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Is bacterial vaginosis a stronger risk factor for preterm birth when it is diagnosed earlier in gestation?

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Received for publication April 6, 2004; revised June 17, 2004

KEY WORDS

Bacterial vaginosis
Preterm birth
Gram stain

Objective: It is stated commonly that the earlier in pregnancy bacterial vaginosis is diagnosed, the greater is the increase in risk of preterm birth compared with women without bacterial vaginosis. However, this contention is based on small numbers of women.

Supported by grants No. U10 HD21410, U10 HD21414, U10 HD27860, U10 HD27861, U10 HD27869, U10 HD27883, U10 HD27889, U10 HD27905, U10 HD27915, U10 HD27917, U10 HD34116, U10 HD34122, U10 HD34136, U10 HD34208, U10 HD34210, and U01 HD36801 from the National Institute of Child Health and Human Development and by grant AI 38514 from the National Institute of Allergy and Infectious Diseases.

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Study design: In this analysis of 12,937 women who were screened for bacterial vaginosis as part of a previously conducted clinical trial, the odds ratio of preterm birth (<7 weeks of gestation) for asymptomatic bacterial vaginosis–positive versus bacterial vaginosis–negative women was evaluated among women who were screened from 8 to 22 weeks of gestation.

Results: The odds ratio of preterm birth among bacterial vaginosis–positive versus bacterial vaginosis–negative women ranged from 1.1 to 1.6 and did not vary significantly according to the gestational age at which bacterial vaginosis was screened. The odds ratio for preterm birth did not vary significantly by gestational age at diagnosis when bacterial vaginosis was subdivided into Gram stain score 7 to 8 or 9 to 10.

Conclusion: Although bacterial vaginosis was associated with an increased risk of preterm birth, the gestational age at which bacterial vaginosis was screened for and diagnosed did not influence the increase.

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Bacterial vaginosis (BV) is a syndrome in which the normal vaginal hydrogen peroxide–producing lactobacilli are replaced by a mixed flora with high concentrations of anaerobic bacteria, *Gardnerella vaginalis* and *Mycoplasma hominis*.¹ The condition is relatively common in pregnant women; 23% of black women and 9% of white women were reported to be affected.² Multiple case-control and prospective cohort studies have demonstrated that BV is associated with an increased risk of preterm birth.³ However, results of clinical trials of treatment of BV to prevent preterm birth have been mixed.³

Some authors have stated that the earlier in gestation at which BV is detected, the greater is the risk of an adverse outcome.^{4,5} A recent meta-analysis concluded that BV that was diagnosed at <16 and <20 weeks of gestation was associated with odds ratios for preterm birth of 7.55 and 4.20, respectively; the odds ratio for diagnosis at ≥ 20 weeks of gestation was 1.53.⁶ However, the studies on which this contention is based were conducted in different countries, had different definitions of BV, and used different definitions of adverse pregnancy outcome. In addition, the studies that reported on BV that was diagnosed at <20 weeks of gestation had relatively small sample sizes, and the odds ratios in the meta-analysis had wide confidence limits.⁶⁻⁸ Recently conducted randomized clinical trials of treatment of BV⁹ and *Trichomonas vaginalis*¹⁰ gave us the opportunity to study, in a large population of women who were evaluated for BV at a wide range of gestational ages according to a single common protocol, whether BV that was diagnosed earlier in pregnancy was associated with a higher risk of preterm birth than BV that was diagnosed later in pregnancy.

Material and methods

The data for this study are from the recently completed National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network BV and *T vaginalis* clinical trials, in which women with these

conditions were assigned randomly to metronidazole or placebo treatment to prevent preterm birth.^{9,10} These 2 trials required that large numbers of women be screened for BV and *T vaginalis* at 8 to 22 completed weeks of gestation. Normally, we did not ascertain the outcome of pregnancies to women who were screened but not enrolled in the clinical trials. However, as part of an ancillary protocol,^{11,12} we obtained pregnancy outcomes for women who were screened from November 1995 to February 1998; during this limited time 15,864 women were screened and are included in this protocol. Not all Maternal-Fetal Medicine Unit centers participated in this ancillary study. The Institutional Review Board at each clinical site approved the protocol, which included screening and obtaining pregnancy outcomes on screened women.

