OBSTETRICS

Pregnancy-specific association of vitamin D deficiency and bacterial vaginosis

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OBJECTIVE: Recent data suggest vitamin D deficiency (VDD) is associated with bacterial vaginosis (BV) during pregnancy. We hypothesized that VDD is a risk factor for BV in nonpregnant women.

STUDY DESIGN: Using National Health and Nutrition Examination Survey data, we conducted multivariable logistic regression analyses stratified by pregnancy.

RESULTS: VDD was associated with BV only in pregnant women (adjusted odds ratio [AOR], 2.87; 95% confidence interval [CI], 1.13–7.28). Among nonpregnant women, douching (AOR, 1.72; 95% CI, 1.25–2.37), smoking (AOR, 1.66; 95% CI, 1.23–2.24), and black race (AOR, 2.41; 95% CI, 1.67–3.47) were associated with BV; oral contraceptive use was inversely associated with BV (AOR, 0.60; 95% CI, 0.40–0.90). VDD moderated the association between smoking and BV in nonpregnant women.

CONCLUSION: Risk factors for BV differ by pregnancy status. VDD was a modifiable risk factor for BV among pregnant women; evaluation of vitamin D supplementation for prevention or adjunct therapy of BV in pregnancy is warranted.

Key words: bacterial vaginosis, National Health and Nutrition Examination Survey, pregnancy, smoking, vitamin D

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Bacterial vaginosis (BV) is exceedingly prevalent, affecting nearly 30% of women of child-bearing age in the United States.[1] Although the dramatic changes in vaginal microflora that characterize BV[2] often occur in the absence of symptoms,[3] they are associated with numerous adverse sequelae including an increased risk of sexually transmitted infections, preterm labor, and postpartum endometritis.[4-7] Although eradication of BV is possible with appropriate antimicrobial therapy, recurrent disease remains a formidable challenge.[8] Treatment of pregnant women with BV is particularly problematic because large clinical trials have failed to demonstrate a reduction in adverse pregnancy outcomes following antibiotic therapy.[9] The identification of potentially modifiable risk factors represents a unique opportunity to reduce the burden of BV and its associated morbidities.

Recently Bodnar et al[10] identified vitamin D deficiency (VDD) as an independent risk factor for BV in pregnant women. This cross-sectional analysis revealed a significant association between serum concentrations of 25-hydroxyvitamin D (25D), the major circulating vitamin D metabolite, and the presence of BV in the first trimester. These findings have enormous public health implications in light of the high prevalence of VDD in the United States, estimated at 78% among nonpregnant women and ranging from 83% in the first trimester to 47% in the third trimester among pregnant women.[11,12] Because VDD is modifiable through supplementation[13] at very low cost,[14] it provides a possible point of intervention in reducing the burden of BV.

It is now well recognized that vitamin D is an important regulator of host immune responses, and VDD has been associated with increased susceptibility to numerous infectious diseases.[15-17] Binding of 1, 25-dihydroxyvitamin D to its receptor ultimately results in the transcription of hundreds of genes, including integral components of the innate immune system.[18] Therefore, vitamin D may locally regulate host immune signaling.[19] Altered immunity in the vaginal microenvironment provides a potential mechanistic explanation for the observed association between VDD and the development of BV.

The relationship between VDD and BV in nonpregnant women has not yet been explored. Furthermore, it is unknown whether other risk factors for BV differ by pregnancy status. We assessed whether BV risk factors differ between pregnant and nonpregnant women with a special focus on VDD across subgroups using a large, nationally representative data set.

