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EDITORS' CHOICE

The International Infections in Pregnancy (IIP) study: Variations in the prevalence of bacterial vaginosis and distribution of morphotypes in vaginal smears among pregnant women

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KEY WORDS
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Objective: The objective of the study was to determine the prevalence of bacterial vaginosis and the distribution of associated morphotypes among asymptomatic pregnant women in different countries.

Study design: In 8 institutions participating in the Global Network for Perinatal and Reproductive Health (www.gnprh.org) from July 1999 to September 2001, 1466 women were enrolled. Vaginal smears were Gram stained and scored with Nugent's method at a reference laboratory. The prevalence of bacterial vaginosis and bacterial morphotype distributions were compared.

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Results: Overall, 12.3% of women had bacterial vaginosis according to Nugent's criteria. Zimbabwe had the highest prevalence (24.4%) when compared with all other sites, except Myanmar ($P < .05$). Among bacterial vaginosis cases, 98.9% of vaginal smears had more than 30 *Gardnerella/Bacteroides* morphotypes present per oil immersion field. Individual centers showed significant differences in the number of *Mobiluncus* and lactobacillus morphotypes ($P < .01$).

Conclusion: The prevalence of bacterial vaginosis and distribution of bacterial morphotypes in vaginal smears among asymptomatic pregnant women vary significantly in populations from different countries.

Bacterial vaginosis (BV) is the most common vaginal infection worldwide and is generally asymptomatic. It is prevalent in 11% to 48% of women of reproductive age.[1-5] BV is characterized by an imbalance in the normal vaginal flora in which the normally abundant hydrogen peroxide-producing *lactobacilli* are depleted and anaerobic and microaerophilic organisms like *Gardnerella vaginalis, Mycoplasma hominis, Ureaplasma urealyticum, Mobiluncus, Prevotella,* and *Bacteroides* are markedly increased.[6,7] BV during pregnancy is linked with adverse outcomes such as increased risk of preterm labor, preterm prelabor rupture of membranes, preterm delivery, and possibly spontaneous abortion.[8-10] In addition, many studies have found that BV is associated with chorioamnionitis and postpartum and postabortion endometritis.[10-12] BV may also be associated with an increased risk for human immunodeficiency virus (HIV) transmission between adults as well as perinatal transmission of HIV.[13]

The social, clinical, and economic implications of adverse outcomes associated with BV have led to increased attention to screening and treatment. Studies conducted in the United States have found that there are significant variations in the prevalence of BV among different population subgroups.[14,15] The rate of BV is higher in black women than in any other ethnic group in the United States. Although often of small sample size, there are a number of published international studies investigating the prevalence of BV predominantly in high-risk populations.[2-5,16,17] In a 4-center study conducted in India, Thailand, Malawi, and Zimbabwe, the prevalence of BV was 30%.[17] Other studies conducted in different countries described the prevalence of BV ranging from 11% to 48%.[1-5]

These differences may be explained by the use of different diagnostic criteria. Lately there have been 2 methods used to evaluate BV. One, described by Amsel et al,[18] is a composite method based on clinical and laboratory criteria. The other described by Nugent et al[19,20] has been described as more reliable. In this technique, the diagnosis of BV is based on the interpretation of a Gram stain of vaginal secretions. A score is assigned on the basis of the proportion of lactobacillus morphotypes and *Gardnerella, Bacteroides*, or *Mobiluncus* morphotypes observed under the microscope.[20] A score of 10 is comprised of 4 points for no lactobacillus, 4 points for 4+ *Gardnerella/Bacteroides* (30 or more morphotypes present per oil immersion field), and 2 points for 3+ or 4+ *Mobiluncus* (30 or more morphotypes present per oil immersion field). Of a possible range of 0 to 10, a score of 7 to 10 is considered positive for BV.

A possible cause of variation in reported prevalence might be the manner in which microscopic analysis criteria are applied, from location to location and the interobserver and intraobserver reliability of the methods used.[21] We are not aware of published studies investigating variations in the prevalence of BV among pregnant women from different geographical regions of the world that have used standardized methods for sample collection and interpretation of the Gram-stained samples at a centralized laboratory.

This multicenter, international study used standardized diagnostic methodology to determine the prevalence of BV and distribution of BV-associated morphotypes among asymptomatic pregnant women in different populations in 7 countries.

