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Risk of Bacterial Vaginosis in Users of the Intrauterine Device: A Longitudinal Study

Tessa Madden, MD, MPH[*], **Jaclyn M. Grentzer, MD, MSCI**, **Gina M. Secura, PhD, MPH**, **Jenifer E. Allsworth, PhD**, and **Jeffrey F. Peipert, MD, PhD**
Division of Clinical Research, Department of Obstetrics and Gynecology, Washington University in St. Louis School of Medicine

Abstract

BACKGROUND—Users of the intrauterine device(IUD) may be at increased risk for bacterial vaginosis (BV). Our objective was to compare the incidence of BV in women using the IUD compared to women using combined oral contraceptives (COC), the contraceptive vaginal ring, and the contraceptive patch.

METHODS—We prospectively recruited women negative for BV at baseline. Monthly, for six months, participants returned a self-obtained vaginal smear for Gram stain by mail. BV was diagnosed by a Nugent score ≥7. We performed Cox proportional hazards regression to investigate associations between demographic and behavioral characteristics, contraceptive method, and incident BV.

RESULTS—We enrolled 153 women negative for BV at baseline; 90(59%) women who chose the IUD and 63 (41%) who chose COC, ring, or patch. There were 35 women with BV at one or more time points. The incidence of BV was 37.0% among IUD users and 19.3% in COC, ring, and patch users (p=0.03). In the univariate analysis, race, IUD use, intermediate flora, and irregular vaginal bleeding were significantly associated with BV. In the adjusted model, IUD users were no more likely to acquire BV (HR_{adj} 1.28, 95%CI 0.53–3.06)than COC, ring, and patch users. The associations between intermediate flora and irregular bleeding and BV remained significant (HR_{adj} 3.3095% CI 1.51–7.21, and HR_{adj} 2.54, 95% CI 1.03–6.24 respectively).

CONCLUSIONS—The association between IUD use and BV may be mediated by irregular vaginal bleeding. Intermediate flora is associated with an increased incidence of BV.

Keywords

Bacterial vaginosis; Intrauterine device; Hormonal contraception; Irregular bleeding

INTRODUCTION

Bacterial vaginosis (BV) is the most common cause of vaginal symptoms prompting women to seek medical care and is widely prevalent, affecting 29% of women in the United States (U.S.).[1] Normal vaginal flora is predominated by hydrogen peroxide-producing lactobacillus species.[2] BV is characterized by a decline in vaginal lactobacilli with an increase in the number of Gram-negative anaerobes such as *Gardnerella vaginalis, Atopobium vaginae*, and Prevotella species.[3,4] Risk factors for BV include, black race, sexual activity, douching, and

[*]Corresponding author: Tessa Madden, MD, MPH, Department of Obstetrics and Gynecology, Washington University in St. Louis School of Medicine, 4533 Clayton Avenue, Campus Box 8219, St. Louis, Missouri 63110; 314-747-6495 (telephone), 314-747-4019 (fax); maddent@wustl.edu.

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cigarette smoking.[1,5,6] BV has been associated with adverse reproductive health outcomes including an increased risk of sexually transmitted infections, pelvic inflammatory disease, and gynecologic post-operative infections.[7–12]

BV is diagnosed clinically by the presence of 3 out of the 4 following criteria described by Amsel et al; homogenous vaginal discharge, vaginal pH >4.5, amine odor upon addition of potassium hydroxide, and the presence of clue cells on saline microscopy >20% per high powered field.[13] Typically, in research studies, the Nugent score based on Gram stain of a vaginal smear is used rather than clinical criteria; a score of 0–3 is consistent with normal flora, 4–6 intermediate flora, and ≥7 is diagnostic of BV.[14] Self-obtained vaginal swabs (SOVS) have been shown to be acceptable to women and slide preparation by study participants has been shown to be reliable for subsequent Gram stain and Nugent score.[15]

