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Bacterial Vaginosis and Prospective Ultrasound Measures of Uterine Fibroid Incidence and Growth

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Abstract

Background: Uterine fibroids often cause intolerable symptoms leading to invasive treatments, most commonly hysterectomy. Reproductive tract infections are hypothesized to influence uterine fibroid development, but few studies exist, especially for the highly prevalent condition bacterial vaginosis (BV). Both fibroids and BV have documented racial–ethnic disparities, with higher burden in Blacks.

Methods: With prospective data from a community-based study (four standardized ultrasound examinations over 5 years) in young Black women, we examined baseline BV associations with fibroid incidence and growth. We computed adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) for incidence comparing BV and no BV (Nugent score ≥7 vs <7) using Cox proportional hazards models among 1,027 women fibroid-free at baseline. Fibroid growth associations were based on linear mixed models estimating volume change between ultrasounds indexed to 18 months. We then expressed BV association as estimated percent difference in growth per 18 months, comparing exposed and unexposed.

Results: There were n=247 incident fibroids and 1,181 growth measures; average fibroid growth per 18 months was a 78% (95% CI: 69, 87) increase in volume. BV prevalence was 51% and not associated with fibroid incidence (aHR: 1.0, 95% CI: 0.80, 1.4) or growth (estimated % difference in growth, −3% (95% CI: −12, 6).

Conclusions: In this first study (to our knowledge) of ultrasound-monitored fibroid development and Nugent-assessed BV, we found no evidence to support the hypothesis that BV increased risk of fibroid incidence or growth or BV's role in the high burden of fibroids in Black women.

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Keywords

Bacterial vaginosis; uterine fibroids; incidence; growth; prospective

Introduction

Uterine fibroids, benign smooth muscle cell tumors, are one of the most common gynecologic conditions affecting women during their reproductive years, with estimated total annual costs in the United States (US) of up to $34 billion [1]. Symptoms resulting from fibroids (pain, severe bleeding, reproductive problems) are the leading indication for hysterectomy in the US, accounting for 40% of all hysterectomies [2]. Black women are two to three times more likely to have diagnosed fibroids than other races–ethnicities[3] and have an approximately 10-year earlier age of onset than White women [4,5]. They also have larger and more tumors at diagnosis [6] and thus are at higher risk of surgical or radiologic treatment [6].

The etiologic causes of fibroids are largely unknown. In addition to Black heritage, other established risk factors are older age (up to the age of menopause), younger age at menarche, nulliparity, and longer time since last birth.[5,7,8] Three studies have reported that the progestin-only injectable (i.e. Depo-Provera) is inversely associated with fibroids.[7,9,10] Other possible risk factors studied show inconsistent associations and/or have undergone limited study.[11]

For decades it has been hypothesized that reproductive tract infections (RTIs) play a role in fibroid development. However, few studies have been conducted, even for the very common condition of bacterial vaginosis (BV).[12] BV is chronic and recurring[13] and characterized by a shift in the vaginal microbiota from the dominant flora of *Lactobacillus spp*. to a mixed vaginal flora with large numbers of anaerobic bacteria[12,14] most of which are also detected (in much lower numbers) in the vaginas of women without BV.[15] Currently, the event(s) leading to the shift in the vaginal flora indicative of BV is unknown although some risk factors include higher number of sex partners, lower age at first sex, lack of condom use, having a previous sexually transmitted infection (STI), douching, Black race/ethnicity, and low socioeconomic status.[16–21] Hormonal contraception tends to be protective.[22]

BV-associated bacteria have also been found in the upper genital tract and are associated with infection and inflammation of the fallopian tubes (salpingitis) and the uterine lining (endometritis).[23,24] BV may increase the risk of STIs such as chlamydia, gonorrhea, herpes, trichomoniasis, and human immunodeficiency virus.[16,25–27] It also has been found to be associated with adverse reproductive outcomes i.e. pelvic inflammatory disease, infertility, spontaneous abortion, and preterm birth;[28–30] however, whether it is a cause remains unclear.[31,32] Nevertheless, the possible adverse health impacts for women may be particularly problematic for Black women because the prevalence of BV among 14–49 year-olds (51%) is 2.8-fold higher than for White women in the US (23%) controlling for other risk factors (National Health and Nutrition Examination Survey).[18] It is important to note that the high prevalence of BV among Black women is not considered to be due to heritage, but social conditions that influence sexual health.[33]