Material and methods

We conducted a study at 8 institutions participating in the Global Network for Perinatal and Reproductive Health (http://www.gnprh.org). Centers were located in Bogotá, Colombia; Dublin, Ireland; Yangon, Myanmar; Manila, The Philippines; Bangkok and Khon Kaen, Thailand; Philadelphia, PA, in the United States; and Harare, Zimbabwe. The study was approved by the institutional review board at each study center and at the Centers for Disease Control and Prevention of the United States. All institutions were urban academic centers providing obstetric care. To ensure that methods were comparable among sites, we held investigators' meetings, conducted site visits, and reviewed collected data centrally.

We enrolled pregnant women between 18 and 35 weeks of gestation receiving routine antenatal care at the 8 study sites after screening for eligibility from July 1999 to September 2001. Women were excluded from the study if they were in active labor or had symptoms of

Table I Characteristics of study participants overall and by study center

	Colombia	Ireland	Myanmar	Philippines	Bangkok, Thailand	Khon Kaen, Thailand	USA	Zimbabwe	Total
n	155	203	227	202	200	200	69	210	1466
Mean age (range), y	28 (14-43)	28 (16-44)	28 (11-42)	26 (15-43)	26 (16-42)	25 (16-42)	31 (15-46)	23 (12-41)	26 (11-46)
Median years of education (range), years	9 (1-20)	14 (9-19)	7 (0-14)	10 (3-15)	9 (0-16)	9 (4-18)	16 (11-20)	11 (0-13)	10 (0-20)
Smoking, %	6.6	26.6	0.9	1	1.5	0	17.9	0	5.7
Ever douched, %	2.6	1	0	96	2	0	49.3	9.6	17.5
Primigravida, %	28	45	44	39	52	48	18	41	42
Median gestational age (range), week at diagnosis	26 (18-32)	28 (19-32)	25 (18-33)	27 (18-34)	27 (20-32)	23 (18-32)	28 (20-32)	27.5 (18-35)	26 (18-35)

vaginitis such as abnormal vaginal discharge, malodor, burning, or itching. Other exclusion criteria included fever, active vaginal bleeding, use of antibiotics in the 2 weeks before entry into the study, or planned use of antibiotics during the remaining time of the pregnancy. Women with asymptomatic *Trichomonas vaginalis* were not excluded but after sampling received a prescription for therapy for themselves and their sexual partners. Overall, the population at each site was one of convenience with no attempt to select participants based on any specific criteria. The populations in general were mid to low income and reflected the ethnic distribution of the country.

After agreeing to participate in the study, participants signed an informed consent statement. An initial questionnaire was conducted by clinic nurses who had been trained as research assistants. The initial data form included a patient identification number, date of enrollment, gestational age (based on reliable last menstrual period or ultrasound), laboratory test results (including wet mount and other tests as per the clinic routine), demographic data, history of past pregnancies, and any infections diagnosed during this pregnancy. Then a pelvic examination was performed by an obstetrician and samples collected.

Using a Dacron swab, a sample was obtained from the lateral wall of the vagina and smeared onto 2 clean glass slides. One vaginal smear was air dried, Gram stained, scored for BV, and stored at the study center. The second slide was sent for Gram staining and scoring at a reference laboratory at the University of Alabama (UAB) in Birmingham, Alabama, in the United States. BV was ascertained using Nugent scores[20] for Gram stain. All slides were read by the experienced observers at UAB who were blinded to the clinical data. The score from UAB was used for data analysis.

Data were entered using Epi-Info software (Centers for Disease Control and Prevention, Atlanta, GA), and the analysis was conducted using SPSS 12.0 for Windows (SPSS Inc, Chicago, IL). Statistical analysis included χ^2 tests and forward stepwise logistic regression; a P value less than.05 was considered significant.

Results

We enrolled 1466 asymptomatic pregnant women in the study. The median age of participants was 26 years (range 11 to 46 years), with a range of 23 to 31 years among the study centers (Table I). The median gestational age at enrollment was 26 weeks (range 18 to 35 weeks). Smoking was common among women in the United States and Ireland but uncommon elsewhere; douching was common among women enrolled in The Philippines and in the U.S. sites.