Prior studies have shown that combined oral contraceptives (COC) and progestin-only contraceptives, as well as condom use, are protective against BV.[16–18] The relationship between BV and IUD use is less clear; some studies have shown an increase in the risk of BV among IUD users[19,20] while other studies have not found any increase in risk.[18,21,22] A longitudinal study comparing the incidence of BV in IUD users to COC users found an almost 3-fold increase in BV among IUD users.[23] Limitations of this study include no description of the type(s) of IUDs used and comparison of new IUD users to established COC users. Possible explanations for an association between IUD use and BV acquisition include increased anaerobic bacteria in the vagina due to the presence of a string in the vagina or a foreign body in the uterus, or increased volume and duration of menstrual flow in users of the copper IUD.[23,24] We hypothesized that among women initiating contraception, the incidence of BV would be higher among new users of the IUD users compared to new users of COC, ring, and patch.

MATERIALS AND METHODS

We conducted a longitudinal study of BV acquisition over the initial 6-months of contraceptive use in women who selected the intrauterine device (IUD) compared to women who selected COC, the vaginal ring, or the contraceptive patch. This study was conducted as a sub-study of a larger, ongoing contraceptive study, the Contraceptive CHOICE Project (CHOICE). This is a prospective cohort study designed to promote the use of long-acting reversible methods of contraception and to evaluate use, satisfaction, and continuation of reversible contraceptive methods. The methods of CHOICE have been described in detail elsewhere.[24] Separate approval was obtained from the Washington University School of Medicine Human Research Protection Office prior to participant recruitment.

Women were eligible to participate in this study if they were between the ages of 18 and 45 years, enrolling into CHOICE and initiating a copper or levonorgestrel IUD, COC, the contraceptive vaginal ring, or the transdermal contraceptive patch. Exclusion criteria included current pregnancy, history of a vaginal infection in the prior 30 days, or BV at the time of enrollment by Amsel criteria and Nugent score.. Other inclusion criteria included English-speaking, willing and able to provide informed consent, and willing and able to comply with the study protocol. All CHOICE participants were asked to collect a self-obtained vaginal swab (SOVS) as part of the CHOICE enrollment process. We used the SOVS to screen eligible women for BV using modified Amsel criteria in which a clinical diagnosis of BV was made if 2 out of 3 of the following criteria were present: vaginal pH >4.5, positive “whiff test” which is a release of amines from vaginal fluid upon the additional of potassium hydroxide, and presence of >20% clue cells per high powered field on saline microscopy.[25] If the participant was negative for BV, she was then approached for participation in the study by a member of the research team. A baseline vaginal smear was

also obtained for Gram stain and Nugent score. Women who were enrolled and subsequently found to have a BV by Nugent score (score ≥7) were excluded from the analysis.

All women who agreed to participate in the study provided written informed consent and completed a baseline questionnaire collecting demographic information as well as sexual history, hygiene, and infection history. We gave participants detailed instructions on how to perform SOVS and to make a smear on a glass slide for subsequent Gram stain and Nugent score. Each participant was provided with a study kit containing a calendar, swabs, slides, instructions, and pre-paid mailing materials.

Each month, for the next 5 months, the participant collected a SOVS and prepared a slide at home. She also completed a questionnaire about vaginal symptoms in the preceding month, douching habits, recent treatment for sexually transmitted infections (STIs) or symptomatic discharge, vaginal bleeding, and new sexual partners. The slides and questionnaire were then mailed back to the research site. Participants also completed a final 6-month in-person visit at our university-based research clinic where they collected a final SOVS, prepared a slide for Gram stain, and completed a final written questionnaire. Participants were provided with an incentive for participation.

After receiving the participant slides, we performed Gram stain and microscopy to determine the Nugent score for each slide as has been previously described.[14] All of the slides were Gram-stained and scored by a single member of the research team. Ten percent of the slides were double-read and scored by a second member of the research team. There was high concordance between the 2 readers with a kappa of 0.81.

The Nugent score was not used for clinical care and women were not treated for BV diagnosed during the study based on their Nugent score alone. If during the study a participant had complaints of vaginal symptoms, she was referred for gynecologic care.

