

## ASSOCIATION BETWEEN BACTERIAL VAGINOSIS AND PRETERM DELIVERY OF A LOW-BIRTH-WEIGHT INFANT

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**Abstract Background.** Bacterial vaginosis is believed to be a risk factor for preterm delivery. We undertook a study of the association between bacterial vaginosis and the preterm delivery of infants with low birth weight after accounting for other known risk factors.

**Methods.** In this cohort study, we enrolled 10,397 pregnant women from seven medical centers who had no known medical risk factors for preterm delivery. At 23 to 26 weeks' gestation, bacterial vaginosis was determined to be present or absent on the basis of the vaginal pH and the results of Gram's staining. The principal outcome variable was the delivery at less than 37 weeks' gestation of an infant with a birth weight below 2500 g.

**Results.** Bacterial vaginosis was detected in 16 percent of the 10,397 women. The women with bacterial vaginosis were more likely to be unmarried, to be black, to have low incomes, and to have previously delivered low-birth-weight infants. In a multivariate analysis, the

presence of bacterial vaginosis was related to preterm delivery of a low-birth-weight infant (odds ratio, 1.4; 95 percent confidence interval, 1.1 to 1.8). Other risk factors that were significantly associated with such a delivery in this population were the previous delivery of a low-birth-weight infant (odds ratio, 6.2; 95 percent confidence interval, 4.6 to 8.4), the loss of an earlier pregnancy (odds ratio, 1.7; 1.3 to 2.2), primigravidity (odds ratio, 1.6; 1.1 to 1.9), smoking (odds ratio, 1.4; 1.1 to 1.7); and black race (odds ratio, 1.4; 1.1 to 1.7). Among women with bacterial vaginosis, the highest risk of preterm delivery of a low-birth-weight infant was found among those with both vaginal bacteroides and *Mycoplasma hominis* (odds ratio, 2.1; 95 percent confidence interval, 1.5 to 3.0).

**Conclusions.** Bacterial vaginosis was associated with the preterm delivery of low-birth-weight infants independently of other recognized risk factors. (N Engl J Med 1995; 333:1737-42.)

PRETERM delivery, low birth weight, and neonatal mortality are the most important problems in obstetrics. From 1970 to 1985, the incidence of low birth weight in the United States declined steadily. From 1986 to 1991, however, the incidence of premature birth of low-birth-weight infants (those born at less than 37 weeks' gestation, weighing less than 2500 g) increased from 6.8 percent to 7.1 percent.<sup>1</sup> Black race, low socioeconomic status, older maternal age, and previous preterm delivery have been consistently related to the preterm delivery of low-birth-weight infants.<sup>2</sup> In 1991, disorders related to preterm delivery and low birth weight were the primary cause of death in the United States among black infants and the third leading cause of death among white infants.<sup>3</sup>

Bacterial vaginosis is a condition in which the normal, lactobacillus-predominant vaginal flora is replaced with anaerobic bacteria, *Gardnerella vaginalis*, and *Mycoplasma hominis*.<sup>4</sup> Bacterial vaginosis has been associated with preterm delivery,<sup>5-10</sup> premature rupture of membranes,<sup>5,7</sup> infection of the chorion and amnion,<sup>11</sup> histologic chorioamnionitis,<sup>11</sup> and infection of amniotic flu-

id.<sup>12-14</sup> In other reports, the microflora associated with bacterial vaginosis, including anaerobic gram-negative rods, *G. vaginalis*, and *M. hominis*, has been linked to preterm delivery.<sup>15-17</sup>

In a multicenter study, we followed a large cohort of pregnant women from five U.S. cities and investigated a large number of risk factors and genital microorganisms for their association with the preterm delivery of low-birth-weight infants.<sup>18</sup> The purpose of the study was to evaluate the association between the incidence of such deliveries and that of bacterial vaginosis in this cohort.

## METHODS

### Study Patients

A total of 13,914 women were enrolled at seven medical centers between 1984 and 1989. Of these, 2449 were excluded because of previous enrollment in another clinical trial.<sup>18</sup> The inclusion of those women would not have altered our findings, but they were excluded both for clarity of presentation and because of the possibility that bias might have been introduced because the women enrolled in the other study had a different follow-up. An additional 509 women were excluded because information about the results of vaginal Gram's staining or pH measurement was missing, and 559 more women were excluded because data on birth outcomes were missing. A total of 10,397 women remained in the study. All questionnaires were administered and all examinations and microbiologic procedures were performed according to a standardized protocol. Samples containing unidentified organisms were used to confirm the adequacy of the testing methods employed at each center.