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TABLE 1
Multivariable analysis of demographic, behavioral, and clinical characteristics associated with BV (n = 3523)

	Overall (n = 3523)	
Characteristic	**AOR (95% CI)**	***P* value[a]**
Vitamin D[b]		
Sufficient	1.00 (reference)	
Deficient	1.03 (0.75–1.44)	.84
Age, y	1.00 (0.98–1.02)	.95
Race/ethnicity		
White	1.00 (reference)	
Black	2.41 (1.64–3.55)	< .01
Mexican American/other	1.54 (1.00–2.37)	.04
Education		
High school graduate/GED or more	1.00 (reference)	
Less than high school	1.12 (0.74–1.70)	.58
Poverty index		
At or below poverty level	1.00 (reference)	
Above poverty level	0.78 (0.60–1.00)	.05
Marital status		
Not married	1.00 (reference)	
Married/living as married	0.89 (0.62–1.27)	.52
Age at first sex, y[c]		
Never had sex	1.00 (reference)	
≤14	3.04 (1.12–8.24)	.03
15 or 16	2.55 (0.94–6.94)	.07
17 or 18	2.24 (0.79–6.33)	.13
≥19	2.16 (0.85–5.49)	.10
Number lifetime partners[c]		
0 or 1	1.00 (reference)	
2-4	0.78 (0.53–1.17)	.23
5-8	0.94 (0.61–1.47)	.80
≥9	0.89 (0.62–1.27)	.51
Ever had female sex partner[c]		
No	1.00 (reference)	
Yes	1.76 (1.07–2.91)	.03
Unprotected sex[c,d]		
No	1.00 (reference)	
Yes	1.13 (0.78–1.64)	.51
Pregnancy status		
Not pregnant	1.00 (reference)	
Pregnant	0.59 (0.32–1.07)	.08

Hensel. Pregnancy, vitamin D, and BV. Am J Obstet Gynecol 2010. *(continued)*

Materials and Methods

The National Health and Nutrition Examination Survey (NHANES) is an ongoing national survey conducted by the National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention, that assesses disease and risk factors among the civilian, noninstitutionalized population of the United States.[20,21] NHANES uses a complex, multistage, probability sample design and oversampled African Americans, Mexican Americans, low-income persons, and adolescents aged 12-19 years during 2001-2004 to obtain sample sizes large enough for stable estimates among these groups. Health examinations and some interviews, including sexual behavior and reproductive health, were conducted at a mobile examination center (MEC).

Inclusion criteria for this analysis were women aged 14-49 years who participated in the MEC components of NHANES. Exclusion criteria included no reported Nugent score for BV and/or no reported 25D serum concentration.

Participants aged 12 years or older provided consent for examination and interview; parents of participants younger than 18 years also provided consent for their children's participation. The National Center for Health Statistics Research Ethics Review Board approved all protocols. The Columbia University Medical Center Institutional Review Board provided exemption for this analysis.

Race/ethnicity was self-reported and classified as non-Hispanic white, non-Hispanic black, Mexican American, and other, including multiracial persons and persons of non-Mexican Hispanic descent. Poverty index was calculated by comparing the family's self-reported income to the family's appropriate poverty threshold.[22] An index less than 1 indicated income below the poverty threshold.[22] Educational attainment, marital status, current oral contraception use, and douching frequency in the past 6 months were self-reported. Sexual behaviors, including ever having sex, number of lifetime sexual partners (including both male and female sexual partners), ever having a female sexual partner, age

at first sex, and unprotected sex in the past 30 days, were self-reported in an audio computer-assisted self-interview.

Participants were instructed to consider oral, anal, and vaginal sex as "sex" in their responses. Only women who reported multiple sex partners in the past year were asked about condom use in the preceding 30 days. Therefore, the classification of having "unprotected sex" is limited to women who had more than 1 sexual partner in the past year and who reported sex without a condom at least once in the preceding 30 days. Women with only 1 sexual partner in the past year were categorized as not having "unprotected sex" because they were not asked about condom use. This analysis includes sexual behavior data only for women 20 years old or older.

Pregnancy status was confirmed by urine testing. Body mass index (BMI) was calculated from height and weight measurements and classified into the following categories: normal, BMI $\geq$18.5 kg/m^2 and $\leq$24.9 kg/m^2; underweight, BMI $<$18.5 kg/m^2; overweight, BMI $\geq$25.0 kg/m^2 and $\leq$29.9 kg/m^2; obese, BMI $\geq$30.0 kg/m^2.[23] Vitamin D and cotinine (a serum metabolite of nicotine) levels were determined using serum collected via venipuncture by certified phlebotomists at the MEC. Analysis methods are described elsewhere.[24,25] In this analysis, VDD was classified as less than 30 ng/mL based on current recommendations.[26] Cotinine levels greater than 3 ng/mL were indicative of active smoking.[27] Vaginal swabs used for determining BV were self-collected in the MEC. The MEC staff then rolled the swabs onto glass slides, which were subsequently shipped to Magee Women's Hospital (Pittsburgh, PA) for Gram staining and Nugent scoring.[28] A Nugent score of 7-10 indicates BV.[29]