The inclusion and exclusion criteria for screening have been described previously.^{9,10} Women were eligible to be screened if they were from 8 to 22 weeks of gestation inclusive; did not report genital itching, burning, or malodor in response to nondirected questioning; had no contraindications to receiving metronidazole; had no major medical or obstetric complications in the current pregnancy; had not received antibiotics within the past 14 days and were not expected to receive them before the intrapartum period; and could be followed up to delivery.

We defined BV as a vaginal Gram-stain Nugent score¹³ of ≥ 7 in conjunction with a vaginal pH of >4.4 . This is the same definition that was used for the clinical trial⁹ and in the Vaginal Infections and Prematurity Study.¹⁴ One Dacron swab sample, which was taken from the junction of the upper third and lower two thirds of the lateral vaginal wall, was rolled on a glass slide and then touched to a ColorpHast pH stick (Curtin Matheson, Grand Prairie, Tex). Slides from women whose vaginal pH was >4.4 were shipped to the laboratory of one of the authors (S.L.H.), where they were stained and interpreted by technicians who were masked to the clinical data. Therefore, according to the study protocol, women with vaginal pH values of ≤ 4.4

were considered not to have BV, although they did not have Gram stains that were read.

Women received routine prenatal care at their institutions. Study personnel abstracted delivery records to determine the date, method and indication of delivery, and birth weight. In this analysis, we defined BV from the initial screening, without regard to Gram stains that were obtained later in pregnancy, because the latter were available only for those women who entered into the trials. The physicians of women who were enrolled in the clinical trial were required to follow a specific protocol, which included sonography, to determine gestational age.⁹ However, there was no protocol to determine gestational duration of pregnancies for women who were screened but not enrolled in the trial; therefore, the gestational age that was used was the best obstetric estimate at delivery. We considered all pregnancy losses after the screening tests, plus all preterm deliveries (<37 completed weeks of gestation) as the outcome of interest. Secondary outcomes included deliveries that were stratified as <23 weeks of gestation and 23 to 36 weeks of gestation inclusive. The former stratum evaluates the association between BV and miscarriage at a time early in pregnancy when women were still being screened and would have a variable time of follow-up, depending on the gestation at which screening occurred. Because all women were screened at <23 weeks of gestation, the latter definition avoided the need to account for the fact that women who were screened earlier in pregnancy had more time than women who were screened later to have had a pregnancy loss. We also studied spontaneous preterm birth, which is defined as preterm birth after spontaneous onset of labor or spontaneous membrane rupture, regardless of the ultimate method of delivery.

Categorical variables were compared with the use of the chi-squared test. When categories were ordered (eg, no BV, Gram stain 7-8, Gram stain 9-10), significance was assessed with the Cochran-Armitage test for trend.¹⁵ To determine whether BV that was diagnosed earlier in gestation carried a greater relative risk of preterm birth than BV that was diagnosed later, we present gestational age at screening from a start of 8 to 12 weeks of gestation to 21 to 22 weeks of gestation, in 2-week intervals. For women who were screened in each gestational age window, we then calculated the odds ratio for preterm birth among BV-positive compared with BV-negative women. If BV that was diagnosed earlier in gestation carried a greater relative risk of preterm birth than BV that was diagnosed later, the odds ratio for BV would be greater the earlier in gestation when women were screened. To test this hypothesis, we used a multiple logistic regression model that included terms for BV (yes/no), gestational age at screening (in weeks, as a continuous variable), and an interaction term between BV and gestational age.

