DIAGNOSTICS

Vaginal leucocyte counts in women with bacterial vaginosis: relation to vaginal and cervical infections

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Objectives: To evaluate whether an elevated vaginal leucocyte count in women with bacterial vaginosis (BV) predicts the presence of vaginal or cervical infections, and to assess the relation of vaginal WBC counts to clinical manifestations.

Methods: We retrospectively analysed the relation of vaginal leucocyte counts to vaginal and cervical infections and to clinical manifestations in non-pregnant women diagnosed with BV at an STD clinic visit.

Results: Of 296 women with BV studied, the median age was 24 years and 81% were African-American. Elevated vaginal leucocyte counts were associated with objective signs of vaginitis and cervicitis and also predicted candidiasis (OR 7.9, 95% CI 2.2 to 28.9), chlamydia (OR 3.1, 95% CI 1.4 to 6.7), gonorrhoea (OR 2.7, 95% CI 1.3 to 5.4), or trichomoniasis (OR 3.4, 95% CI 1.6 to 7.3). In general, as a screening test for vaginal or cervical infections, vaginal leucocyte count had moderate sensitivities and specificities, low positive predictive values, and high negative predictive values.

Conclusions: An elevated vaginal leucocyte count in women with BV was a strong predictor of vaginal or cervical infections. Vaginal leucocyte quantification may provide an alternative approach to assessing need for empirical therapy for chlamydia and gonorrhoea, particularly in resource-limited high STD risk settings that provide syndromic management.

Bacterial vaginosis (BV) is a common disorder of the genital tract in women characterised by an alteration of a normal acidic lactobacilli predominant vaginal ecosystem to a vaginal environment dominated by organisms such as *Gardnerella vaginalis*, *Mycoplasma* sp, and anaerobes, with an accompanying increase in pH. BV has been associated with upper genital tract infection,¹ and has been reported to be a strong predictor of chlamydial and gonococcal cervicitis.² While diagnosis of BV is based on reliable established criteria,³ diagnosis of cervical infection is more problematic and the significant medical and economic implications of untreated chlamydial or gonococcal infection influence empirical approaches to these disorders.

Although BV has traditionally been considered a non-inflammatory syndrome without an association with increased vaginal leucorrhoea,⁴ several studies have demonstrated the presence of vaginal leucocytes (white blood cells, WBCs)^{4–8} in women with bacterial vaginosis. Recent studies have reported an association of BV with elevated inflammatory cytokines.^{8–10} Some studies have reported an association of vaginal WBCs in women who have BV with concomitant chlamydial or gonococcal cervicitis^{5–6} or histological endometritis,⁷ though possible limitations in some of these studies may have influenced the validity of the findings. Such limitations include small sample size, provider inexperience, having multiple providers, use of a vaginal WBC count definition with lower sensitivity, and not addressing concomitant vaginal infections. There is also a paucity of studies characterising the relation of vaginal WBC counts to clinical manifestations of vaginal and cervical infections.

An improved understanding of the relation of vaginal WBC counts to vaginal and cervical infections, along with associated clinical manifestations of these diseases, would be important in the assessment of risk for sexually transmitted diseases (STDs) and need for empirical therapy, particularly for chlamydia and gonorrhoea, in a resource limited setting with a high prevalence of STDs that may practise syndromic management because of insufficient

means to further test for these pathogens. Addressing limitations of previous related studies, we evaluated whether an elevated vaginal WBC count in women with BV diagnosed at a routine first time STD clinic visit predicted the presence of vulvovaginal candidiasis (VVC) or STDs, and we explore the relation of vaginal WBC counts to clinical manifestations of such diseases. Further, we assess how the finding of mucopurulent cervical discharge compares to vaginal WBC count in predicting chlamydial and gonococcal infections.