There are two main methods to diagnose BV. In the clinical setting, the Amsel criteria[34] based on signs and symptoms (e.g. vaginal discharge) are used. In the research/laboratory setting the gold standard for BV diagnosis is the Nugent's scoring system (0–10; 7+ indicative of BV, 4–6 intermediate, <4 normal) which is based on gram stain of vaginal smears.[35–37] Also, the development of new methods to examine the microbiota, such as quantitative PCR or 16s RNA, are compared against Nugent's criteria as the gold standard.[38,39]

BV could plausibly increase fibroid development by inducing an inflammatory environment that can promote cell proliferation, increased extracellular matrix production and decreased apoptosis, leading to formation and growth of these tumors.[40,41] Three prior studies, including two from the same population as the current study, have reported suggestive associations between BV and increased risk of fibroids; however, all used self-report of a clinical diagnosis of BV.[5,42,43] Relying on self-report of BV diagnosis is a major limitation because of the potential for misclassification due to reporting error and underdiagnosis; diagnosis is typically based on symptoms and up to 40% of BV positive women do not present with lower genital tract symptoms.[44,45] The aim of this current study is to use Nugent scoring to investigate the association between BV and uterine fibroids. In a large prospective study of young Black women, we used standardized ultrasound examinations to prospectively monitor fibroid incidence among women who were fibroid-free at their baseline examination and measure fibroid growth among women who had fibroids present at baseline or developed them during the study.

Methods

We used data from the Study of Environment, Lifestyle and Fibroids, designed to prospectively investigate fibroid incidence and growth with standardized ultrasound examinations. In 2010–2012, they recruited a community sample from the Detroit, Michigan area, aged 23–34 years, who self-identified as African–American or Black, the ethnic group with the greatest burden of disease. Women were ineligible for the study if they had: a prior clinical diagnosis of uterine fibroids; a hysterectomy; ever taken medication to treat lupus, Grave's disease, Sjögren's scleroderma, or multiple sclerosis; or any type of cancer treated with radiation or chemotherapy.

Four clinic visits were conducted approximately every 20 months over 5 years. At each visit, participants completed computer-assisted web questionnaires and telephone interviews and provided non-fasting blood samples. In addition, Epicentre (Madison, WI) vaginal swabs, were self-collected with a standardized protocol. Swabs were stored dry and frozen at −80°C. Details of recruitment and specimen collection have been described previously.[46] The study was approved by the institutional review boards of our institution and collaborating institution and all participants gave informed consent.

Exposure Measurement

BV status at baseline was determined using Nugent scoring for 1,431 (85%) study participants who did not report using antibiotics in the 4 weeks prior to baseline and had a baseline vaginal swab available. Vaginal swabs from all 1,431 participants were

smeared on slides for Gram staining and Nugent scoring. Out of the 1,431 slides, 1,231 were created by our contract lab, Social and Scientific Systems, and 200 were created by Medical Diagnostics Laboratory using the same procedure. These slides were sent to the laboratory of Dr. Jane Schwebke at the University of Alabama at Birmingham for Nugent scoring. The slides were read under a microscope and a Nugent score of 0 to 10 (0–3, normal; 4–6, intermediate; 7–10, BV) was assigned based on the relative proportion of bacterial morphotypes (large gram-positive rods, small gram-negative or variable rods, or curved rods) found.[35] No difference in Nugent score distribution was found when comparing results from the two labs that made the slides.

Outcomes

Fibroids were assessed at each visit with transvaginal ultrasound, the standard clinical procedure for the detection of fibroids. Examinations were conducted by certified gynecologic sonographers with specific training on the standardized study protocol.[46,47] For fibroids ≥0.5cm in any diameter, the longitudinal (L), anterior-posterior (A), and transverse (T) diameters were measured in triplicate and recorded by sonographers. Fibroid volume (cm^3) was calculated using the ellipsoid formula (L x A x T x 0.5233) and averaged across the triplicates. For the current analyses, examinations with poor ultrasound quality (only transabdominal ultrasound or sonographer identified imaging difficulty) were excluded from analyses (<1%). Details of ultrasound methods have been described elsewhere.[46]