Statistical Methods

Based on results of prior published studies, we anticipated a BV incidence of 10% among COC, ring and patch users and 30% among IUD users.[23] We calculated that a total of 144 women (72 in each group) would be required to find a statistically significant difference in the rate of BV between the 2 groups with an alpha of 0.05 and 80% power. Assuming a 20% loss-to-follow-up we planned to enroll 84 women into each group for a total of 168 participants.

Demographic characteristics were described using frequencies, percentages and means. Baseline differences between the IUD users and COC, ring and patch users were analyzed using chi-square and t-test and Fisher exact tests as appropriate. Additionally, based on prior studies, we hypothesized that several variables would be associated with BV acquisition including age, race, condom use, and douching. We planned to include these variables in our final model regardless of statistical significance. For condom use and douching, we collected information about baseline use. For variables where we collected the information at multiple time points, we created a second variable to evaluate use over the 6-month study period based on whether the participant reported the behavior on any follow-up survey. We hypothesized that women with intermediate flora at baseline would also be more likely to acquire BV over the study period. Cox Proportional Hazards regression was performed using these variables to estimate the hazards ratio (HR) and 95% confidence interval (CI) for the association between demographic and behavioral characteristics and contraceptive method use and acquisition of BV. Proportional hazards assumptions were tested and found to be appropriate. Interaction terms between covariates significant in the univariate model

were tested and found not to be statistically significant. All analyses were performed using in Stata 11 (StataCorp LP, College Station, TX).

RESULTS

We recruited and enrolled 157 women into the study. There were 153 women who were negative for BV at baseline by both clinical criteria and Nugent score. Of these, 90 (58.8%) were new IUD users and 63 (41.2%) were new users of COC (16.3%), ring (20.3%), or patch (4.6%). Among the 90 IUD users, 59 (65.6%) chose the levonorgestrel intrauterine system(LNG-IUS) and 31 (34.4%) chose the copper IUD. Due to slower than expected recruitment, we were unable to reach our target enrollment of 168 women. Additionally, because of the high rate of IUD uptake in CHOICE (>50%), there was a greater proportion of IUD users resulting in unequal distribution between the 2 groups.

Over the course of the study, each woman could submit a maximum of 6 slides. The mean number of slides submitted was 3.7 (SD 2.1). There were 19 (12.4%) women who did not submit any slides or complete any questionnaires over the study period; 4 of these women withdrew from the study (3 women cited lack of time and 1 woman withdrew from the parent study).. An additional participant became pregnant after 4 months of participation and was withdrawn from the study at this time as pregnancy was a criterion for exclusion. At least 2 slides were available for 133 (87.9%) women. There were 120 (78.4%) women who returned 2 or more slides and 49 (32.0%) women who submitted all 6 slides. One hundred and fourteen (74.0%) women returned for the 6-month in-person visit and gram stain results were available for 104 women (68.0%). Nine slides were not scored due to discarded or damaged slides or an inadequate sample.

Baseline characteristics of women who contributed 2 or more slides for gram stain are shown in Table 1 by contraceptive method. Women in the IUD group were slighter older (mean age 26.7 years) compared to COC, ring and patch users (mean age 24.4 years, p=0.01). Race, ethnicity, educational level, marital status, insurance coverage, and low SES status were similar between groups. The groups did not differ in previously described risk factors for BV such as number of mean number of lifetime sexual partners, history of douching ever or in the 6 months prior to enrollment, current smoker, tampon use, or prior history of BV or a STI. IUD users were almost twice as likely to have intermediate flora at baseline (18.4% versus 10.3%, p = 0.19) although this was not a statistically significant difference.

COC, ring and patch users were more likely to report using condom use at baseline and over the study period condoms than women using IUDs. At baseline, 58.6% of COC, ring and patch users reported “always” or “almost always” using condoms compared to 36.8% of IUD users (p=0.05). Over the study period, 29.0% of IUD users and 58.6% of COC, ring and patch users reported “always” or “almost always” using condoms at one or more time points (p=.001) and only 15.8% of IUD users and 36.2% of COC, ring and patch users reported “always” or “almost always” using condoms at every time point (p<.001). Self-report of condom use at every time point was associated with a reduction in incident BV, although this was not a statistically significant finding (HR 0.69, 95%CI 0.24–1.96).