Statistical analysis was conducted using survey procedures in SAS (version 9.2; SAS Institute, Cary, NC), which account for the unequal weighting of persons in the complex NHANES sample design, and missing data were excluded from analysis. Weights reported by NCHS for the 2001-2002 and 2003-2004 data cycles were used to reflect the unequal probability of selection and to adjust for nonresponse among sample persons.[30] Taylor series linearization was used for variance estimation to produce unbiased estimates.[30]

In bivariable analyses, unadjusted logistic regression was used to compute crude odds ratios with 95% confidence intervals. Associated P values were calculated using Wald χ^2 tests. Variables with $P \leq .10$ were included as covariates in the multivariable logistic regression analysis as were age, which was included out of convention, and pregnancy status, which was of interest based on the literature.[10]

A second analysis stratified the study population by pregnancy status. Bivariable analyses for pregnant and nonpregnant women were conducted as described earlier. Multivariable logistic regression analyses were conducted separately for pregnant and nonpregnant women and included the same covariates used in the unstratified multivariable logistic regression analysis, excepting pregnancy status.

Finally, a multivariable logistic regression analysis was stratified by vitamin D status. Results of other multivariable logistic regression models in this larger analysis suggested the association between cotinine levels and BV may be dependent on vitamin D status. Stratifying by vitamin D status allowed an examination of this hypothesized moderating effect. Covariates included in this model were the same as those used in the unstratified multivariable logistic regression analysis, excepting vitamin D status.

TABLE 1
Multivariable analysis of demographic, behavioral, and clinical characteristics associated with BV (n = 3523) *(continued)*

	Overall (n = 3523)	
Characteristic	**AOR (95% CI)**	***P* value[a]**
Current oral contraception use		
No	1.00 (reference)	
Yes	0.60 (0.40–0.90)	.01
Douching frequency last 6 months		
Never	1.00 (reference)	
At least once	1.68 (1.21–2.33)	$<$ .01
Cotinine level		
$<$3 ng/mL	1.00 (reference)	
$\geq$3 ng/mL	1.63 (1.22–2.16)	$<$ .01
BMI[e]		
Normal	1.00 (reference)	
Underweight	0.82 (0.38–1.77)	.62
Overweight	1.29 (0.88–1.90)	.19
Obese	1.26 (0.87–1.81)	.22

AOR, adjusted odds ratio; *BMI*, body mass index; *BV*, bacterial vaginosis; *CI*, confidence interval; *GED*, general educational development; *OC*, oral contraceptive.

[a] By Wald χ^2 test; [b] Vitamin D deficiency defined as $<$30 ng/mL; [c] Included only for women aged 20-49 years; [d] Unprotected sex: no condom 1 time or more in past 30 days among women with multiple partners in past year; [e] Normal, BMI $\geq$18.5 kg/m^2 and $\leq$24.9 kg/m^2; underweight, BMI $<$18.5 kg/m^2; overweight, BMI $\geq$25.0 kg/m^2 and $\leq$29.9 kg/m^2; obese, BMI $\geq$30.0 kg/m^2.

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RESULTS

Of 3527 women who satisfied the inclusion and exclusion criteria, 4 women who reported never having sex had positive urine pregnancy tests at time of examination. These women were excluded from the analysis resulting in an n = 3523 for the sample. BV prevalence was 29%.