Covariates

Age, years since last use of the injectable contraceptive, depot medroxyprogesterone acetate (DMPA) (<4 years, 4+ years ago, never), and recent birth (<3 years) (yes, no) were included as a priori adjustment factors (Model 2), DMPA and recent birth were included due to the strong protective associations we found with fibroids in this study population[10] and income ($0-$20,000, >$20,000-$50,000, >$50,000) was included as a measure of socioeconomic status. Covariates were updated at each visit. The information on births was anchored to the end of each study interval as an efficient way to capture the strong inverse association with fibroids for births during an interval between visits.[48] Though data on risk factors for both BV and initial fibroid development are limited, we used the available literature to select additional factors for a further-adjusted model (Model 3). The factors that were updated at each visit were: current smoker (yes, no), current use of oral contraception (yes, no), body mass index (BMI) kg/m^2 (18.5 to <25, 25 to <30, 30 to <35, 35 to <40, 40+), and number of cumulative births (0, 1–2, 3+); age at menarche (modeled on an ordinal scale: ≤10, 11, 12, 13, 14+), was captured at baseline. We also described other characteristics in Table 1 including educational attainment (≤High School, >High School), currently employed (yes, no), current heavy alcohol use (yes, no), along with the following BV related factors: douching in the past 12 months (yes, no), number of lifetime sex partners (0–5, 6–10, 11+), age at first sex (≤14, 15–16, 17+ years), and both chlamydia[49] and herpes[50] serostatus (yes, no).

Assessment of Incident Fibroids

Out of the 1,431 study participants with Nugent scoring, 1,032 (73%) were fibroid-free at baseline and had at least one follow-up ultrasound visit with quality ultrasound data. We

examined the association between BV status and incident fibroids using a Cox proportional hazards model with age as the timescale. We computed hazard ratios (HRs) and 95% confidence intervals (CIs) for three models, unadjusted (Model 1), a priori-adjustment (Model 2), and further-adjusted (Model 3) each including the corresponding covariates listed above. We used complete case analysis and restricted the models so that all three had the same N. Also, among participants with incident fibroids (n=247), we computed the HR and 95% CI between BV and incidence of 2+ fibroids (n=57) vs. 1 fibroid (n=190).

As sensitivity analyses (conducted for Model 2, the model with a priori covariates), we excluded participants who reported factors at the time of swab collection that might be related to fluctuations in the vaginal microbiota: menstruation (n=147), and exposure to sperm or semen (n=119 + one missing), lubricant (n=25 + three missing), or douching (n=30 + two missing) in the past 24 hours. In addition, given the ambiguity of the intermediate Nugent score category, we conducted sensitivity analyses separately examining the BV category (Nugent score ≥7) compared to no BV (<4), and the intermediate category (Nugent score 4–6) compared to no BV (<4). We also explored four categories of Nugent score [0–3 (ref), 4–6, 7–8, 9+)]and continuous Nugent score. Last, to evaluate the time period between Nugent scoring and fibroid incidence, we computed the by-interval estimates for the first (baseline to follow-up 1), second (follow-up 1 to follow-up 2) and third (follow-up 2 to follow-up 3) follow-up intervals.

Fibroid Growth

Fibroid growth was estimated for individual fibroids that were identifiable as the same fibroid across two successive ultrasounds based on the position in the uterus and/or by assessments of the archived ultrasound videos and images by the head sonographer. There were 1,194 growth measurements from 386 women with Nugent results available. Growth was estimated by finding the difference in the natural log volume of matched fibroids across successive visits and scaling that to 18 months (dividing by the days between visits to get daily growth and multiplying by 540 for 18-month growth). We chose this timeframe of a year and a half because it is close to our median interval between visits (19 months with IQR 18–21) and would be clinically meaningful.

We examined the influence of baseline BV on fibroid growth over the three follow-up intervals using a linear mixed model (GLIMMIX procedure) with a random intercept for participant and fibroid accounting for possible correlations between fibroids within the same woman and fibroids across time, as previously described.[51] For ease of interpretation, we rescaled the log volume change for BV-exposed fibroids vs BV-unexposed fibroids to an estimated percent difference in growth per 18 months by using the resulting beta from the regression and applying the formula [exp(β)-1] x 100. As an example, an estimated percent difference of 10% indicates that the average volume change per 18 months for the exposed was an estimated 10% greater than the volume change of the unexposed fibroids. Model 1 included age and fibroid-related factors:[52] fibroid volume (cubic centimeters, cm^3) (<0.52, 0.52 to <4.19, 4.19 to <14.1, 14.1+), and fibroid number on an ordinal scale (1, 2, 3, 4+) at the start of the interval. Models 2 and 3 included the corresponding covariates listed in the covariate section above. We used complete case analysis and restricted the models so that all

three had the same N. All further analyses were performed using Model 2, the model with a priori covariates.