Women were enrolled in the study during routine prenatal visits after 23 to 26 weeks of gestation had been completed; for each woman, a medical, obstetrical, sexual, and social history was taken and cultures of the vagina and cervix were obtained. The reasons for exclusion from the study were age less than 16 years, Rh isoimmunization, use of antibiotics in the preceding two weeks, multiple gestation, cervical cerclage, prior use of tocolytic agents during the current pregnancy, hypertension requiring treatment with medication, insulin-

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dependent diabetes, current use of corticosteroids, chronic renal or symptomatic organic heart disease, and the intention to deliver at a nonstudy hospital. The women gave written informed consent, and the protocol was approved by the institutional review board at each center.

### Collection of Specimens

A clean, unlubricated speculum was placed in the vagina, and the vaginal pH was measured with pH strips (ColorpHast, MCB Reagents, Gibbstown, N.J.). Sterile cotton swabs were used to obtain material from the posterior vaginal fornix for a vaginal smear. A sterile, oxygen-reduced solution of phosphate-buffered saline (3 ml) was placed in the vagina, and a wash suspension was prepared by swabbing the lateral vaginal walls. The suspension was then removed with a syringe and injected into an oxygen-free tube for transport. A cervical specimen was obtained. The methods used to detect microbiologic organisms have been described elsewhere.<sup>19</sup>

Because anaerobic, gram-negative rods have been reported as part of the normal flora of most women,<sup>4</sup> such organisms were identified only when they were found in the third or fourth streak zone of the agar plate. During this study, several species of bacteria belonging to the genus *bacteroides* were reassigned to the newly described genera *prevotella* and *porphyromonas*. In this report, therefore, the term "bacteroides" includes species belonging to any of the three genera.

### Evaluation of Vaginal Smears

Vaginal smears were air dried, subjected to Gram's staining, and evaluated under magnification ( $\times 1000$ ). A score of 0 to 10 was assigned on the basis of the relative proportions of easily distinguished bacterial morphologic types (i.e., large gram-positive rods, small gram-negative or variable rods, and curved rods). A score of 0 was assigned to the most lactobacillus-predominant vaginal flora, and a score of 10 was assigned to a flora in which lactobacilli were largely replaced by *gardnerella*, *bacteroides*, and *mobiluncus*. Scores for Gram's staining were calculated by the method of Nugent et al.<sup>20</sup>

### Diagnosis of Bacterial Vaginosis

Women with a vaginal pH above 4.5 and a score of 7 or more on Gram's staining of the vaginal smear were considered to have bacterial vaginosis. The diagnosis was not disclosed to the women or their care providers. The investigators who interpreted the results of the Gram's staining were not aware of the patients' clinical assessments. Data on the reproducibility of this method<sup>20</sup> and its relation to clinical signs have been published elsewhere.<sup>19</sup>

### Definitions of Outcome

Estimates of gestational age were based on the date of the last menstrual period and were adjusted by the obstetrical provider as needed on the basis of the results of pregnancy tests and the first pelvic examination, the fetal heartbeat, and available results of ultrasonography. If the date of a woman's last menstrual period was considered accurate, that date was the principal factor used to estimate gestational age. If the date was not considered accurate, the clinical examination, history, and findings of ultrasonography (if available) were used. No corrections to the estimate of gestational age were made by the study personnel. Preterm delivery was defined as delivery at less than 37 weeks' gestation. An infant weighing less than 2500 g was defined as having a low birth weight. Premature rupture of membranes was defined as the rupture of membranes before the onset of regular uterine contractions.