Among 1461 vaginal smears available for evaluation, 12.3% (n = 179) were consistent with a diagnosis of BV according to Nugent's criteria. The highest prevalence was in Zimbabwe (24.4%) and the lowest prevalence in Philadelphia, PA (5.8%) (Table II). There were statistically significant differences in prevalence between Zimbabwe and all other sites ($P < .05$). The mean Nugent score was 2.8 ($\pm$2.5) overall and, consistent with the prevalence of BV, was highest in Zimbabwe (4.1). ($\pm$2.7).

By multivariate analysis, the prevalence of BV was associated with women's age, decreasing with each year of age. It was associated with study center but not associated with education level, smoking, or douching (Table III). After accounting for age, education, douching, and smoking, the prevalence of BV in each of the other sites with the exception of Myanmar was significantly less than Zimbabwe with an odds ratio between 0.24 and 0.51.

There were variations in the component scores for lactobacillus, *Gardnerella*/*Bacteroides*, and *Mobiluncus* from the individual centers (Figure 1). The mean scores of all morphotypes were highest for Zimbabwe. Among BV cases (n = 179), nearly all vaginal smears (98.9%) had more than 30 *Gardnerella*/*Bacteroides* morphotypes present per oil immersion field (Figure 2). However,

Table II Prevalence of BV (Nugent score 7 to 10) overall and at individual study sites

Site	n	Prevalence of BV, %	Mean Nugent score (±SD)
Colombia	14/155	9.0	2.6 (2.3)
Ireland	12/201	5.9	2.3 (2.1)
Myanmar	35/225	15.6	2.9 (2.7)
Philippines	15/200	7.5	2.1 (2.2)
Bangkok, Thailand	25/200	12.5	3.0 (2.4)
Khon Kaen, Thailand	23/200	11.5	2.2 (2.3)
United States	4/69	5.8	1.9 (2.0)
Zimbabwe	51/209	24.4	4.1 (2.7)
Total	179/1461	12.3	2.8 (2.5)

Table III Logistic regression analysis for BV, adjusting for age, education, center, smoking, and vaginal douching

Variables	Odds ratio	95% CI for OR	*P* value
Age	0.95	0.92-0.98	.001
Education	1.00	0.95-1.06	.93
Center			
Zimbabwe	1		
Colombia	0.35	0.18-0.68	.002
Ireland	0.24	0.12-0.48	<.001
Myanmar	0.71	0.43-1.17	.17
Philippines	0.29	0.16-0.55	<.001
Bangkok	0.51	0.30-0.86	.01
Khon Kaen	0.41	0.24-0.72	.002
United States	0.28	0.09-0.81	.02
Smoking			
No	1		
Yes	1.25	0.46-3.44	.66
Douched			
No	1		
Yes	1.75	0.69-4.46	.24

individual centers showed significant differences in the number of *Mobiluncus* morphotypes and lactobacillus morphotypes ($P < .01$). None of the samples from subjects with BV in Ireland had *Mobiluncus* morphotypes. In contrast, the prevalence of *Mobiluncus* species at Myanmar, Colombia, Zimbabwe, and the United States was 88.5%, 78.6%, 76.5%, and 75%, respectively. The expected absence of lactobacillus morphotypes was found in only 5.9% of BV cases in Zimbabwe, whereas the proportions in Khon Kaen, Thailand, and Ireland were 43.5% and 41.7%, respectively.

Comment

Our study found important differences in the prevalence of BV among asymptomatic pregnant women from different geographical regions of the world. In addition, we describe significant variation in the distribution of morphotypes in vaginal smears. In Ireland, where the participants were predominantly white, none of the subjects with BV had *Mobiluncus* morphotypes in their vaginal smears, whereas nearly half of the cases had a complete absence of lactobacillus. In Zimbabwe, where all the subjects were black, BV was predominantly the result of a higher proportion of the *Mobiluncus* species, but only 5.9% of women with BV had a complete absence of lactobacillus.

Previously conducted studies in the United States[14,15] also found substantial ethnic differences in the rates of microbial colonization of the vagina. Asian-Pacific Islander and white women had the lowest percentages of positive test results, whereas black women had the highest for nearly every organism studied. Black women were colonized with BV in 23% versus only 9% in white women. After adjustment for potential confounders including certain health behaviors, the odds ratio of a black woman having colonization with BV is 2.9 (95% confidence interval 2.5 to 3.4) when compared with a white woman.