We performed multiple sensitivity analyses in the fibroid-growth analysis. We excluded statistical outliers (studentized residuals > +/-3).[51] As with the incidence analyses, we also restricted to those who reported no factors that could lead to vaginal microbiota fluctuations, examined variations in the way Nugent scores were used to define BV, and performed by-interval analyses.

All analyses were conducted with SAS 9.4 (SAS Institute, Inc., Cary, NC).

Results

Fibroid Incidence

Of the 1,032 women without fibroids at baseline, 1,027 were included in the analytic data set. N=247 (24%) had an incident fibroid and n=525 (51%) had BV. The age of those with BV and without BV was the same [median (IQR): 29 (26–32)]. Compared to women without BV, those who had BV tended to have a lower income, have higher BMI, have lower education level, have heavier alcohol use, be unemployed, be current smokers, have douched in last 12 months, have higher numbers of sex partners, have a lower age at first sex, and be chlamydia- and HSV-2-seropositive (Table 1). A similar proportion of women developed fibroids in the BV group and no BV group (25% and 24%). In all three models (unadjusted, a priori-adjusted, and further adjusted), BV was not associated with an increased risk of fibroid incidence (aHR: 1.0 95% CI: 0.80, 1.3, aHR: 1.0 95% CI: 0.80, 1.4, and aHR: 1.2 95% CI: 0.91, 1.6, respectively) [Table 2]. The results were similar across most of the sensitivity analyses with aHRs ranging from 1.0 to 1.1 (eTable 1). When we conducted the by-interval analyses, the estimates for the first and third follow-ups were higher than for the full dataset while the estimate for the second follow-up was lower, but confidence intervals were broad for all three (eTable 1). Also, among those with incident fibroids, BV was not associated with an increased risk of 2+ incident fibroids (HR: 0.87 95% CI: 0.51, 1.47), but the small sample size for multiple tumors precluded adjustment.

Fibroid Growth

Of the 1,194 growth measurements, 1,181 were included in the analytic dataset. The average growth per 18 months was an increase of 78% (95% CI: 69, 87). Women with BV contributed 574 (49%) of the growth measurements. The adjusted estimated percent difference in growth per 18 months was −4% (95% CI: −13, 6), −3% (95% CI: −12, 6), and −5% (95% CI: −13, 5) in Models 1, 2 and 3, respectively, among fibroids from women who had BV compared to fibroids from women without BV (Table 3). The results were similar across all sensitivity analyses with adjusted percent difference in growth estimates ranging from −10% to 3% with all confidence intervals including the null (eTable 2).

Discussion

In this prospective study among a community-based sample of young Black women, we did not find an increase in incidence or growth of fibroids for women with BV. These

findings contrast with three past studies, that suggested positive associations using self-reported history of BV diagnoses. Two investigated prevalent [5,42] and one incident fibroids. The cross-sectional Uterine Fibroid Study found suggestions of a positive association for prevalent fibroids among the ~600 Black women studied.[5] The other two studies were from the same population as the current study. The first analysis which was cross-sectional at baseline examined self-report of ever being diagnosed with BV and ultrasound detected fibroids at baseline. We reported that the baseline prevalence of any fibroid was not associated with self-reported history of BV, but having multiple fibroids (≥2) and larger total fibroid volume (≥2 cm^3) was.[42] The second analysis used self-report of any BV history as the exposure and examined incidence of ultrasound detected fibroids at the first follow-up visit. With this prospective incidence measure we found a marginally increased risk for fibroid incidence aRR: 1.4 95%CI (0.93, 2.0). [43] However, for comparison we now assessed self-reported BV with the full prospective data, and find little association aHR 1.2 (0.89, 1.5). Thus, we suspect that the difference in our current and past results are due both to more stable estimates due to the larger sample size in the current analysis as well as a better measure of BV.

Previous studies used only self-reported diagnosis of BV as the exposure measurement which is a limitation. The criteria for clinical “diagnosis” of BV can vary and actual dysbiotic changes in the vaginal flora are not directly measured. As many as 40% of women with BV based on Nugent scoring do not report experiencing any symptoms such as odor or discharge, which are typically what lead to a diagnosis.[44,45] The self-reported prevalence of ever being diagnosed with BV at any time in the past was <6% for Black women in the UFS and 38% in SELF. These were both lower than the 51% point-in-time prevalence of Nugent-diagnosed BV at baseline in SELF. Also, in SELF, only 34% of those with Nugent-diagnosed BV at baseline had self-reported a prior BV diagnosis.

