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Racial differences in cervical cytokine concentrations between pregnant women with and without bacterial vaginosis

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Abstract

We have examined the association between cytokine, chemokine and growth factor concentrations with bacterial vaginosis (BV) in pregnant white and black women. A nested case-control analysis was performed to examine twenty-eight cervical cytokine, chemokine and growth factor concentrations in 83 white women (55 with normal flora and 28 with BV) and 81 black women (39 with normal flora and 42 with BV). White women with BV had significantly lower IP10 ($P = 0.001$) and MCP1 ($P = 0.006$) concentrations compared to women with normal flora. Black women with BV had higher IL-1 α ($P < 0.001$) concentrations than those with normal flora. In women with normal flora, whites had significantly higher levels of IL-1 α ($P = 0.047$), IL-6 ($P = 0.010$), IL-10 ($P = 0.016$) and PDGF-BB ($P = 0.010$) than blacks. There were no significant concentration differences between white and black women with BV. These results demonstrate significant differences in cytokine and chemokine concentrations between women with and without BV. Ethnic differences in cytokine concentrations were also observed in women with normal flora, indicating that white and black women with normal flora have different cytokine levels, but respond to BV in a similar manner.

Keywords

bacterial vaginosis; cytokine levels; ethnic differences

1. Introduction

Bacterial vaginosis (BV) is one of the most prevalent vaginal disorders in adult women affecting 15–20% of pregnant women (Eschenbach, 1993; Hillier et al., 1995; McGregor and French, 2000; Cauci et al., 2002). BV is a syndrome characterized by a relative lack of *Lactobacillus* spp. and an increased prevalence of anaerobic bacteria, *G. vaginalis*, *Mobiluncus* spp. and *M. hominis*. Numerous studies have demonstrated a strong and consistent association of BV with preterm birth (Gravett et al., 1986; McGregor et al., 1994; Hillier et al., 1995; Goldenberg et al., 1996) and, yet, most women with BV do not have preterm births. This

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suggests that a sub-group of women with BV are at risk for adverse outcome. We (Simhan et al., 2003a, 2005b) and others (Cakmak et al., 2005) have shown that, among women with BV, it is the presence of lower genital tract inflammation that places women at highest risk for preterm labor and preterm rupture of membranes.

Black women are at a 3 times greater risk for BV than white women (10–20% in white women and 30–50% in black women (Eschenbach, 1993; Hillier et al, 1995; McGregor and French, 2000; Cauci et al, 2002)), and this disparity remains after controlling for most of the common risk factors, many of which occur more frequently in black women (Koumans and Kendrick, 2001; Ness et al., 2003). Furthermore, the risk of preterm birth attributable to BV (Hillier et al, 1995) and vaginal inflammation (Simhan et al, 2005b) is greater among black women than their white counterparts. The reasons for this racial disparity are unclear, and few studies have directly addressed this issue.

Several studies have explored the relationship between BV status and vaginal cytokine concentrations. Higher vaginal levels of IL-1 α , IL-1 β and IL-6 have been observed in women with BV compared to those with normal flora (Platz-Christensen et al., 1993; Mattsby-Baltzer et al., 1998; Cauci et al., 2003; Wasielea et al., 2005; St John et al., 2007). However, these results are not consistent and there are few data to inform our understanding of population differences in the lower genital tract inflammatory milieu among gravidas with bacterial vaginosis compared to those without BV. Our purpose was to compare the cervical inflammatory milieu, as represented by a panel of 28 cytokines, chemokines and growth factors, among black and white women with and without BV.

2. Materials and Methods

2.1 Study participants

A nested case control analysis was performed from a prospective cohort study done at Magee-Womens Hospital in Pittsburgh, USA. 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. 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 which would confound the associations we proposed to examine. All women provided demographic, medical and clinical information through standardized, closed question, research interviews administered by research personnel. This study was approved by the University of Pittsburgh and Vanderbilt University Institutional Review Boards.