The findings had the potential to explain in part the disparity in pregnancy outcomes, especially rates of spontaneous preterm birth, between black and white women. The prevalence rates we report generally fall within previously reported ranges. Goldenberg et al[14] and Hillier et al[8] reported rates ranging from 9% to 23% and 9% to 28%, respectively, in populations in the United States. Purwar et al[16] reported a rate of 11.5% in India. We confirmed a higher rate in the population from Zimbabwe, as described by other investigators.[2] The low prevalence in the center in the United States in our study (5.8%) could be explained as a result of a small sample size for that center. It could also be explained as a result of a selection bias because these women were from a private practice and were mostly white women. We believe that the rates we report are generally representative of the rate of BV in pregnancy in asymptomatic women from the population at each of the sites.

We used standardized methods for collection of the samples, with dedicated, trained staff and had all the slides stained and read at a central, experienced laboratory. These procedures assure that the explanation for the variation in the prevalence of BV by site is not the result of methodological issues.

Many questions about the association of BV and poor pregnancy outcome remain. Whether these variations in BV prevalence or distribution of morphotypes are related to different outcomes in different populations is unclear. In addition, it is not known which morphotypes of BV, if any, contribute to the adverse outcomes previously associated with BV, such as preterm birth or acquisition of HIV infection. In fact, the mechanisms that trigger

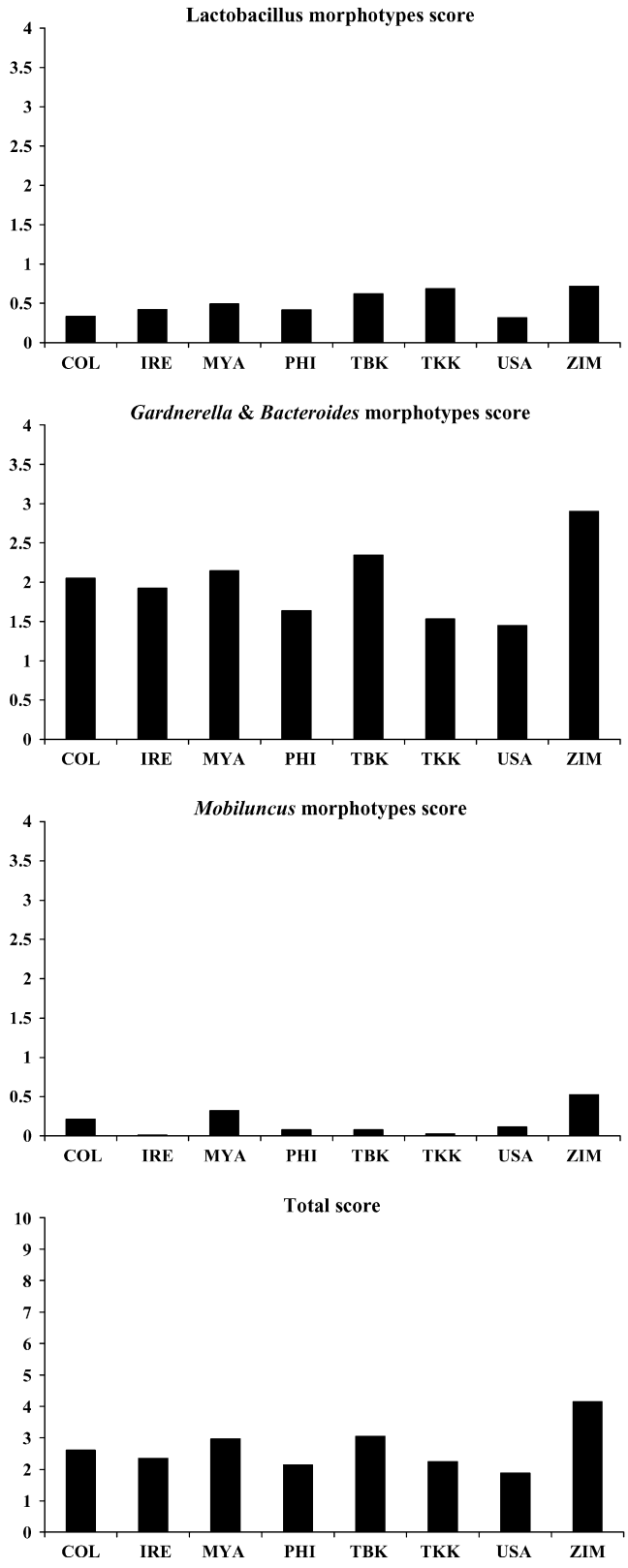

Figure 1 Mean total and component Nugent score for all women evaluated at each study site. *COL,* Colombia; *IRE,* Ireland; *MYA,* Myanmar; *PHI,* The Philippines; *TBK,* Bangkok, Thailand; *TKK,* Khon Kaen, Thailand; *USA,* Philadelphia, USA; *ZIM,* Zimbabwe.