Similar to previous findings,[1] several demographic, behavioral, and clinical

TABLE 2
Multivariable analysis of demographic, behavioral, and clinical characteristics associated with BV according to pregnancy status

	Nonpregnant (n = 3044)		Pregnant (n = 440)	
Characteristic	**AOR (95% CI)**	***P* value[a]**	**AOR (95% CI)**	***P* value[a]**
Vitamin D[b]				
Sufficient	1.00 (reference)		1.00 (reference)	
Deficient	0.99 (0.69–1.40)	.93	2.87 (1.13–7.28)	.03
Age, y	1.00 (0.98–1.02)	.94	1.01 (0.91–1.13)	.84
Race/ethnicity				
White	1.00 (reference)		1.00 (reference)	
Black	2.41 (1.67–3.47)	< .01	2.10 (0.59–7.54)	.25
Mexican American/other	1.63 (1.09–2.44)	.02	0.61 (0.16–2.36)	.48
Education				
High school graduate/GED or more	1.00 (reference)		1.00 (reference)	
Less than high school	1.12 (0.74–1.70)	.59	1.61 (0.42–6.21)	.49
Poverty index				
At or below poverty level	1.00 (reference)		1.00 (reference)	
Above poverty level	0.76 (0.58–1.01)	.05	0.96 (0.32–2.89)	.94
Marital status				
Not married	1.00 (reference)		1.00 (reference)	
Married/living as married	0.89 (0.63–1.26)	.51	0.79 (0.22–2.90)	.73
Age at first sex, y[c,d]				
Never had sex	1.00 (reference)		—	
≤14	3.02 (1.07–8.58)	.04	—	—
15 or 16	2.64 (0.97–7.17)	.06	—	—
17 or 18	2.14 (0.76–6.03)	.15	—	—
≥19	2.21 (0.88–5.56)	.09	—	—
Number of lifetime partners[c]				
0 or 1	1.00 (reference)		1.00 (reference)	
2-4	0.80 (0.52–1.22)	.29	0.40 (0.11–1.44)	.16
5-8	0.93 (0.58–1.49)	.76	1.39 (0.43–4.54)	.58
≥9	0.86 (0.58–1.28)	.46	1.56 (0.51–4.80)	.43
Ever had female sex partner[c]				
No	1.00 (reference)		1.00 (reference)	
Yes	1.66 (0.96–2.86)	.07	4.51 (0.97–21.07)	.06
Unprotected sex[c,e]				
No	1.00 (reference)		1.00 (reference)	
Yes	1.22 (0.82–1.81)	.33	0.33 (0.07–1.54)	.16
Current OC use[d]				
No	1.00 (reference)		—	
Yes	0.60 (0.40–0.90)	.01	—	—

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(continued)

TABLE 2
Multivariable analysis of demographic, behavioral, and clinical characteristics associated with BV according to pregnancy status *(continued)*

	Nonpregnant (n = 3044)		Pregnant (n = 440)	
Characteristic	**AOR (95% CI)**	***P* value[a]**	**AOR (95% CI)**	***P* value[a]**
Douching frequency last 6 months				
Never	1.00 (reference)		1.00 (reference)	
At least once	1.72 (1.25–2.37)	< .01	1.06 (0.22–5.13)	.95
Cotinine level				
<3 ng/mL	1.00 (reference)		1.00 (reference)	
≥3 ng/mL	1.66 (1.23–2.24)	< .01	0.77 (0.22–2.64)	.67
BMI[f]				
Normal	1.00 (reference)		1.00 (reference)	
Underweight	0.79 (0.35–1.77)	.57	3.56 (0.32–39.42)	.30
Overweight	1.30 (0.87–1.95)	.20	1.21 (0.31–4.68)	.78
Obese	1.26 (0.85–1.85)	.25	1.27 (0.40–3.97)	.69

AOR, adjusted odds ratio; *BMI*, body mass index; *BV*, bacterial vaginosis; *CI*, confidence interval; *GED*, general educational development; *OC*, oral contraceptive.

[a] By Wald χ^2 test; [b] Vitamin D deficiency defined as <30 g/mL; [c] Included only for women aged 20-49 years; [d] Dashes indicate zero count cell for reference category; AOR not available; [e] Unprotected sex: no condom 1 or more times in past 30 days among women with multiple partners in past year; [f] Normal, BMI ≥18.5 kg/m^2 and ≤24.9 kg/m^2; underweight, BMI <18.5 kg/m^2; overweight, BMI ≥25.0 kg/m^2 and ≤29.9 kg/m^2; obese, BMI ≥30.0 kg/m^2.