METHODS

Study population and data collection

Through a computerised databank, we identified all women who were seen by a single, experienced provider for a routine first time visit from 1998 through 2002 at the Jefferson County Department of Public Health (JCDH)-STD Clinic and who were diagnosed with BV at that visit. BV affects a significant proportion of women presenting to the JCDH-STD Clinic. A routine visit consisted of data collection and laboratory testing for either screening for STDs or evaluation of a specific complaint. Individuals presenting for treatment of a laboratory confirmed STD, those pregnant, women with a previous hysterectomy, and those with missing data relative to vaginal WBC counts or the diagnoses of BV, VVC, or concomitant STDs were excluded.

Demographic, clinical, and laboratory data (relevant to vaginal WBC counts and clinical disease) on study subjects were retrospectively collected from the JCDH-STD Clinic computerised database. Laboratory data routinely collected included vaginal WBC counts and results of evaluation for BV, chlamydia, gonorrhoea, trichomoniasis, and VVC. Vaginal WBCs were previously quantified after visualisation of a minimum of five fields (range 5–15 based on whether there was a paucity of WBCs present) under light microscopy at $\times 400$. Vaginal WBC counts were routinely categorised into

Abbreviations: BV, bacterial vaginosis; OCP, oral contraceptive pill; VVC, vulvovaginal candidiasis; WBCs, white blood cells

either ≤ 5 WBCs per $\times 400$ in all visualised fields (representing minimal or no inflammation) or > 5 WBCs per $\times 400$ in at least one field visualised (considered elevated and more suggestive of significant inflammation). During the study period, the diagnosis of BV was routinely made based on the criteria of Amsel *et al*³ and required the presence of three of the following findings: (1) vaginal pH > 4.5 ; (2) visualisation of clue cells by light microscopy at $\times 400$; (3) a positive whiff test on application of 10% potassium hydroxide to vaginal fluid; or (4) homogeneous vaginal discharge. *Chlamydia trachomatis* was detected by culture of an endocervical swab specimen using DEAE pretreated McCoy cells on 96 well microtitre plates and identification of chlamydial inclusions as previously described.¹¹ *Neisseria gonorrhoeae* was detected by culture of an endocervical swab specimen on modified Thayer-Martin medium using a standard method¹² or by Gonostat (Sierra Diagnostics, Inc, Sonora, CA, USA). Trichomoniasis was detected in most women by visualisation of trichomonads on a vaginal wet preparation by light microscopy at $\times 400$. Some women, who were being screened for future enrolment in other research studies, also had additional testing by culture for *Trichomonas vaginalis* in modified Diamond's media as previously described¹³; proportion of individuals receiving culture did not differ by vaginal WBC count category. VVC was diagnosed based on the presence of vaginal discharge on examination and visualisation of budding yeast or pseudohyphae on a vaginal wet preparation by light microscopy at $\times 400$. The diagnosis of genital herpes was based on characteristic clinical findings. The study was approved by the institutional review boards of the University of Alabama at Birmingham and JCDH.

Data analyses

Statistical analyses were conducted on Stata (Stata Corp, Release 6.0, College Station, TX, USA). Significance of differences in demographic and clinical characteristics by leucocyte count category was determined by univariate logistic regression or Fisher's exact test, with the exception of the co-variate age, which was non-normally distributed and therefore its association was analysed by the Wilcoxon rank-sum (Mann-Whitney) test. The relation of vaginal leucocyte count category in women with BV to VVC and STDs was assessed through univariate regression and then through a multivariate regression controlling for age, oral

contraceptive pill (OCP) use, VVC, gonorrhoea, chlamydia, trichomoniasis, and genital herpes. Age and OCP use were included in the multivariate model a priori as they were considered to be potential confounders; age data were transformed into the natural log. The sensitivity, specificity, and predictive values of vaginal WBC count for the diagnosis of VVC or an STD were calculated by using 2×2 tables. To assess correlation between vaginal WBC count and the finding of mucopurulent cervical discharge, a correlation coefficient was determined. The relation of either mucopurulent cervical discharge alone or combined with vaginal WBC count to cervical chlamydia and gonorrhoea was assessed through multivariate analysis controlled for co-variables as described above.