Table I Characteristics of study population

Characteristic	N (%)	Women who were delivered, from screening to <37 weeks of gestation (%)	Women with BV (%)
Race/ethnicity*			
Black	7209 (56%)	15	45
Other	2765 (21%)	10	29
White	2955 (23%)	11	20
Nulliparous*			
Nulliparous*	4913 (39%)	13	35
Multiparous*			
Multiparous*	7743 (61%)	13	37
Gestational age at screening (wk)			
<13	5032 (39%)	15	40
13-14.9	1633 (13%)	15	40
15-16.9	1448 (11%)	13	41
17-18.9	1737 (13%)	11	31
19-20.9	1784 (14%)	11	28
21-22.9	1303 (10%)	11	24

* Numbers do not equal 12,937 because data were missing.

Determination of the actual probability value for the interaction was based on gestational age as a continuous variable. When we assessed the degree of BV, we defined 2 interaction terms, 1 for Gram stain scores of 7 to 8 and 1 for Gram stain scores of 9 to 10. In either case, if BV that was diagnosed earlier in pregnancy carried a greater relative risk of preterm birth than BV that was diagnosed later, the interaction term would be statistically significant and have a negative value. This assumes that the log of the odds ratio for preterm birth among BV-positive versus BV-negative women decreases linearly with advancing gestation, which appears reasonable on the basis of previous work.⁶ Finally, the association between BV and pregnancy loss at <23 weeks of gestation was assessed by a proportional hazards model.¹⁶ This allowed for staggered entry into the study (ie, women who were screened at different gestational ages); the model estimates a hazard ratio, which is akin to a relative risk. Statistical analysis was performed with SAS statistical software (version 8.2; SAS Institute Inc, Cary, NC). In all analyses, 2-tailed probability values of <.05 were considered statistically significant.

Results

There were 15,864 women who were screened for BV, 5449 (34.4%) of whom had BV. Pregnancy outcome was available for 12,937 of these women, and 1704 pregnancies (13.2%) lasted <37 weeks. The exclusion of the 263 pregnancy losses at <23 weeks of gestation reduced the preterm birth fraction to 11.4%. The characteristics of the women in the study are given in Table I. Most women

Table II Pregnancy outcome by gestational age at screening among women with and without BV

Gestation at screening	No. screened	<37 weeks (%)	Birth from screening to <37 weeks of gestation	
			Women who were delivered from screening to <23 weeks of gestation (%)	Women who were delivered from 23 to <37 weeks of gestation*
<13 wk				
BV—positive	2036	15.6	4.1	12.0
Bacterial vaginosis—negative	2996	14.0	2.9	11.4
13-14 wk				
BV—positive	652	15.3	2.6	13.1
Bacterial vaginosis—negative	981	14.0	2.7	11.6
15-16 wk				
BV—positive	587	15.5	1.9	13.9
Bacterial vaginosis—negative	861	11.7	1.0	10.8
17-18 wk				
BV—positive	541	13.3	1.7	11.8
Bacterial vaginosis—negative	1196	9.8	0.7	9.2
19-20 wk				
BV—positive	500	15.4	0.6	14.9
Bacterial vaginosis—negative	1284	10.0	0.6	9.4
21-22 wk				
BV—positive	318	13.2	0.3	12.9
Bacterial vaginosis—negative	985	10.5	0.1	10.4

* Only patients who were still pregnant at 23 weeks of gestation are included in this column. Therefore, percentages for being delivered from screening to <23 weeks of gestation and 23 to <37 weeks of gestation do not sum to the percentage for being delivered from screening to <37 weeks of gestation.

were screened at <15 weeks of gestation; slightly more than one half of the women were black, and 39% of the women were nulliparous. No other descriptive data were collected about the women. As has been described in other studies, the prevalence of BV was lower among women who are screened later in pregnancy, and the 24% prevalence of BV among women who are screened at 21 to 22.9 weeks of gestation is only slightly greater than the 16% that was observed in the Vaginal Infections and Prematurity Study, which screened women at 23 to 26 weeks of gestation.¹⁴