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characteristics were significantly associated with BV in the bivariable analysis, including black race ($P < .01$), Mexican American/other race/ethnicity ($P < .01$), less than a high school education ($P < .01$), ever having sex ($P = .05$), sexual debut 14 years old or younger ($P < .01$) or at ages 15 or 16 years ($P = .03$), number of lifetime sexual partners (5-8; 9 or more; $P < .01$ for each), douching at least once in the past 6 months ($P < .01$), and being overweight ($P = .03$) or obese ($P < .01$).

VDD ($P < .01$), having unprotected sex in the last 30 days ($P < .01$), and cotinine levels of 3 ng/mL or greater ($P < .01$) were also significantly associated with BV. Income above the poverty level ($P < .01$), being married/living as married ($P < .01$), and current oral contraceptive (OC) use ($P < .01$) were significantly inversely associated with BV. Median serum concentration of 25D was 23.00 ng/mL (interquartile range [IQR], 17.00–30.00).

In the bivariable analysis stratified by pregnancy status, among nonpregnant women, VDD ($P < .01$), black race ($P < .01$), Mexican American/other race/ethnicity ($P < .01$), less than a high school education ($P = .02$), ever having sex ($P = .05$), sexual debut at age 14 years or younger ($P < .01$) or at age 15 or 16 years ($P = .02$), number of lifetime sexual partners (5-8; ≥9; $P < .01$ for each), ever having had a female sexual partner ($P < .01$), unprotected sex in the past 30 days ($P < .01$), douching at least once in the past 6 months ($P < .01$), cotinine levels of 3 ng/mL or greater ($P < .01$), and being overweight ($P = .03$) or obese ($P < .01$) were all significantly associated with BV. Income above the poverty level ($P < .01$), being married/living as married ($P < .01$), and current OC use ($P < .01$) were significantly inversely associated with BV among nonpregnant women.

Among pregnant women, VDD ($P < .01$), black race ($P = .02$), and ever having a female sexual partner ($P < .01$) were significantly associated with BV in the bivariable analysis; marital status ($P < .01$) was significantly inversely associated with BV. Median serum concentrations of 25D were 23.00 ng/mL (IQR, 17.00–30.00) among nonpregnant women and 25.00 ng/mL (IQR, 17.00–31.00) among pregnant women.

Several characteristics remained associated with BV in the multivariable logistic regression analysis (Table 1). Black race (adjusted odds ratio [AOR], 2.41; 95% confidence interval [CI], 1.64–3.55), Mexican American/other race/ethnicity (AOR, 1.54; 95% CI, 1.00–2.37), sexual debut at age 14 years or younger (AOR, 3.04; 95% CI, 1.12–8.24), ever having a female sexual partner (AOR, 1.76; 95% CI, 1.07–2.91), douching at least once in the past 6 months (AOR, 1.68; 95% CI, 1.21–2.33), and serum cotinine level of 3 ng/mL or greater (AOR, 1.63; 95% CI, 1.22–2.16) were significantly associated with BV. Current OC use (AOR, 0.60; 95% CI, 0.40–0.90) was significantly inversely associated with BV.

Characteristics significantly associated with BV differed by pregnancy status in the stratified multivariable model (Table 2). Among nonpregnant women, black race (AOR, 2.41; 95% CI, 1.67–3.47), Mexican American/other race/ethnicity (AOR, 1.63; 95% CI, 1.09–2.44), sexual debut at 14 years old or younger (AOR, 3.02; 95% CI, 1.07–8.58), douching at least once in the past 6 months (AOR, 1.72; 95% CI, 1.25–2.37), and cotinine levels of 3 ng/mL or greater (AOR, 1.66; 95% CI, 1.23–2.24) were significantly as-

TABLE 3
Multivariable analysis of demographic, behavioral, and clinical characteristics associated with BV according to vitamin D status