Our study is, to our knowledge, the first to investigate the relationship between BV and fibroids with the laboratory gold standard for BV diagnosis, the Nugent score [53], and systematic ultrasound screening rather than the selective process of clinical detection. We also had data to assess potential confounding, and we conducted sensitivity analyses to evaluate potential bias. In addition, we had data to exclude women with antibiotic use within the previous 4 weeks.

The main limitation of our study was a single assessment of BV at baseline which could have been up to 5 years before fibroid detection [median (IQR) total follow-up time: 4.8 (4.7–5.0) years]. However, even when we restricted analysis to the first follow-up, we did not see evidence of an increased risk of fibroid incidence or growth. Though a single Nugent score may not represent some women’s predominant BV status over time given that rapid fluctuations in the vaginal microbiome have been documented, especially for women with high diversity,[54–59] profiles dominated by “optimal” *Lactobacillus* spp., especially *L. crispatus*, appear more stable over time. Also, studies find that even after treatment for BV, most women return to their pretreatment state within 1–4 weeks,[56,60] suggesting that our vaginal assessment may have general long-term validity. We also did not have sign or symptom information for Amsel criteria. Additionally, we did not have data on condom use, recent sexual activity (number of partners/vaginal–penile acts), reporting of vaginal

symptoms, or diagnoses of trichomoniasis, cervicitis, or pelvic inflammatory disease. These most likely would not impact the relationships we found between BV and fibroids but would provide more insight on the study sample and the factors associated with BV in this group of women. In addition, ascending infection to the upper genital tract could not be determined, and the Nugent score may not adequately reflect the importance of a specific bacteria. Thus, if there are certain BV-associated bacteria that can ascend that are associated with fibroids (via upper genital inflammation and cellular changes), we were not able to determine that.

Last, the study participants were recruited from a single geographic region. However, they were recruited by numerous community methods, and prevalence of BV in this cohort (51%) was the same as for Black women ages 14–49 in the US,[18] suggesting that findings may be generalizable to other Black women. Similar research in other groups is needed.

In summary, our prospective findings in a large cohort of young Black women, suggest that BV is unlikely to be an important risk factor for fibroid incidence or growth in this group and does not help explain their high fibroid burden.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability:

The data and computer code are not available for replication because the data are not publicly available. Data may be requested by contacting the Principal Investigator, Dr. Donna Baird, baird@niehs.nih.gov.

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TABLE 1.

Selected Characteristics of Fibroid Free Black Women Aged 23–35 Years According to Bacterial Vaginosis (Nugent ≥7) at Baseline (n = 1,032)

	Bacterial Vaginosis		Total
Baseline Variable	**No n=507 n(%)**	**Yes n=525 n(%)**	**1,032**
Income			
<20K	179 (36)	301 (58)	480
20-<50K	209 (42)	177 (34)	386
50K+	112 (22)	44 (8)	156
Missing		10	
Education			
≤ High School	76 (15)	161 (31)	237
> High School	430 (85)	364 (69)	794
Missing		1	
Employed			
No	178 (35)	234 (45)	412
Yes	327 (65)	290 (55)	617
Missing		3	
Body Mass Index [a]			
<25	123 (24)	83 (16)	206
25–29	117 (23)	103 (20)	220
30–34	96 (19)	99 (19)	195
35–40	72 (14)	96 (18)	168
40+	99 (20)	144 (27)	243
Heavy Alcohol Use (past year) [b]			
No	437 (86)	391 (74)	828
Yes	70 (14)	134 (26)	204
Currently Married			
No	343 (68)	392 (75)	735
Yes	164 (32)	133 (25)	297
Current Use of Oral Contraception			
No	439 (87)	481 (92)	920
Yes	68 (13)	44 (8)	112
Number of Births			
Never Pregnant	168 (33)	105 (20)	273
0 Births	50 (10)	54 (10)	104
1–2 Births	214 (42)	253 (48)	467
3+ Births	75 (15)	113 (22)	188
Recent Birth			
<3 years	396 (78)	421 (80)	817