In the entire population, delivery at <37 weeks of gestation was more frequent among the 4634 women with BV (15.1%), than among the 8303 women without BV (12.1%; $P < .001$). Furthermore, there was a significant trend ($P < .001$) for women with more abnormal Gram-stain values to have a higher incidence of preterm birth; 13.9% of the 2523 women with scores 7 to 8 were delivered preterm compared with 16.5% of the 2111 women with scores 9 to 10. Results were similar for spontaneous preterm birth, for total and spontaneous delivery from 23 to 36 weeks of gestation, and for both black women and non-black women (data not shown). The hazard ratio for pregnancy loss at <23 weeks of gestation was 1.4 (95% CI, 1.1-1.8), which was comparable to the odds ratio for birth at 23 to 36 weeks (odds ratio, 1.2; 95% CI, 1.1-1.4).

The probabilities of all preterm birth, delivery from screening to 23 weeks of gestation, and delivery at 23 to 36 weeks of gestation are presented by BV status and gestational age at screening in Table II. Although there was a trend for the probabilities of all the outcomes to decrease, the later in gestation screening occurred, the trends were similar in BV-positive and BV-negative women. The odds ratios for preterm and spontaneous preterm birth, along with their 95% CIs, for BV-positive compared with BV-negative women are presented in Figure 1. BV was associated with an elevated risk of both outcomes, although there was no evidence that the odds ratio that was associated with BV was higher when screening occurred earlier in gestation than when it occurred later. Figure 2 shows the odds ratios for delivery at <23 weeks of gestation and 23 to 36 weeks of gestation according to the time of screening. In Figures 1 and 2, there were trends of borderline significance for the odds ratio of all preterm births ($P = .06$) and for all deliveries at 23 to 36 weeks of gestation ($P = .0502$) to be higher when BV was diagnosed later in gestation; the probability values increased to .09 and .08, respectively, when there was adjustment for maternal race and parity, which were the only potentially confounding factors that we collected about women who were not in the clinical trial. However the probability values for trend in odds ratios with

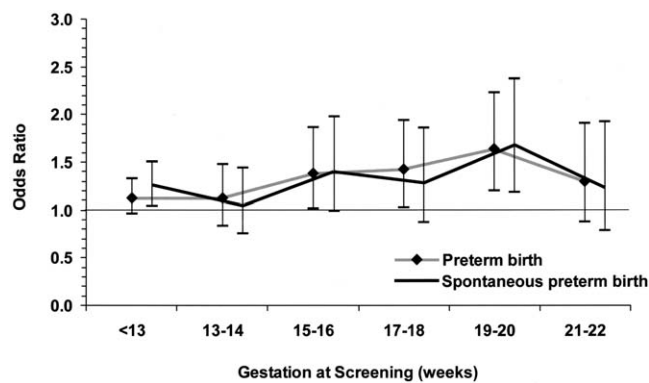


Figure 1 Odds ratio and 95% CI for preterm birth and spontaneous preterm birth among women with BV, compared with women without BV, by gestational age at screening.

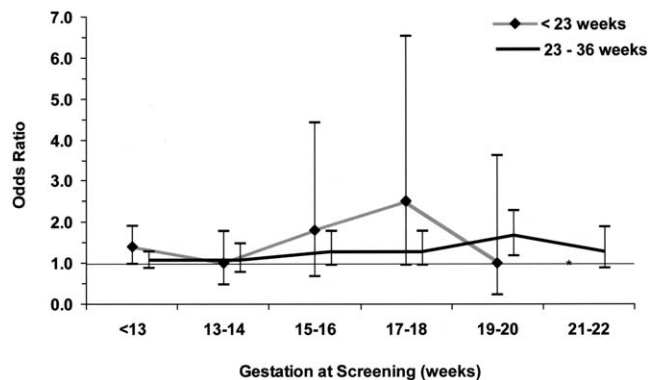


Figure 2 Odds ratio and 95% CI for birth at <23 and at 23-36 weeks' gestation among women with BV, compared with women without BV, by gestational age at screening. *Gray line with closed diamonds, <23 weeks of gestation; black line, 23 to 36 weeks of gestation; asterisk, only 2 pregnancies of women who were screened at 21 to 22 weeks of gestation were delivered at <23 weeks of gestation.*

increasing gestational age did not approach statistical significance for spontaneous preterm birth ($P = .44$) or for delivery at <23 weeks of gestation ($P = .24$).