	Vitamin D sufficient (n = 736)		Vitamin D deficient (n = 2787)[a]	
Characteristic	**AOR (95% CI)**	***P* value[b]**	**AOR (95% CI)**	***P* value[b]**
Age, y	0.97 (0.93–1.01)	.09	1.01 (0.99–1.03)	.54
Race/ethnicity				
White	1.00 (reference)		1.00 (reference)	
Black	1.78 (0.25–12.54)	.56	2.60 (1.79–3.78)	< .01
Mexican-American/other	3.37 (1.26–9.02)	.02	1.45 (0.93–2.29)	.10
Education				
High school graduate/GED or more	1.00 (reference)		1.00 (reference)	
Less than high school	1.29 (0.39–4.24)	.68	1.08 (0.69–1.69)	.73
Poverty index				
At or below poverty level	1.00 (reference)		1.00 (reference)	
Above poverty level	0.36 (0.18–0.72)	< .01	0.92 (0.67–1.26)	.60
Marital status				
Not married	1.00 (reference)		1.00 (reference)	
Married/living as married	1.29 (0.62–2.67)	.50	0.86 (0.61–1.23)	.42
Age at first sex, y[c,d]				
Never had sex	—		1.00 (reference)	
≤14	—	—	2.31 (0.82–6.53)	.11
15 or 16	—	—	2.01 (0.75–5.36)	.17
17 or 18	—	—	2.00 (0.72–5.56)	.19
≥19	—	—	1.86 (0.73–4.73)	.19
Number lifetime partners[c]				
0 or 1	1.00 (reference)		1.00 (reference)	
2-4	1.61 (0.63–4.15)	.32	0.70 (0.48–1.04)	.08
5-8	1.94 (0.76–4.99)	.17	0.92 (0.61–1.18)	.69
≥9	1.71 (0.71–4.11)	.23	0.85 (0.61–1.18)	.32
Ever had female sex partner[c]				
No	1.00 (reference)		1.00 (reference)	
Yes	1.83 (0.47–7.09)	.38	1.64 (0.95–2.84)	.08
Unprotected sex[c,e]				
No	1.00 (reference)		1.00 (reference)	
Yes	1.87 (0.58–5.98)	.29	0.98 (0.63–1.52)	.92
Pregnancy status				
Not pregnant	1.00 (reference)		1.00 (reference)	
Pregnant	0.14 (0.06–0.31)	< .01	0.82 (0.41–1.64)	.58
Current OC use				
No	1.00 (reference)		1.00 (reference)	
Yes	0.44 (0.22–0.91)	.03	0.65 (0.37–1.16)	.15

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(continued)

TABLE 3
Multivariable analysis of demographic, behavioral, and clinical characteristics associated with BV according to vitamin D status *(continued)*

	Vitamin D sufficient (n = 736)		Vitamin D deficient (n = 2787)[a]	
Characteristic	**AOR (95% CI)**	***P* value[b]**	**AOR (95% CI)**	***P* value[b]**
Douching frequency last 6 months				
Never	1.00 (reference)		1.00 (reference)	
At least once	3.12 (1.33–7.31)	< .01	1.50 (1.20–1.87)	< .01
Cotinine level				
<3 ng/mL	1.00 (reference)		1.00 (reference)	
≥3 ng/mL	1.13 (0.46–2.79)	.80	1.72 (1.23–2.39)	< .01
BMI[f]				
Normal	1.00 (reference)		1.00 (reference)	
Underweight	2.18 (0.33–14.41)	.42	0.48 (0.12–1.91)	.30
Overweight	1.85 (1.03–3.32)	.04	1.16 (0.75–1.80)	.50
Obese	0.99 (0.36–2.76)	.99	1.22 (0.77–1.94)	.40

AOR, adjusted odds ratio; *BMI*, body mass index; *BV*, bacterial vaginosis; *CI*, confidence interval; *GED*, general educational development; *OC*, oral contraceptive.

[a] Vitamin D deficiency defined as <30 ng/mL; [b] By Wald χ^2 test; [c] Included only for women aged 20-49 years; [d] Dashes indicate zero count cell for reference category; AOR not available; [e] Unprotected sex: no condom 1 or more times in past 30 days among women with multiple partners in past year; [f] Normal, BMI ≥18.5 kg/m^2 and ≤24.9 kg/m^2; underweight, BMI <18.5 kg/m^2; overweight, BMI ≥25.0 kg/m^2 and ≤29.9 kg/m^2; obese, BMI ≥30.0 kg/m^2.