RESULTS

Characteristics of subjects and relation to vaginal leucocyte count

From 1998 through 2002, 296 women seen for a routine first time visit at the JCDH-STD Clinic were diagnosed with BV and were eligible for study. The median age was 24 years (range 14–61). Eighty one per cent of women were African-American and 19% were of other racial/ethnic backgrounds (predominately white). Sixteen per cent of women used OCPs for contraception. The most frequent symptom reported was vaginal discharge (46%), with vaginal odour (28%), genital itching (15%), lower abdominal pain (13%), and dysuria (7%) being reported less frequently. The most common examination finding was abnormal vaginal discharge (87%), with vaginal erythema (20%), mucopurulent cervical discharge (16%), cervical friability (10%), adnexal tenderness (6%), cervical motion tenderness (4%), fundal tenderness (4%), and abdominal tenderness (3%) being found less commonly.

Demographic and clinical characteristics of the study population stratified by vaginal WBC count category are presented in table 1. Vaginal WBC count was elevated in 125 (42%) women. Age, race, OCP use, and symptoms reported did not significantly differ by vaginal WBC count category. Women with an elevated vaginal WBC count were significantly more likely to present with objective evidence of vaginitis (abnormal vaginal discharge, $p < 0.0001$; vaginal erythema, $p = 0.008$) and cervicitis (mucopurulent cervical discharge, $p < 0.0001$; cervical friability, $p = 0.10$). Women

Table 1 Demographic and clinical characteristics of women with bacterial vaginosis, stratified by vaginal leucocyte count (WBC per $\times 400$)

Characteristic	WBC ≤ 5 (n = 171)	WBC > 5 (n = 125)	p Value
	No (%)	No (%)	
Age, median (years) (range)	25 (14–61)	23 (14–48)	0.39
Race			0.78
African-American	139 (81)	100 (80)	–
Other	32 (19)	25 (20)	–
OCP use	23 (14)	24 (19)	0.18
Reported abdominal pain	19 (11)	18 (14)	0.40
Reported dysuria	13 (8)	8 (6)	0.69
Reported vaginal odour	48 (28)	34 (27)	0.87
Reported genital itching	28 (16)	16 (13)	0.39
Reported vaginal discharge	73 (43)	63 (50)	0.19
Vaginal discharge finding	137 (80)	120 (96)	< 0.001
Vaginal erythema	25 (15)	34 (27)	0.008
Cervical friability	12 (7)	16 (13)	0.10
Mucopurulent cervical discharge	10 (6)	36 (29)	< 0.001
Cervical motion tenderness	2 (1)	10 (8)	0.01
Fundal tenderness	4 (2)	7 (6)	0.16
Adnexal tenderness	8 (5)	11 (9)	0.16
Abdominal tenderness	2 (1)	8 (6)	0.03

Table 2 Multivariate model assessing the relation of an elevated vaginal leucocyte count (WBC per $\times 400$) in women with bacterial vaginosis to vaginal or cervical infections

Predictor	WBC ≤ 5 (n = 171)	WBC > 5 (n = 125)	OR (95% CI)*	p Value*
	No (%)	No (%)		
Age, median (years) (range)	25 (14–61)	23 (14–48)	0.9 (0.4 to 2.3)	0.85
OCP use	23 (14)	24 (19)	1.4 (0.7 to 2.8)	0.32
Vulvovaginal candidiasis	3 (2)	15 (12)	7.9 (2.2 to 28.9)	0.002
Trichomoniasis	14 (8)	27 (22)	3.4 (1.6 to 7.3)	0.001
Cervical chlamydia	14 (8)	29 (23)	3.1 (1.4 to 6.7)	0.004
Cervical gonorrhoea	17 (10)	30 (24)	2.7 (1.3 to 5.4)	0.005
Genital herpes	6 (4)	2 (2)	0.7 (0.1 to 3.7)	0.67

*Odds ratios, 95% confidence intervals, and p values were determined by multivariate regression controlling for age (log transformed), OCP use, vulvovaginal candidiasis, trichomoniasis, and genital chlamydia, gonorrhoea, and herpes.

with an elevated vaginal WBC count were also significantly more likely to present with some objective evidence of upper genital tract disease (cervical motion tenderness, $p = 0.01$; abdominal tenderness, $p = 0.03$), though some objective findings did not significantly differ by vaginal WBC count category (fundal tenderness, $p = 0.16$; adnexal tenderness; $p = 0.16$).

