5 (5–13)	10 (4–13)	8.5 (5–13)	8.5 (4–13)	0.52*
Less than high school education, n(%)	28 (21.7)	8 (22.1)	3 (25.0)	35 (23.5)	0.55#
Number of sexual partners in year prior to pregnancy Median (range)	1 (1–20)	1 (1–5)	1 (1–3)	1 (1–22)	0.80*
Number of sexual partners in 3 months prior to pregnancy Median (range)	1 (1–20)	1 (1–2)	1	1 (1–20)	0.80*
Times per week of vaginal intercourse in year prior to pregnancy Median (range)	2.5 (0–21)	3 (0–14)	4 (1–14)	3 (0–21)	0.65*
Times per week of vaginal intercourse in 3 months prior to pregnancy Median (range)	2.5 (0–21)	4 (0–14)	5 (1–14)	3 (0–20)	0.11*
Times per week of vaginal intercourse since pregnancy Median (range)	1 (0–21)	2 (0–7)	1.5 (0–7)	1 (0–7)	0.70*
Parity Median (range)	2 (1–7)	4 (1–8)	2 (1–6)	4 (1–13)	0.001*
Married N (%)	35 (27.3)	4 (11.8)	2 (16.7)	14 (9.4)	0.001#
Unemployed N(%)	60 (46.9)	17 (50.0)	6 (50.0)	82 (55.0)	0.58#
Smoker N(%)	78 (60.9)	20 (58.8)	4 (33.3)	69 (46.6)	0.05#

*Kruskal-Wallis test

#χ^2 test

Table II

Relation between Couple Race and Bacterial Vaginosis

Couple Race	Bacterial vaginosis, n(%)	Unadjusted risk ratio for bacterial vaginosis (95% confidence interval)	Adjusted risk ratio* for bacterial vaginosis (95% confidence interval)
Female white/Male white	27 (20.9)	referent	referent
Female white/Male black	16 (45.7)	2.4 (1.5–3.8)	2.2 (1.4–3.5)
Female black/Male white	5 (41.6)	2.1 (1.1–4.2)	2.1 (1.1–4.2)
Female black/Male black	68 (35.7)	2.2 (1.6–3.2)	2.0 (1.4–2.8)

*Adjusted for gestational age at enrollment, parity, cigarette smoking, and marital status