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sociated with BV. Current OC use (AOR, 0.60; 95% CI, 0.40–0.90) was significantly inversely associated with BV among nonpregnant women. Among pregnant women, VDD (AOR, 2.87; 95% CI, 1.13–7.28) was significantly associated with BV.

In the multivariable model stratified by vitamin D status (Table 3), Mexican American/other race/ethnicity (AOR, 3.37; 95% CI, 1.26–9.02), douching at least once in the past 6 months (AOR, 3.12; 95% CI, 1.33–7.31), and being overweight (AOR, 1.85; 95% CI, 1.03–3.32) were significantly associated with BV among vitamin D-sufficient women. Income above the poverty level (AOR, 0.36; 95% CI, 0.18–0.72), being pregnant (AOR, 0.14; 95% CI, 0.06–0.31), and current OC use (AOR, 0.44; 95% CI, 0.22–0.91) were significantly inversely associated with BV among vitamin D-sufficient women. Among vitamin D-deficient women, black race (AOR, 2.60; 95% CI, 1.79–3.78), douching at least once in the past 6 months (AOR, 1.50; 95% CI, 1.20–1.87), and cotinine levels of 3 ng/mL or greater (AOR, 1.72; 95% CI, 1.23–2.39) were significantly associated with BV.

Comment

Characteristics associated with BV in the multivariable model were consistent with previous findings.[1] Smoking, black race, Mexican American ethnicity, and douching are known risk factors for BV[1,31,32] and were significantly associated with BV prevalence in this analysis (smoking AOR, 1.63; 95% CI, 1.22–2.16; black race AOR, 2.41; 95% CI, 1.64–3.55; Mexican American/other race/ethnicity AOR, 1.54; 95% CI, 1.00–2.37; douching AOR, 1.68; 95% CI, 1.21–2.33). Ever having a female sex partner, a characteristic inconsistently associated with BV in the literature[1,33-35] was also significantly associated with BV (AOR, 1.76; 95% CI, 1.07–2.91). Current OC use, which was previously found to be protective against BV[1,36] and may modulate local host immunity in the setting of BV[37] was inversely associated with BV (AOR, 0.60; 95% CI, 0.40–0.90). Sexual debut at age 14 years or younger was also significantly associated with BV in this analysis (AOR, 3.04; 95% CI, 1.12–8.24). These associations with BV held in the multivariable analysis, even after adjustment for several other characteristics associated with BV. This suggests that BV is a complex disease with many risk and protective factors that contribute to its prevalence in the reproductive-aged population.

Risk factors for BV differed by pregnancy status. VDD was associated with BV among pregnant women (AOR, 2.87; 95% CI, 1.13–7.28), consistent with previous findings.[10] In contrast to our initial hypothesis, VDD was not significantly associated with BV among nonpregnant women (AOR, 0.99; 95% CI, 0.69–1.40). Among nonpregnant women, sexual debut at age 14 years or younger (AOR, 3.02; 95% CI, 1.07–8.58), douching (AOR, 1.72; 95% CI, 1.25–2.37), smoking (AOR, 1.66; 95% CI, 1.23–2.24), black race (AOR, 2.41; 95% CI, 1.67–3.47), and Mexican American/other race/ethnicity (AOR, 1.63; 95% CI, 1.09–2.44) were significantly associated with BV; current OC use was inversely associated with BV (AOR, 0.60; 95% CI, 0.40–0.90).

In the multivariable analysis stratified by pregnancy status, active smoking, indicated by cotinine levels of 3 ng/mL or greater, was associated with BV among nonpregnant women (AOR, 1.66; 95%

CI, 1.23–2.24) but not among pregnant women (AOR, 0.77; 95% CI, 0.22–2.64). Furthermore, we noted smoking was associated with BV when VDD was not significantly associated with BV. Subsequently we stratified the multivariable model by vitamin D status to examine the association between smoking and BV. Among vitamin D-deficient women, smoking was significantly associated with BV (AOR, 1.72; 95% CI, 1.23–2.39). Among vitamin D-sufficient women, however, smoking was not significantly associated with BV (AOR, 1.13; 95% CI, 0.46–2.79).

