Published in final edited form as:

Ann Epidemiol. 2017 November ; 27(11): 749–751.e1. doi:10.1016/j.annepidem.2017.10.003.

Self-reported Bacterial Vaginosis and Risk of Ultrasound Diagnosed Incident Uterine Fibroid Cases in a Prospective Cohort Study of Young African-American Women

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BACKGROUND

Uterine fibroids, benign smooth muscle cell tumors, are a very common gynecological condition ¹ and the leading indication for hysterectomy in the US ². Though hormonally dependent, the causes of fibroids are unknown. For decades it has been hypothesized that reproductive tract infections (RTIs) play a role in fibroid development ³. However, few studies have been conducted, even for the leading cause of symptomatic vaginal discharge, bacterial vaginosis (BV). BV is characterized by a shift from the dominant flora of *Lactobacillus spp.* to a mixed vaginal flora with large numbers of anaerobic bacteria ^{4,5}. BV also may increase the risk of RTIs, human immunodeficiency virus, pelvic inflammatory disease, spontaneous abortion and preterm birth ^{6–11}.

Two studies investigated BV and fibroids using cross-sectional data ^{12,13}. One was the Uterine Fibroid Study which found suggestions of a positive association between “other” infections (mainly BV) and fibroids among ~600 African-American women ¹². The other was our recent study which found that African-American women self-reporting a BV diagnosis had elevated odds of multiple fibroids (2) and larger total fibroid volume (2 cm³) ¹³. In this current study in the same population, a group at high risk of BV ¹⁴, we prospectively followed women for incident fibroids. This is the first study to investigate the relationship between BV and fibroids prospectively.

MATERIALS AND METHODS

We used transvaginal ultrasound results and self-reported questionnaire data from participants in the ongoing National Institute of Environmental Health Sciences (NIEHS) Study of Environment, Lifestyle & Fibroids (SELF) described previously ¹⁵. In brief, starting in 2010, the study enrolled a volunteer sample of 1,695 African-American women

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ages 23–34 living in the Detroit, Michigan area. Follow-up visits continue approximately every 20 months for 5 years. Women were ineligible if they had previously been diagnosed with fibroids; had a hysterectomy; had ever taken medication to treat lupus, Grave's disease, Sjogren's scleroderma, or multiple sclerosis; or ever had any type of cancer treated with radiation or chemotherapy. The study was approved by the institutional review boards of NIEHS and Henry Ford Health System.

At enrollment ultrasound screening, 22% of participants had fibroids. This follow-up analysis was among women who did not have a fibroid detected at enrollment and completed both baseline and follow-up 1 data collection. The median interval between baseline and follow-up 1 was 19 months (interquartile range (IQR): 18–20 months). We excluded women who had a birth during the interval because birth has been shown to be protective of fibroids, most likely due to postpartum uterine remodeling^{16,17}.

Self-reported history of doctor-diagnosed BV (yes/no) at baseline was the exposure of interest. Fibroid status measured by ultrasound at follow-up 1 was the outcome. Fibroids were assessed by study sonographers as described previously¹⁸ using transvaginal ultrasound, the standard procedure for the detection and diagnosis of fibroids¹⁹. Participants with 1 fibroid 0.5 cm at the follow-up 1 visit ultrasound were considered to have incident fibroids.

Binomial regression models were used to compute risk ratios (RRs) and 95% confidence intervals (CIs) to evaluate the risk of incident fibroids for women with a history of BV compared to women without a history of BV. Time since first BV diagnosis was also examined. Among women with incident fibroids, we examined the risk of having multiple fibroids by BV status. Potential covariates were determined based on a review of the literature and their association with BV and the risk of fibroids (among unexposed, i.e., women without BV) in our data. The following baseline covariates were included in the full model: age in years (continuous), parity (nulliparous/parous), and alcohol (drinking level at the age when drinking the most: low, moderate, heavy). In addition, we conducted a sensitivity analysis excluding women who reported a new BV diagnosis at the first follow-up visit among those who had not previously reported a diagnosis (n=35) to make sure they were not influencing the results.

RESULTS

Of the 1,695 women enrolled, 660 were excluded (384 had a fibroid at enrollment, 1 was missing baseline BV data, 179 did not attend the follow-up visit, and 96 had a birth during the interval) leaving 1,035 eligible participants (characterized in Suppl. Table 1). Thirty-seven percent (n=385) reported a history of BV at baseline. The median time since first BV diagnosis was 6 years (IQR: 3–9 years). Ten percent (n=103) of women had fibroids discovered at ultrasound screening, 78% of whom had a single fibroid.