Over the 6-month study period, there were 35 new cases of BV with an incidence of 29.2%. The incidence of BV was higher among IUD users at 37.0% compared to 19.3% in COC, ring, and patch users (p=0.03). The incidence of BV did not differ significantly among COC, ring and patch users (15.0% versus 16.7% versus 22.4% respectively, p=0.24). There was a trend towards increased BV incidence among LNG-IUS users (41.8% compared to 28.0% of copper IUD users); however, this was not a statistically significant finding p=0.23). The

majority of cases of BV were asymptomatic; only 23.6% of women with a Nugent score ≥ 7 reported vaginal symptoms at the time of slide collection.

Table 2 shows the results of the Cox proportional hazards model; black race, intermediate vaginal flora at baseline, irregular bleeding over the study period, and IUD use were associated with an increased acquisition of BV in the univariate analysis. Condom use, douching, smoking, or new sexual partner over the 6-month study period were not associated with BV acquisition in the proportional hazards model.

In our multivariable model (also shown in Table 2), we adjusted for the above covariates as well as age, baseline condom use, and douching in the 6 months prior to enrollment. In the adjusted model, neither IUD use nor race remained significantly associated with BV. Women with intermediate vaginal flora at baseline were more than 3 times as likely to develop BV (HR 3.15, 95%CI 1.46–6.80) and women who reported any irregular bleeding during the study period were more than twice as likely to acquire BV(HR 2.60, 95%CI 1.04–6.50).

At baseline, women in the IUD group were more likely to have intermediate flora than women in the COC, ring, and patch group. Women with intermediate flora were more likely to acquire BV regardless of contraceptive method chosen; 60% of IUD users with intermediate flora acquired BV over the study period compared to 67% of COC, ring, and patch users, which is shown in Table 3. Women in the IUD group were also more likely to report irregular bleeding over the study period than women in the COC, ring and patch group (73.8% versus 42.5%; $p<0.01$). Irregular bleeding was more common among LNG-IUS users compared to copper IUD users (41.9% versus 30.5%), although this was not a statistically significant difference ($p=0.28$). After stratifying by irregular bleeding, we found that, in the absence of irregular bleeding, there was no increase in the risk of BV among IUD users (HR 01.02, 95%CI 0.20–5.24) compared to COC, ring and patch users. However, IUD users who reported irregular bleeding had an increased risk of BV (HR 1.83, 95%CI 0.69–4.81), although this difference was not statistically significant due to the small sample size in each IUD subgroup.

DISCUSSION

In this study, we found an association between IUD use and BV in our crude analysis. However, after controlling for confounders, the effect size of the hazards ratio was greatly attenuated and was no longer statistically significant. There were 2 factors that emerged as stronger predictors of BV acquisition; intermediate vaginal flora at the time of contraceptive initiation and irregular vaginal bleeding during the first 6-months of contraceptive method use. Stratification by irregular bleeding showed no association between IUD use and BV in the absence of irregular bleeding. However, IUD users with irregular bleeding were almost twice as likely to develop BV. This finding was not statistically significant; however, our study was not powered to find a statistically significant difference in these small subgroups. The difference in the effect size of the hazards ratios for BV acquisition in IUD users with and without irregular bleeding suggests that irregular bleeding may be in the causal pathway for an association between IUD use and BV.