A total of 372 women were initially enrolled in this study. A total of 208 (55.9%) women were excluded from this analysis. Exclusion criteria included: absence of a BV score (1.1%), no cytokine measurements (16.1%), presence of *Trichomonas vaginalis* (10.2%), presence of *Neisseria gonorrhoeae* (0.3%), presence of *Chlamydia trachomatis* (4.0%), antibiotic use three months prior to pregnancy (18.0%) and race other than self-identified white or black (14.0%). Women with an intermediate BV score (Nugent score of 4–6, 15.3%) were also excluded because of small numbers. These exclusion criteria were chosen before data analysis because these variables could bias the cytokine measurements being examined. A total of 164 women were included for analysis. There were 28 white women with BV, 42 black women with BV, 55 white women with normal flora and 39 black women with normal flora.

2.2 Microbiologic assessment

Two vaginal swabs were collected for culture and identification of vaginal flora. BV 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 (Nugent et al., 1991). The identification of *T. vaginalis* was by culture using Diamonds media, incubated at 37°C in 5% CO₂ 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 using nucleic acid amplification tests and culture, respectively.

2.3 Cytokine measurements

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 for the assay of cytokines. These swabs were placed in a plastic tube containing 4ml of purified bovine serum (final dilution of 1:5) and stored at -80°C until assay. The sample was thawed at room temperature, placed in a spin-X centrifuge filter unit and centrifuged at 12,000 rpm for 20 minutes. Multiplex-based platforms quantify cytokine concentrations in plasma with a high degree of agreement and correlation to ELISA, while providing improved sensitivity (Prabhakar et al., 2002; Pickering et al., 2002; Nelson et al., 2003; Biagini et al., 2004). We used the Luminex LabMAP™ and a Beadlyte® analyte kit (Upstate, Charlottesville, Virginia) designed to assay 28 of the following cytokines; Eotaxin (chemokine CC motif ligand 11), granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon-gamma (IFN- γ), interferon-gamma inducible protein 10 (IP10), interleukins (1 α , 1 β , 2, 3, 4, 5, 6, 7, 8, 10, 12 subunit p40, 12 subunit p70, 13, 15), monocyte chemotactic protein 1 (MCP1), platelet-derived growth factor (PDGF-AA and PDGF-BB), fms-related tyrosine kinase 3 (FLT3), macrophage inflammatory protein 1-alpha (MIP1 α), regulated upon activation, normally T-expressed and presumably secreted (RANTES), tumor necrosis factor (TNF), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF) and fibroblast growth factor 2 (FGF2) from single aliquot of 50 μ l of specimen. These factors were chosen because they are early response cytokines as well as molecules important in the downstream cascade of inflammatory events. A monoclonal antibody specific for a cytokine is covalently linked to a fluorescent bead set, which captures the cytokine. A complementary biotinylated monoclonal cytokine antibody then completes the immunological sandwich and the reaction is detected with streptavidin-phycoerythrin. Each sample was frozen at -80°C after initial collection and never thawed until this study. After thawing, multiplex assays were performed. These samples were previously analyzed in duplicate using ELISA for IL-1 β , IL-6 and IL-8. We found a very high degree of correlation between concentrations determined by ELISA and by multiplex assay ($r^2 = 0.95$ to 0.97) for each of the cytokines. The cervical fluid collection protocol used in this study has served as the validated methodology for several large multi-center trials (Carey et al., 1993, 2000; Goldenberg et al, 1996). The inter-swab change in weight (pre- vs post-collection) is $\pm 1.2\%$ and the inter-assay variation for cervical cytokines has been consistently $< 8\%$ (Simhan et al., 2003b, 2005a). Microbiologic and cytokine assays were performed in the Research Microbiology Laboratory at the Magee-Womens Research Institute by laboratory technologists blinded to any clinical or identifying data from the study subjects.

2.4 Statistical analysis

Statistical analyses were performed using Stata® (StataCorp, 2007). Differences between women with BV and those with normal flora were determined by Fisher's exact test for several baseline characteristics, such as marital status, income, education, smoking and medical history. Cytokine distributions were not normally distributed; therefore, a Mann-Whitney U

test was used to examine differences between BV statuses within each population. A total of 56 comparisons were made and false discovery rate (FDR) (Benjamini and Hochberg, 1995) was used to correct for multiple testing. An alpha of 0.2 was used to determine the FDR threshold value.