Frequency of vaginal and cervical infections and relation to vaginal leucocyte count

VVC and genital herpes were diagnosed in 6% and 3% of women, respectively. *C. trachomatis* and *N. gonorrhoeae* cervical infection was detected in 15% and 16% of women, respectively. Trichomoniasis was identified in 14% of women. Stratified by vaginal WBC count, women with an elevated vaginal WBC count were significantly more likely on univariate analysis to have VVC (OR 7.6, 95% CI 2.2 to 27.0, $p = 0.002$), chlamydia (OR 3.4, 95% CI 1.7 to 6.7, $p < 0.0001$), gonorrhoea (OR 2.9, 95% CI 1.5 to 5.5, $p = 0.001$), or trichomoniasis (OR 3.1, 95% CI 1.5 to 6.2, $p = 0.001$). The proportion of women with VVC or STDs stratified by vaginal WBC count category and significance of these relations by multivariate analysis is presented in table 2. Controlling for logage, OCP use, and concomitant VVC or STDs, the statistical association of an elevated vaginal WBC count with VVC, chlamydia, gonorrhoea, or trichomoniasis remained just as highly significant. Genital herpes was not associated with vaginal WBC count on univariate or multivariate analysis, though this clinical diagnosis was made infrequently in our study population.

Performance characteristics of vaginal leucocyte count as a screening test

The diagnostic test characteristics of vaginal WBC count for predicting VVC or STDs are presented in table 3. In general, the sensitivities and specificities of vaginal WBC count for diagnosing VVC or STDs were moderate; the positive predictive values of this screening test were low, but the negative predictive values were high (especially for VVC).

Comparison of mucopurulent cervical discharge finding to vaginal leucocyte count in predicting vaginal and cervical infections

For comparison with vaginal WBC counts, we assessed whether the presence of mucopurulent cervical discharge also independently predicted the presence of cervicitis due to chlamydia or gonorrhoea. As found with elevated vaginal WBC counts on multivariate analysis, the presence of mucopurulent cervical discharge was significantly associated with gonorrhoea (33% v 13%, OR 3.5, 95% CI 1.7 to 7.4, $p = 0.001$). In contrast with vaginal WBC counts, the presence of mucopurulent cervical discharge was not significantly associated with chlamydia (17% v 14%, $p = 0.72$).

Elevated vaginal WBC counts significantly correlated with the finding of mucopurulent cervical discharge ($R^2 = 0.31$; $p < 0.001$). On multivariate analysis, the combined finding of elevated vaginal WBC count and mucopurulent cervical discharge still significantly predicted cervical gonococcal infection (36% v 13%, OR 3.7, 95% CI 1.6 to 8.2; $p = 0.002$), but in contrast with elevated vaginal WBC count alone, did not significantly predict cervical chlamydial infection (22% v 14%, $p = 0.36$).

DISCUSSION

Detection of vaginal WBCs is a simple, inexpensive means to assess for inflammation in the vaginal or cervical tissue and may serve as an important marker for underlying infection. The presence of vaginal WBCs has previously been shown to be a predictor of infectious cervicitis¹⁴ and upper genital tract infection.^{15–16} Although BV has traditionally been considered a non-inflammatory syndrome without an association with increased vaginal leucorrhoea,⁴ several studies have demonstrated the presence of vaginal WBCs in women with BV^{4–8} and recent studies have reported an association of BV with elevated inflammatory cytokines.^{8–10} It is possible that the vaginal microbial flora present in BV, independent of concomitant vaginal or cervical infections, may induce an inflammatory response. Yudin *et al* demonstrated a decline in IL-1 β with cure of bacterial vaginosis in pregnant women treated with oral or topical metronidazole and a decrease in

Table 3 Sensitivity, specificity, and predictive values of vaginal leucocyte count for predicting vaginal or cervical infections in women with bacterial vaginosis

	VVC*	Chlamydia	Gonorrhoea	Trichomoniasis	Any infection**
Sensitivity (%)	83	67	64	66	65
Specificity (%)	60	62	62	62	72
Positive predictive value	12	23	24	22	59
Negative predictive value	98	92	90	92	77

*Vulvovaginal candidiasis.