This association between irregular bleeding and BV was an unanticipated finding of our study. There are several potential mechanisms by which irregular bleeding could increase the risk of BV acquisition. Blood has a neutral pH which raises the pH of the normally acidic vagina. Association between menses and BV recurrence has been described[26] with an increase in anaerobic bacteria and a decrease in lactobacilli.[27] In addition, lactobacilli agglutinate to red blood cells which may result in a decreased vaginal lactobacillus

concentration in women with frequent or persistent uterine bleeding.[28] Alternatively, the irregular bleeding could be secondary to endometritis resulting from IUD placement in a woman with BV. In our study, we found that the incidence of BV was higher at each time point in women who reported irregular bleeding over the prior 30 days than in women without irregular bleeding (data not shown) which suggests that the irregular bleeding may have preceded the change in vaginal flora. As irregular bleeding is a frequent side effect of hormonal contraception and is particularly common during the first 6 months of LNG-IUS use, this finding may be important for patient counseling. The observed association between intermediate flora and BV acquisition may be due to rapid fluctuation of the vaginal microbiota which has been described in women who acquire BV.[29]

Our study had several strength, including a prospective longitudinal design which allowed us to evaluate incident BV. In addition, our participants were all new users of their contraceptive method avoiding a comparison between new users and long-term users. Our cohort was a racially and socio-economically diverse cohort increasing the generalizability of our findings.

It is important to recognize that this study has several limitations. Due to our low rate of participant follow-up, we may have underestimated the true incidence of BV in our study population. However, there were no statistically significant differences in the demographics and reproductive characteristics between women lost to follow-up and the other participants (data not shown), suggesting that loss to follow-up was not differential. In addition, we had limited power to evaluate our outcomes of interest and to perform a stratified analysis to investigate the effect of irregular bleeding on incident BV. Another limitation is that we compared women using IUDs to women using COC, ring, and patch. Nugent scores have been shown to be similar in users of COC and the vaginal ring;[25] however, hormonal contraceptives have a protective effect against BV which may have over-estimated the effect of IUD use on incident BV. In our study, the incidence of BV was similar among COC, ring and patch users, suggesting no difference in the effect on vaginal flora between these combined hormonal contraceptive methods." Identification of an appropriate comparison group among women using contraception is challenging as reproductive-age women not using contraception are often seeking pregnancy or are demographically distinct from women using contraception. However, given the high prevalence of COC use in the U.S., COC users may be the most appropriate comparison group.[30]

Irregular bleeding secondary to hormonal contraception usually improves over time; therefore, the association between IUD use and BV may be greatest during the initial use of the method. Further studies with a longer duration of follow-up are needed to investigate whether this association persists overtime as the irregular bleeding secondary to hormonal contraception resolves.

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Table 1

Baseline Characteristics of Participants by Method Chosen at Baseline for Participants Who Submitted Two or More Slides Over the Study Period

	IUD (n=76)	CHC (n=58)	*P*
Age, Mean (SD)	26.7 (5.4)	24.4 (4.8)	0.01¥
Race	N (%)	N (%)	
White	42 (55.3)	31 (54.4)	0.33^
African American	31 (40.8)	20 (35.1)	
Other	3 (4.0)	6 (10.5)	
Hispanic	1 (1.3)	2 (3.5)	0.58^
Education			
Less than High School	2 (2.6)	5 (8.6)	0.19^
High School/Some college	53 (69.7)	34 (58.6)	
College/Grad School	21 (27.6)	19 (32.8)	
Marital Status			
Single	36 (47.4)	35 (60.3)	0.33^
Married/living with partner	36 (47.4)	21 (36.7)	
Separated/divorced	4 (5.3)	2 (3.5)	
Insurance			0.48^
None	28 (36.8)	27 (46.6)	
Private	40 (52.6)	27 (46.6)	
Medicaid/Medicare	8 (10.5)	4 (6.9)	
Low SES*	38 (50.0)	33 (56.9)	0.49
Current smoker	19 (25.03)	10 (17.2)	0.28
Use tampons	54 (71.14)	48 (83.8)	0.12
Use condoms always or mostly at baseline	28 (36.8)	34 (58.6)	0.05
Ever douched	29 (38.9)	18 (31.6)	0.40
Douched in the past 6 months	13 (17.1)	8 (13.8)	0.60
Lifetime # of male sexual partners, Mean (SD)	7.5 (8.4)	7.1 (8.3)	0.78¥
History of BV	57 (75.0)	47 (81.0)	0.41
History of any STI§	25 (32.9)	21 (36.2)	0.69
Baseline Nugent score			
0–3 (negative)	61 (80.3)	55 (89.7)	0.19
4–6 (intermediate)	14 (18.4)	6 (10.3)	