The odds ratios for all preterm births among women with elevated pH and Gram stain scores of 7 to 8 or 9 to 10, compared with women with normal pH or Gram stain scores of 0 to 6, are presented for total preterm birth in Figure 3. Although higher Gram stain scores were associated with an increased risk of preterm birth at most gestations, the odds ratio for all preterm births among women with scores of 9 to 10 was not higher when screening occurred earlier in gestation (probability value for interaction of score 9-10 with gestational age, .28). The odds ratio for all preterm birth among women with scores of 7 to 8 actually increased with increasing gestational age ($P = .049$), although this was no longer significant after adjustment was made for race and

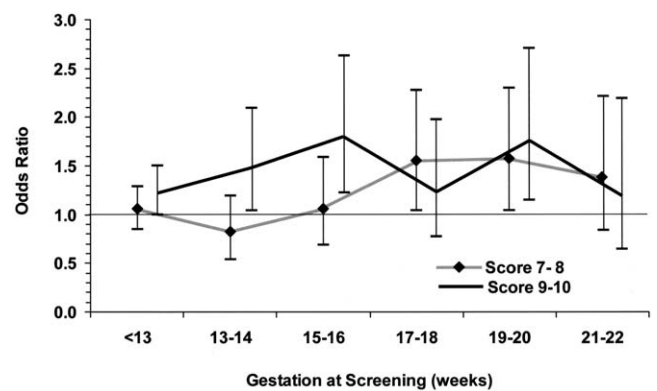


Figure 3 Odds ratio and 95% CI for perterm birth among women with Nugent Gram stain scores 7-8 and 9-10, compared with women without BV, by gestational age at screening.

parity ($P = .079$). Results for spontaneous preterm birth were not substantially different from the corresponding values for all preterm births. In no case was there a trend for the odds ratio for preterm birth to be greater when BV was screened for and diagnosed earlier in gestation.

Information about pregnancy outcome was missing for 2927 screened women (18%), and women with BV were less likely to have missing pregnancy information (15%) than were women without BV (20%; $P < .001$). This was entirely due to participation in the clinical trial; among trial participants, 1.9% of women with BV and 2.0% of women without BV had missing pregnancy outcome information ($P = .92$) versus 22% of women with BV and 21% of women without BV among women not in the clinical trial ($P = .17$). When women enrolled in the clinical trial were excluded from this analysis, the results were not substantially changed (data not shown).

Comment

This study, which included more women who were screened at <20 weeks of gestation ($n = 10,746$) than all previous studies combined, did not find that BV, when diagnosed earlier in gestation, carried greater odds of pregnancy loss at <23 weeks or of preterm birth than when it was diagnosed later. This is in contrast to the results of a recent meta-analysis that reported an odds ratio of 7.55 for BV that was diagnosed at <16 weeks of gestation, 4.20 for BV that was diagnosed at <20 weeks of gestation, and 1.53 for BV that was diagnosed at ≥ 20 weeks of gestation.⁶

There are several possible explanations for our failure to confirm the results of the meta-analysis. First, our study was conducted in clinic populations in the United States, whereas most previous studies of women at <20 weeks of gestation were conducted outside of the United States. The rate of preterm birth among BV-negative women in these studies ranged from <2%⁸ to 11.8%¹⁷;

most studies reported rates considerably lower than the preterm birth rate of 12.1% among BV-negative women in our population. This suggests that there are multiple other causes of preterm birth that are more common in the United States than in many other countries, which might obscure the relative increase in risk among BV-positive women here. Of note, our estimate of the odds ratio for preterm birth among BV-positive women was very similar to the odds ratio of 1.4 for the preterm low birth weight that is reported in the Vaginal Infections and Prematurity Study,¹⁶ which screened for BV at 23 to 26 weeks of gestation and was conducted in a population similar to ours.