To examine the possibility of differences between black women and white women, a Mann-Whitney U test was used to compare black women with normal flora to white women with normal flora, and black women with BV to white women with BV. The results of these 56 comparisons were corrected also for multiple tests with FDR.

3 Results

3.1 Baseline characteristics

Among white women, those with BV were more likely to report prior episodes of BV than those with normal flora ($P = 0.004$) (Supplemental Table 1). Among black women, cigarette use prior to pregnancy ($P = 0.031$) and number of sexual partners prior to pregnancy ($P = 0.020$) were greater in women with BV compared to those with normal flora. Black women were heavier ($P = 0.010$), had a higher BMI ($P = 0.008$), were more likely to have had a previous pregnancy ($P = 0.002$) and report previous episodes of BV ($P < 0.001$) than white women. Black women were less likely to smoke both prior to ($P = 0.001$) and after pregnancy ($P = 0.038$) than white women.

3.2 Differences in cytokine concentrations by BV status

In whites, IP10 (medians 1807.8 and 3972.8ng/ml) and MCP1 (medians of 348.0 and 859.0ng/ml) were decreased in women with BV compared to those with normal flora (Table 1A; Supplemental Table 2). In black women, IL-1 α (medians of 1165.2 and 558.4ng/ml) concentrations were elevated among women with BV compared to those with normal flora (Table 1B; Supplemental Table 3).

3.3 Cytokine concentrations by race

White women with normal flora had higher levels of IL-1 α (medians of 904.9 and 558.4ng/ml), IL-6 (3967.1 and 2162.2ng/ml), IL-10 (medians of 73.3 and 43.0ng/ml) and PDGF-BB (medians of 2362.2 and 1204.7ng/ml) compared to black women with normal flora (Table 2; Supplemental Table 4). However, these results did not hold up to correction for multiple testing. There were no significant differences between races for women with BV (Supplemental Table 5).

3.4 Cytokine concentrations excluding women with *C. albicans*

In order to ensure that the cytokine concentrations differences observed were not driven by infection with *C. albicans*, all women with this infection were excluded from the analysis (38 total women). After correcting for multiple testing, white women with BV had significantly lower concentrations of IP10 ($p = 0.003$) compared to women with normal flora. Black women with BV had significantly higher concentrations of IL-1 α ($p = 0.002$) compared to women with normal flora. When comparing concentrations by race, white women with normal flora had higher levels of IL-10, IL-12(p40) and PDGF-BB than black women with normal flora. There were no significant differences between races in women with BV.

4 Discussion

Our findings support the notion that the nature of the inflammatory milieu in the cervix is different between women with and without BV. We have identified also several cytokines that may differ between black and white women with normal flora. Genc and colleagues (2004)

have demonstrated previously that activation of the IL-1 system accompanies disruption of vaginal flora, particularly among women who go on to have a preterm birth. Our data are in agreement with this concept; IL-1 α concentrations were significantly higher in black women with BV, and were almost significant after FDR corrections in white women.

In white women, IP10 and MCP1 concentrations were decreased in women with BV compared to those with normal flora. IP10 and MCP1 are both chemokines that function primarily as chemoattractants for human monocytes and T cells. Women who were in preterm labor were found to have higher amniotic levels of MCP1 in the presence of intra-amniotic infection compared to women in preterm labor where infection was not present (Esplin et al., 2005). Also, MCP1 and IP10 are found in breast milk and may be critical components transferred to the infant that fight infection (Garofalo and Goldman, 1998; Takahata et al., 2003). While this is not the primary focus of this study, it is possible that lower amounts of IP10 and MCP1 found in women with BV could be a mechanism for adverse pregnancy outcomes associated with this disease.