In multivariable analysis (Table 1), those with a self-reported BV diagnosis had a 35% increased risk of fibroids [aRR: 1.35 95% CI (0.93–1.95)]. Results were similar for the sensitivity analysis (data not shown). Among the 103 women with incident fibroids, those

with a previous BV diagnosis were twice as likely to have 2 fibroids compared to 1 fibroid [aRR: 2.21 95% CI (1.01–4.81)]. Women whose first BV diagnosis was 3–5 years before baseline were the group that had a statistically significant increased risk of developing fibroids compared to those with no BV [aRR: 2.42 95% CI (1.42–4.11)].

DISCUSSION

We observed a positive association between BV and the risk of developing fibroids, but timing of BV may be important. BV was also associated with developing more than a single fibroid, consistent with our previous cross-sectional analysis of this same population ¹³.

BV can be chronic and recurring ²⁰ with adverse upper-tract sequelae ⁹. This could plausibly increase the risk of fibroids through a hypothesized injury/abnormal wound-healing process ²¹, but our findings need further replication.

Self-reported doctor-diagnosed BV may be subject to recall error and may under-estimate the relevant bacterial changes. Vaginal bacterial shifts may be non-symptomatic in as many as 40% of BV-positive cases based on Nugent scoring ^{22,23}. This likely accounts for our relatively low BV prevalence (37%) compared to the prevalence of BV for African-American women in the National Health and Examination Survey by Nugent score (51%) ¹⁴. Furthermore, we had small numbers and limited power to detect an association for time since BV diagnosis. However, our study has unique strengths. We used prospective data on incident fibroids with a standardized measure based on systematic ultrasound screening. We also had extensive data to assess confounding and minimal missing data. Studies using Nugent scoring or polymerase chain reaction for BV detection are needed to investigate the association of BV bacterial changes with fibroid development.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors thank Drs. Lauren Wilson and Katie O'Brien for review of a draft of the manuscript. We also thank our collaborators and study staff at Social and Scientific Systems in Research Triangle Park, NC and Henry Ford Health System in Detroit, MI.

This work was supported by the Intramural Research Program of the National Institute of Environmental Health Sciences of the National Institutes of Health [grant number 10-E-N044]. Funding also came from the American Recovery and Reinvestment Act funds designated for National Institute of Health research.

Conflict of interest: none declared.

Abbreviations

BV	bacterial vaginosis
CI	confidence interval
NIEHS	National Institute of Environmental Health Sciences

RR	risk ratio
RTI	reproductive tract infection
SELF	the Study of Environment, Lifestyle and Fibroids
US	United States

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Self-Reported Bacterial Vaginosis and Time Since Bacterial Vaginosis Diagnosis and Risk of Incident Uterine Fibroids and Multiple Fibroids among 23–34-Year-Old African-American Women in the Study of Environment, Lifestyle and Fibroids (SELF), Detroit, MI Metropolitan Area: Risk Ratios and 95% Confidence Intervals

Table 1

Incident Fibroids	Age-adjusted RR		95% CI	Multivariable-adjusted RR ^a	95% CI
	No	Yes			
n%					
History of Bacterial Vaginosis at Baseline					
No	591 (91)	59 (9)	1.00	ref	1.00
Yes	341 (89)	44 (11)	1.25	0.87, 1.81	1.35
Time Since 1 st Bacterial Vaginosis Diagnosis ^b					
No Bacterial Vaginosis	591 (91)	59 (9)	1.00	ref	1.00
0–2 years	78 (92)	7 (8)	1.02	0.48, 2.16	1.05
3–5 years	87 (84)	16 (16)	2.02	1.20, 3.41	2.42
6 years	179 (90)	20 (10)	1.02	0.63, 1.67	1.12
Among women with Incident Fibroids					
Number of Fibroids					
1		2			
n%		n%			
History of Bacterial Vaginosis at Baseline					
No	49 (83)	10 (17)	1.00	ref	1.00
Yes	31 (70)	13 (30)	1.73	0.84, 3.58	2.21

CI, confidence interval; RR, risk ratio

^a Adjusted for age, parity and alcohol at age when drinking most

^b 1 participant was missing data on time since 1st bacterial vaginosis diagnosis