Second, most previous studies of women at <20 weeks of gestation have been comparatively small, which results in statistically imprecise estimates of the association between BV and preterm birth. Even when these studies were combined in a meta-analysis,⁶ the odds ratio for preterm birth when BV was diagnosed at <20 weeks of gestation had a 95% CI of 2.11 to 8.39; the 95% CI for BV that was diagnosed at <16 weeks of gestation was 1.80 to 31.65.

Third, previous studies have used varying definitions of BV. These definitions include a clinical definition according to the Amsel criteria; Gram stains interpreted according to the Nugent or Spiegel method; Gram stain plus elevated pH, clue cells, or abnormal vaginal culture; or clue cells only. Cut-points for preterm delivery ranged from <32 to <37 weeks of gestation. Although unlikely, it is possible that different definitions of BV might account for our discordant results.

There are possible reasons that our study failed to find that BV that was diagnosed early in pregnancy carried a large relative risk of preterm birth. We did not use a standardized protocol for the assessment of gestational age among women who were ineligible for the clinical trial, and errors in gestational age measurement may have obscured our ability to observe an increased risk. However, we collected data on birth weight for these women, and when the analyses were repeated for low birth weight (<2500 g) and very low birth weight (<1500 g) the results were virtually identical to those for preterm birth, which suggests that differences in gestational age measurement did not account for our results.

We did not read the Gram stains of women who had vaginal pH values ≤ 4.4 . Because the definition of BV for the clinical trial required both abnormal pH and abnormal Gram stain, screening for the trial was more efficient. However, it limits our ability to study the joint effects of pH and flora. In the Maternal-Fetal Medicine Unit Preterm Prediction Study,¹⁸ only 11.6% of women with normal pH had Gram stain scores of ≥ 7 , versus 48.3% of women with pH > 4.4 (unpublished data). There were 5194 women in the present study who had normal pH values and therefore did not have a Gram stain evaluated, so we estimate that we misclassified as normal 603 women

who would have had Nugent scores of ≥ 7 had we read their Gram stains. Our current definition identified 4634 women as having BV and 8303 women as being normal, so we believe that the misclassification of 603 women, although not optimal, is acceptable.

We did not collect extensive data on antibiotic use after screening among women who were not in the clinical trial. Treatment of BV might have blunted an adverse effect on preterm birth. However, women who had received antibiotics recently were ineligible for screening, and we collected data on which of the women were ineligible for the trial because they received antibiotics after screening but before they would have been assigned randomly to therapy. We also collected extensive data on antibiotic use among women in the clinical trial. When we eliminated women who received these clinically indicated antibiotics and those who were assigned randomly to receive metronidazole in the trial, our results were not changed substantially. Therefore, we do not believe that unrecorded antibiotic use was responsible for the lack of an increased risk of preterm birth among women with BV compared with women without BV when they were screened early in pregnancy.

No outcome data were found for 18% of screened women. To determine the maximum effect that missing outcomes might have had on the results, we made the extreme worst-case assumption that all of the BV-positive and none of the BV-negative women with missing outcomes were delivered at <37 weeks of gestation. In this unlikely situation, the odds ratio for preterm birth among BV-positive women who were screened at <13 weeks of gestation would have been 3.7 (95% CI, 3.3 to 4.3). Although elevated, this is still considerably less than the value of 7.55 that was noted by Leitich et al⁶ for women with BV at <16 weeks of gestation.