	Bacterial Vaginosis		Total
Baseline Variable	**No n=507 n(%)**	**Yes n=525 n(%)**	**1,032**
3+ years or no birth	111 (22)	104 (20)	215
Depo-Provera Use			
Never	295 (58)	265 (50)	560
<4 years since last use	96 (19)	104 (20)	200
4+ years since last use	116 (23)	156 (30)	272
Age at Menarche (years)			
≤10	73 (14)	101 (19)	174
Age 11	110 (22)	98 (19)	208
Age 12	150 (30)	145 (28)	295
Age 13	87 (17)	83 (16)	170
14+	87 (17)	98 (19)	185
Current Smoker			
No	454 (90)	383 (73)	837
Yes	53 (10)	142 (27)	195
Current Douching			
No[c]	392 (77)	330 (63)	722
Yes	114 (23)	195 (37)	309
Missing		1	
Number of Sex Partners			
0–5	174 (35)	141 (27)	315
6–10	151 (30)	145 (28)	296
≥ 11	173 (35)	235 (45)	408
Missing		13	
Age at 1st Intercourse (years)			
≤ 14	124 (25)	164 (31)	288
15–16	163 (33)	191 (37)	354
≥ 17[d]	210 (42)	166 (32)	376
Missing		14	
Chlamydia Seropositive			
No	233 (49)	171 (35)	404
Yes	240 (51)	323 (65)	563
Missing		65	
HSV-2 Seropositive			
No	301 (61)	241 (47)	542
Yes	193 (39)	275 (53)	468
Missing		22	

Abbreviations: HSV-2, herpes simplex virus type 2

[a]Body mass index was calculated using clinic-measure values as weight (kg)/height (m)^2

[b]The alcohol-consumption variable reflected the drinking level each woman reported for the age(s) at which she was drinking the most. Heavy drinkers were those who usually consumed 6 or more drinks on days when they had alcohol or who consumed 4 or more drinks per sitting at least 2–3 times a month.

[c]Participants who douched less than 10 times in their life or currently less than once per year

[d]Includes participants who reported never having had sex

TABLE 2.

Nugent-Assessed Bacterial Vaginosis and Fibroid Incidence among 1,027 23–35 Year-Old Black Women with 2,547 Eligible Follow-up Visits Across 3 Follow-up Intervals: Hazard Ratios and 95% Confidence Intervals

Counts Across 3 Follow-up Intervals			Incident Fibroids		Unadjusted HR (95% CI)	Adjusted HR (95% CI)	
Nugent BV	**Women**	**Visits**	**n**	**% of Women**	**Model 1**	**Model 2[a]**	**Model 3[b]**
No	502	1,238	118	24	1.0 (ref)	1.0 (ref)	1.0 (ref)
Yes	525	1,309	129	25	1.0 (0.80, 1.3)	1.0 (0.80, 1.4)	1.2 (0.91, 1.6)

Abbreviation: BV, bacterial vaginosis; CI, confidence interval; HR, hazard ratio

[a]Adjusted for years since depo medroxyprogesterone acetate use, income, and recent birth anchored at the end of the interval; age is the time scale

[b]Adjusted for years since depo medroxyprogesterone acetate use, income, recent birth and number of cumulative births anchored at the end of the interval, age at menarche, smoking, oral contraceptive use, and BMI; age is the time scale

TABLE 3.

The Association Between Nugent-Assessed Bacterial Vaginosis and Fibroid Growth per 18 Months Among Fibroids from 382 Black Women with Growth Data for 1,181 Intervals of Growth

Bacterial Vaginosis	# Growth Measurements[a] N=1,181	Adjusted Estimated Percent Difference in Growth / 18 Months (95% CI)[b]		
		Model 1[c]	Model 2[d]	Model 3[e]
No	607	ref		
Yes	574	−4% (−13, 6) [c]	−3% (−12, 6)	−5% (−13, 5)

Abbreviation: CI, confidence interval

[a] Growth is modelled as the difference in the natural log volume from 1 visit to the next visit, scaled to 18 months

[b] An estimated difference in growth of −3% indicates that the average growth (volume change per 18 months) for fibroids from women with BV was 3% less than that for fibroids from women without BV

[c] Adjusted for fibroid volume, fibroid number, and age at the beginning of the interval

[d] Adjusted for fibroid volume, fibroid number, age at the beginning of the interval, years since depo medroxyprogesterone acetate use, income, and recent birth anchored at the end of the interval,

[e] Adjusted for fibroid volume, fibroid number, age at the beginning of the interval, years since depo medroxyprogesterone acetate use, income, recent birth and number of cumulative births anchored at the end of the interval, age at menarche, smoking, oral contraceptive use, and BMI