IUD – intrauterine device; CHC – combined hormonal contraception; SES – socioeconomic status; BV – bacterial vaginosis; SD – standard deviation; STI – sexually transmitted infection

Percentage may not equal 100 due to missing data

All p-values calculated using chi-square unless otherwise specified

¥ Value calculated using t-test

^ Value calculated using Fisher exact test

* Receipt of public assistance or report of difficulty paying for basic necessities such as food, housing, transportation and medical care.

§ Any self-reported history of STI including gonorrhea, chlamydia, *Trichomonas vaginalis*, syphilis, and genital herpes simplex infection

Table 2

Crude and Adjusted Cox Proportional Hazards Regression Model of Factors Associated with Acquisition of Bacterial Vaginosis over the 6-Month Study Period.

	Univariate HR (95% CI)	Adjusted HR (95% CI)^
Age		
18–20	Ref	Ref
21–29	1.50 (0.52–4.33)	1.02 (0.33–3.17)
30–45	1.19 (0.33–4.20)	0.77(0.19–3.19)
Race		
White	Ref	Ref
African American	2.33 (1.16–4.68)	1.83 (0.82–4.08)
Other	1.08 (0.24–4.78)	1.25 (0.26–5.93)
Hispanic	0.65 (0.09–4.73)	
Education		
Less than High School	Ref	--
High School/Some college	0.64 (0.15–2.75)	--
College/Grad School	0.74 (0.17–3.33)	--
Marital Status		
Single	Ref	--
Married/living with partner	0.78 (0.38–1.58)	--
Separated/divorced	0.95 (0.22–4.06)	--
Insurance		
None	Ref	--
Private	0.85 (0.42–1.73)	--
Medicaid/Medicare	1.36 (0.45–4.10)	--
Low SES*	1.30 (0.67–2.56)	--
Current smoker	1.12 (0.50–2.41)	--
Use condoms always or mostly at baseline	0.95 (0.69–1.29)	--
Use condoms always or mostly over 6-month study period	0.72 (0.32–1.65)	0.68 (0.27–1.69)
Use tampons	1.32 (0.55–3.20)	--
Ever douched	1.28 (0.65–2.52)	--
Douched in the past 6 months	2.07 (0.97–4.41)	1.62 (0.67–3.94)
History of BV	1.06 (0.48–2.33)	--
History of any STI§	1.27 (0.65–2.50)	--
Baseline Intermediate flora (Nugent score 4–6)	4.93 (2.46–9.88)	3.14 (1.46–6.80)
Any irregular bleeding over 6-month study period	2.88 (1.25–6.59)	2.60 (1.04–6.50
IUD use	2.18 (1.04–4.54)	1.19 (0.48–2.92)

^Adjusted for age, race, condom use over the study period, douching in the 6 months before enrollment, baseline intermediate flora, irregular bleeding, and IUD use.

SES – socioeconomic status; BV – bacterial vaginosis; STI – sexually transmitted infection; IUD – intrauterine device;

[*] Receipt of public assistance or report of difficulty paying for basic necessities such as food, housing, transportation and medical care.

[§] Any self-reported history of STI including gonorrhea, chlamydia, *Trichomonas vaginalis*, syphilis, and genital herpes simplex infection

Table 3

Baseline Vaginal Flora and Percent of Participants Who Developed Bacterial Vaginosis Stratified by Contraceptive Method

Contraceptive Method	Baseline Vaginal Flora (Nugent Score)	Number	Acquired BV N (%)
IUD users	Normal 0–3	n=61	16 (26.3)
	Intermediate 4–6	n=15	9 (60.0)
COC, ring and patch users	Normal 0–3	n=52	6 (11.5)
	Intermediate 4–6	n=6	4 (66.6)

IUD – intrauterine device; COC – combined oral contraception; BV – bacterial vaginosis;