In women with normal flora, our data are consistent with black women having lower concentrations of IL-1 α , IL-6, IL-10 and PDGF-BB than white women. Recent research examining the distribution of cytokine gene polymorphisms between whites and blacks has found that these two populations differ significantly in allelic distribution at commonly assayed sites in IL-1 α , IL-6 and IL-10 that could give rise to differential inflammatory response (Ness et al., 2004; Zabaleta et al., 2007). Therefore, this could alter the production of the cytokines, possibly explaining why lower levels of these cytokines are observed in black women with normal flora compared to white women. It is recognized also that white and black women have differing immune responses to infection (Myslobodsky, 2001; Hoffmann et al., 2002; Blake and Ridker, 2003; Ness, 2004). While we did not observe differing cytokine concentrations in women with BV, it is possible that because white women have higher levels of both pro- and anti-inflammatory cytokines they are less susceptible to infection with BV. This mechanism could help to explain why black women are at a greater risk of developing BV compared to white women even after accounting for socio-demographic risk factors. However, our findings should be taken as exploratory as these results did not hold up after correcting for multiple tests and the p values are not highly significant.

A study examining cytokine output in vaginal epithelial cells found that, in response to *C. albicans*, high levels of IL-1 α are produced while there is little to no production of IL-6, IL-10 and MCP-1 (Steele and Fidel, 2002). When removing the 38 individuals infected with *C. albicans* from our study, white women with BV still had significantly lower levels of IP10, black women with BV still had significantly higher levels of IL-1 α and white women with normal flora had significantly higher levels of IL-10, IL-12(p40) and PDGF-BB than black women with normal flora. There were no significant differences in cytokine concentrations between white and black women with BV. This demonstrates that, while *C. albicans* does affect the vaginal cytokine milieu, there are still strong cytokine level differences between women with and without BV. Also, it is important to note that, when removing women with *C. albicans* infection, the differences in cytokine levels between white and black women with normal flora were even stronger and remained significant after correcting for multiple tests. However, removing these individuals made the sample size even smaller and, therefore, the power to detect effects may be limited. Our study was a nested case control analysis from a prospective cohort study and we were not able to examine the temporal relationship between cytokine levels and BV. It is unclear, based on our or any other data, whether BV infection induces an altered cytokine response or if altered vaginal immunity predisposes an individual to BV. Future research will need to be conducted to determine this relationship.

In conclusion, we have demonstrated that women with and without BV differ in a number of cytokines that are related to inflammation and that these differences appear to be population-specific. In addition, our data support the conclusion that cytokine levels are similar in black and white women in the presence to BV, but that there may be differences between these populations in the absence of BV. If this is true, it would suggest that BV either fosters or is fostered by a common set of cytokine and chemokine changes, regardless of race or ethnicity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Significant concentration differences after correction for multiple testing between women with and without BV for whites (A) and for blacks (B)

A)			
<i>Cytokine</i>	<i>Normal flora</i>	<i>BV</i>	<i>p value</i>
IP10	3972.8 (5.0 – 30181.9)	1807.8 (146.6 – 25000.0)	0.001
MCP1	859.0 (40.0 – 30631.9)	348.0 (48.0 – 22146.0)	0.006
B)			
<i>Cytokine (ng/ml)</i>	<i>Normal</i>	<i>BV</i>	<i>p value</i>
IL-1 α	558.4 (104.0 – 5554.6)	1165.2 (163.8 – 33876.5)	<0.001

The median cytokine concentration (range) is presented.

Table 2

Comparison of cytokine concentrations between races in women with normal flora

Cytokine (ng/ml)	White women	Black women	p value
IL-1 α	904.9 (166.0 – 11098.1)	558.4 (104.0 – 5554.6)	0.047
IL-6	3967.1 (62.2 – 25000.0)	2162.2 (5.0 – 14744.0)	0.010
IL-10	73.3 (0.0 – 497.4)	43.0 (1.3 – 391.0)	0.016
PDGF-BB	2362.2 (236.2 – 33201.0)	1204.7 (12.0 – 9651.0)	0.010

The median cytokine concentration (range) is presented. *