Our study was not truly longitudinal—we screened each woman once, rather than multiple times in pregnancy so each week's comparison was based on different women. However, of the 18 studies included in the meta-analysis of Leitich et al,⁶ only the studies by Meis et al¹⁹ and Riduan et al¹⁷ evaluated women more than once during pregnancy; the meta-analysis drew its conclusion by comparing results across the different studies.⁶ Although a single large study that would evaluate women at multiple times during pregnancy would be optimal, we believe that our study that evaluated women once according to a common protocol is an improvement over existing research. One way to assess the importance of this limitation is to determine whether, among women without BV (the control group), those women who were screened earlier in pregnancy had a different risk of preterm birth from 23 to 36 weeks of gestation than women who were screened later. As can be seen in Table II, there was a small, but statistically

significant, trend ($P = .03$) for BV-negative women who were screened earlier in the 8- to 22-week interval to have a higher risk of delivery from 23 to 36 weeks of gestation than women who were screened later. However, after adjustment for race and parity, this trend was no longer statistically significant ($P = .11$). Therefore, the baseline risk of preterm birth among women without BV did not differ by when in pregnancy they were screened, which suggests that the inherent risk of preterm birth among these women was not influenced by the timing of screening.

Perhaps a more important issue is that, like almost all previous research on this topic, we know the time in pregnancy when BV was first diagnosed, but we do not know the actual time when women initially acquired BV. It seems likely that, for many, if not most, of these women, BV antedated the pregnancy.²⁰ Longitudinal data from nonpregnant women indicate that occasional days of genital flora that are compatible with BV are common.²¹ In that context, it is not certain how to define an actual new incident case of BV. In addition, spontaneous resolution of BV may not result in a reduced risk of preterm birth, although this conclusion is based on small numbers of women.²² The chronic nature of BV and the lack of benefit with its resolution argue against an elevated risk of BV when it is diagnosed early in pregnancy.

Women who had lower genital tract symptoms were ineligible for screening and not included in the study. However, only 5% of women were excluded from screening because of symptoms,⁹ not all of whom would have had BV, making this an unlikely explanation for our failure to find a larger relative risk of BV that was diagnosed early in pregnancy. Kurki et al⁸ also excluded symptomatic women and still found a greatly increased relative risk of preterm birth among women with BV that was diagnosed early in pregnancy.

In conclusion, we evaluated whether BV that was diagnosed earlier during the 8 to 22 weeks of gestation interval was associated with a greater increase in risk of preterm birth than BV that was diagnosed later and found that the gestation at screening and diagnosis in BV-positive women did not influence the relative risk of preterm birth.

Acknowledgments

Other members of the Maternal-Fetal Medicine Units Network are as follows: University of Alabama at Birmingham: R.J. Copper, A. Northen, W.W. Andrews; University of Chicago: P. Jones, M.D. Lindheimer; University of Cincinnati: N. Elder, T.A. Siddiqi; George Washington University Biostatistics Center: E.A. Thom, S. Leindecker, M.L. Fischer; Magee Women's Hospital: S.N. Caritis, M. Cotroneo, T. Kamon, R.P. Heine;

University of Miami: S. Beydoun, C. Alfonso, F. Doyle; National Institute of Child Health and Human Development: D. McNellis, C.S. Catz, S.J. Yaffe; Ohio State University: F. Johnson, M.B. Landon; University of Oklahoma: G. Thurnau, A. Meier; Medical University of South Carolina: B.A. Collins, F. LeBoeuf, R.B. Newman; University of Tennessee: B.M. Mercer, R. Ramsey; University of Texas at San Antonio: M. Berkus, S. Nicholson; University of Texas Southwestern Medical Center: S. Bloom, M.L. Sherman; Thomas Jefferson University: M. DeVito, J. Tolosa; University of Utah: D. Dudley, L. Reynolds; Wake Forest University: P. Meis, E. Mueller-Heubach, M. Swain; Wayne State University: S. F. Bottoms (deceased), G.S. Norman.

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