**Positive for VVC, chlamydia, gonorrhoea, or trichomoniasis.

IL-6 when cured following oral metronidazole treatment, although IL-8 levels did not change significantly following therapy (abstract presented at the 2002 Annual Meeting and Scientific Symposium of IDSOG, Banff, Canada). Schwebke and Weiss demonstrated a univariate association between the use of metronidazole gel and resolution of clinical cervicitis (mucopurulent endocervical discharge finding) in women with bacterial vaginosis, irrespective of concomitantly treated chlamydia or gonorrhoea, although these findings did not reach statistical significance on multivariate analysis.¹⁷

It may be more likely that vaginal inflammation in BV is due to concomitant vaginal or cervical infections. There has been a paucity of studies specifically evaluating the relation of vaginal WBCs to cervical chlamydial and gonococcal infections in women with BV. Hakakha and colleagues demonstrated that in 22 women with clue cells, nine had a positive chlamydial or gonococcal culture; eight of these nine women had vaginal leucorrhoea (>10 vaginal WBCs per high power field) and three women with leucorrhoea did not meet Amsel criteria.⁶ Their study included pregnant and non-pregnant women. Steinhandler *et al* reported that the finding of BV and vaginal leucorrhoea (more WBCs than epithelial cells on high power field) in 32 non-pregnant women was associated with a positive test for chlamydia or gonorrhoea when compared with 216 non-pregnant women with neither BV nor vaginal leucorrhoea.⁵ Yudin *et al* reported that 161 non-pregnant women with BV and vaginal neutrophils (one or more per oil field) were significantly more likely to have histological endometritis on endometrial biopsy when compared to 48 women with neither BV nor vaginal neutrophils.⁷

We demonstrated that in 296 non-pregnant women with BV, elevated vaginal WBC counts (>5 WBCs per $\times 400$) were associated with VVC, trichomoniasis, chlamydia, or gonorrhoea. Our study design addressed potential limitations in some of the previous studies looking at the relation of vaginal WBCs to vaginal or cervical infections in women with BV. Firstly, we limited our population to non-pregnant women and controlled for use of OCPs, both which could influence the degree of vaginal or cervical inflammation. Secondly, we limited our study to only women with a diagnosis of BV by Amsel criteria. In the JCDH-STD Clinic population, there is a high background prevalence of BV and also women with some findings of BV but not meeting Amsel criteria. Including women with altered vaginal flora who do not meet Amsel criteria (for example, only having clue cells) in the same category as those with normal vaginal flora may confound the relation of vaginal WBCs to STDs. It has been shown recently that indole produced by non-lactobacilli vaginal microbial flora (such as some organisms present in BV) may provide a substrate for tryptophan synthesis allowing continued survival of chlamydia (with ability to replicate and increase inflammation)¹⁸; such bacteria may alter inflammation induced by other infectious causes of vaginitis or cervicitis. Thirdly, we looked for vaginal candidiasis and trichomoniasis, which also increase vaginal inflammation, and controlled for their presence when assessing the relation of vaginal WBCs to cervical infections. Fourthly, a single, experienced provider collected the laboratory and clinical data for our study, which avoids non-differential misclassification bias that can result from the inaccuracy in classification of data (such as vaginal WBC count, diagnosis of BV, etc) when multiple individuals collect data and can attenuate the significance of possible important associations.¹⁹ Finally, we evaluated a large sample size to increase power to detect associations of interest.