The results of these 2 stratified analyses indicate that although the association between VDD and BV differs by pregnancy status, VDD may be important in elevated BV prevalence among both pregnant and nonpregnant women. For pregnant women, VDD is directly associated with increased odds of BV and is a potentially modifiable risk factor for disease. In nonpregnant women, VDD may moderate the relationship between smoking and increased odds of BV. Therefore, treatment of VDD among both pregnant and nonpregnant women could theoretically reduce the prevalence of BV in the general population.

Discrepancies in BV risk factors with a previous NHANES analysis[1] merit discussion. Our analysis demonstrated that elevated cotinine levels, which correlate with active smoking, were significantly associated with BV in the multivariable model. Cotinine levels were available for all but a limited number of women in our sample. In the prior analysis, smoking data had been unavailable for the 2003-2004 data cycle, and 2001-2002 data were available only for women 20 years old or older. Ever having a female sexual partner and sexual debut at 14 years old or younger were significantly associated with BV in the current analysis but not in the previous analysis. Increasing number of lifetime sexual partners was not significant in this multivariable logistic regression analysis but had been previously.[1,38] These discrepancies may be due to differences in sample sizes in data for sexual behavior.

This analysis has several strengths and some limitations. First, this analysis examined VDD and its association with BV prevalence among a general, nationally representative population of adolescent and adult women. Previous research on VDD and BV has been conducted among an exclusively obstetric population.[10] Second, this analysis used serum cotinine levels to evaluate the association between smoking and BV prevalence. Previous studies have relied on self-reported smoking status.[1,32] Third, this analysis included a multivariable model stratified by pregnancy status. This allowed a side-by-side examination of risk factors for both pregnant and nonpregnant women among a nationally representative sample of women.

This analysis was limited by its cross-sectional design; temporality between characteristics and BV could not be established. Additionally, sexual behavior data were limited to women 20 years old or older, and information on unprotected sex was asked only of women reporting multiple sexual partners in a year. Variability in the vitamin D assay because of changes in laboratory methods over time has been noted as a limitation. [24] Finally, this analysis did not examine the association between VDD and BV by trimester of pregnancy. The percentage of vitamin D–sufficient women increases from the first to third trimester as duration of supplementation increases, and odds of BV are lower among vitamin D-sufficient women in the first trimester.[10,12] Therefore, we speculate that BV prevalence may decrease from the first to third trimester as vitamin D sufficiency increases.

Our findings on VDD and BV among pregnant women validate those of a previous study.[10] Because limited data are available on VDD and BV in pregnancy and the strength of association in our analysis is significant but moderate, additional studies are needed. Particularly, prospective studies are necessary to establish temporality in the relationship between VDD and BV in pregnancy. Further epidemiologic studies of VDD and BV among nonpregnant women are also needed to confirm our findings.

Because antimicrobial treatment for BV has failed to reduce some adverse sequelae of this disease in pregnancy,[9] BV prevention is paramount. VDD is highly prevalent among women in the United States[11] and can be corrected through supplementation.[13] Therefore, identification of VDD as a modifiable risk factor for BV among pregnant women may be important in improving health outcomes among this population.

Smoking also remains prevalent in the United States despite declines in recent years.[39] Whereas smoking is an independent and modifiable risk factor for BV in nonpregnant women, VDD may provide another point of intervention. Both smoking[40] and VDD[41] may decrease innate immune responses at the mucosal level, but the mechanistic relationship among vitamin D, smoking, and BV needs further exploration.

VDD was identified as the only modifiable risk factor among pregnant women. VDD may also moderate the relationship between smoking and BV among nonpregnant women. Vitamin D supplementation may have a role in new preventive and therapeutic strategies for BV in both obstetric and nonobstetric populations, although additional study is needed prior to implementation of these proposed interventions. In addition, optimization of strategies for the use of prenatal vitamins, including preconceptual use, may aid in the prevention of BV during pregnancy. ■

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