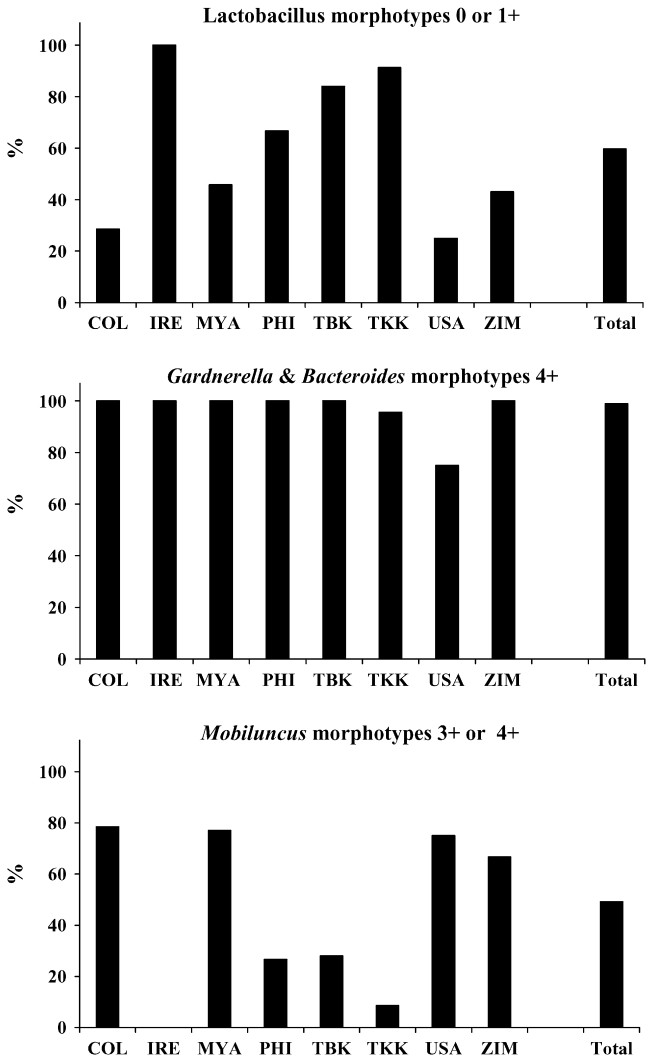

Figure 2 Distributions of morphotypes in BV cases with a Nugent score of 7-10. *COL,* Colombia; *IRE,* Ireland; *MYA,* Myanmar; *PHI,* The Philippines; *TBK,* Bangkok, Thailand; *TKK,* Khon Kaen, Thailand; *USA,* Philadelphia, USA; *ZIM,* Zimbabwe.

change in the vaginal ecology and the roles of the individual microbes causing BV are poorly understood. Other studies have shown increased proinflammatory cytokines, such as tumor necrosis factor-α, interleukin-1, interleukin-6, interleukin-8, granulocyte colony-stimulating factor, fetal fibronectin, and metalloproteinases in conjunction with BV, even though BV is customarily regarded as a noninflammatory condition.[22-26]

The strength of this study was that it is the first multicenter, international study on BV conducted in diverse racial and ethnic populations. Because the methods were standardized across all centers and laboratory tests were done at a central location, the chance of bias resulting from multiple observers reading the slides was eliminated. A limitation was that there was a

small sample from 1 center (the United States), and a single study site may not be representative of the general population in the countries represented.

In conclusion, with Gram stains performed and read in a single reference laboratory, our findings suggest that the prevalence of BV and the distribution of bacterial morphotypes in vaginal smears among asymptomatic pregnant women differ in different countries. Why these differences occur and whether the variation in the distribution of morphotypes associated with BV leads to differences in pregnancy outcomes needs to be further studied.

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