As a screening test, we found vaginal WBC counts in general to have moderate sensitivity and specificity, a low positive predictive value, and a high negative predictive value for vaginal and cervical infections. While this may limit the

use of vaginal WBC counts as a screening test in settings with readily available access to more sensitive and specific chlamydial and gonococcal assays, there is a potential role for this screening test in assessing STD risk and need for empiric therapy in more resource limited high STD risk settings which rely predominately on syndromic management for cervical infections. In our study, we found that reported symptoms were not associated with vaginal WBC count. Ryan *et al* found a chief complaint of vaginal discharge actually predicted a lower rate of gonorrhoea or chlamydial infection compared with rates observed in patients with no such complaint.²⁰ They also found that the addition of speculum and bimanual examinations as well as microscopy to an algorithm of risk assessment and symptom review increased the specificity and positive predictive value for chlamydial and gonococcal infection.²⁰ Given the limited ability of syndromic management algorithms to predict those with chlamydial or gonococcal infections and the potential for such algorithms to lead to overtreatment of a significant portion of uninfected individuals, vaginal WBC measurements, with high negative predictive value for chlamydia and gonorrhoea, could provide an alternative non-invasive method (compared with addition of speculum examination) for screening for chlamydia and gonorrhoea in such settings.

The finding of mucopurulent discharge correlated significantly with an elevated vaginal WBC count in our study and was a predictor of cervical gonococcal infection. In contrast with vaginal WBC count, mucopurulent discharge did not predict cervical chlamydial infection. Other studies have also reported that neither mucopurulent discharge²¹ nor endocervical swab test²² strongly predicted chlamydial infection. It is plausible that chlamydial infection may induce only a minimal inflammatory response, which has been demonstrated in men,²³ and microscopic measurement of inflammation as was done with vaginal WBC counts in our study may provide a more sensitive measure for predicting chlamydial infection. Use of a more sensitive cut-off value for elevated vaginal WBC count in our study (>5 WBCs per $\times 400$) may have increased the likelihood that vaginal WBC count would predict chlamydial infection.

The retrospective design of this study is a limitation that may influence clinical and laboratory data. The number of fields counted during vaginal WBC quantitation varied depending on the paucity or abundance of WBCs, though since WBC counts were categorised by a cut-off value rather than total number, this probably had minimal influence on the relations studied. The chlamydial and gonococcal assays that had been utilised in our study population are not the most sensitive assays available, which may confound the association of vaginal WBC counts with cervical infections; use of more sensitive nucleic acid amplification tests may identify a few more cases of cervical chlamydial or gonococcal infections and may aid in more accurately evaluating vaginal WBC counts as a screening tool for cervical infections. It is unclear whether findings from our study could be extrapolated to populations with a lower incidence of vaginal or cervical infections. The higher risk STD clinic population in this study may be more likely to have had previous vaginal or cervical infections, in which partial cell or humoral mediated immune responses could attenuate the inflammatory response; if this were the case, then the association of vaginal WBC counts with vaginal or cervical infections in women with BV may actually be stronger in an STD naive population. Reliable data on STD history were not available in these patients.

It remains unclear whether inflammation is induced by the vaginal microbes present in BV in the absence of concomitant vaginal or cervical infections. Use of more sensitive assays for routinely tested vaginal and cervical pathogens in future

studies may help clarify this issue, as would attempting to identify subpopulations of women with BV, by Nugent score classification or quantitation of vaginal microbes, who may be more likely to have vaginal inflammation. Other directions in improving our understanding of the relation of vaginal WBCs to BV may include measuring for other potential vaginal or cervical pathogens, such as *Mycoplasma* or *Ureaplasma*, that may induce inflammation but that are not routinely tested. A better understanding of the relation of vaginal WBCs to VVC and STDs in women with BV has important implications in assessment of STD risk and need for empirical therapy in certain settings.

CONTRIBUTORS

WG and MV conceived and designed the study; WG performed the data analyses; SY extracted data from the databank and assisted in data analyses; WG and JS drafted the manuscript; SY and MV reviewed the manuscript.

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