Estimates of gestational age based on the date of the last menstrual period have known inaccuracies.<sup>21</sup> Estimates based on exact menstrual histories are accurate to within two weeks on either side of the estimated age, but those based on uncertain histories or examinations performed in the second trimester are accurate only to within four weeks.<sup>21</sup> In our study, 10 percent of women could not recall the month of their last menses, and among those who could do so, 55 percent presented for prenatal care in the second trimester and 19 percent presented after 20 weeks' gestation. Only 30 percent of the patients underwent ultrasonography before enrollment. Among the 10,397 women, 1193 (11.5 percent) delivered before term (regardless of the

infant's birth weight). However, only 504 infants (4.8 percent) were born prematurely with low birth weight, whereas the remaining 689 infants (6.6 percent) born at less than 37 weeks' gestation weighed 2500 g or more. These data suggested that many infants classified as premature on the basis of the mother's last menstrual period may not have been premature. To correct for potential misclassification, the group of infants born prematurely was divided into those who had low birth weight and those who did not. The group with low birth weight had a mean ( $\pm$ SD) gestational age of  $32.4 \pm 3.2$  weeks and a mean birth weight of  $1822 \pm 556$  g. In comparison, the group without low birth weight had a mean gestational age of  $35.0 \pm 1.5$  weeks and a mean birth weight of  $3054 \pm 393$  g. In addition, the infants in the low-birth-weight group were significantly more likely than the other infants to have respiratory distress syndrome (36 percent vs. 4 percent,  $P < 0.001$ ) and to spend more than one week in the neonatal intensive care unit (44 percent vs. 15 percent,  $P < 0.001$ ). The preponderance of serious sequelae among the infants born prematurely occurred in the group with low birth weight.<sup>1</sup> Thus, preterm delivery of an infant with low birth weight was the primary outcome, both because it is clinically important and because it helped correct for any misclassification of gestational age.

### Statistical Analysis

Data were entered on forms and sent to the Data Coordinating Center, where the forms were edited and returned to the clinical centers for corrections as needed. Categorical variables were compared by the chi-square test or Fisher's exact test.<sup>22</sup> Woolf's method was used to calculate 95 percent confidence intervals for the univariate odds ratios.<sup>23</sup> A two-tailed P value less than 0.05 was considered to indicate statistical significance. Multivariate analyses were performed with logistic-regression procedures that incorporated other variables predictive of the delivery of an infant with low birth weight.

## RESULTS

Of the 10,397 women followed through delivery, 504 (4.8 percent) were delivered of premature infants with low birth weight. The preterm delivery of such an infant was associated with black race, primigravidity, prior delivery of an infant with low birth weight, loss of an earlier pregnancy, and smoking during the current pregnancy (Table 1). Women who had urinary tract infections or used antibiotics before enrollment were also more likely to deliver infants with low birth weight prematurely. The microorganisms significantly associated with such deliveries included *bacteroides*, *M. hominis*, *G. vaginalis*, *Ureaplasma urealyticum*, group B streptococci, *Chlamydia trachomatis*, and *Trichomonas vaginalis*, whereas lactobacillus was inversely associated with preterm delivery of an infant with low birth weight.

Bacterial vaginosis was diagnosed in 1645 of the 10,397 women (16 percent). The prevalence of this condition ranged from 9 to 28 percent among centers. The relations between demographic, obstetrical, and behavioral characteristics and genital flora and the presence of bacterial vaginosis are shown in Table 1. Characteristics significantly related to the presence of bacterial vaginosis included being black or Hispanic, being unmarried, and having an annual income less than \$10,000. Among the women who had previously had live births, those with bacterial vaginosis were more likely to have given birth to infants with low birth weights. Women who reported using antibiotics during the current pregnancy but before their enrollment in the study and those who reported having yeast vaginitis were both less likely to have bacterial vaginosis than

Table 1. Association of Preterm Delivery of Low-Birth-Weight Infants and Bacterial Vaginosis with Demographic, Obstetrical, and Behavioral Characteristics and Genital Flora in 10,397 Pregnant Women.

CHARACTERISTIC	WOMEN WITH PRETERM DELIVERY		WOMEN WITH BACTERIAL VAGINOSIS	
	WITH CHARACTERISTIC	WITHOUT CHARACTERISTIC	WITH CHARACTERISTIC	WITHOUT CHARACTERISTIC
	<i>percent</i>			
Age <20 yr	5.1	4.8	16.4	15.6*
Race or ethnic group				
Black	6.3	4.3*†	23.0	8.2
Hispanic	3.4	4.3†	14.8	8.2*
Marital status: unmarried	5.2	4.4	18.5	12.2*
Education <12 yr	5.1	4.7	16.1	15.6*
Income <\$10,000/yr	5.1	4.0	18.1	11.8*
Primigravidity	4.7	3.1*‡	16.3	15.6
Previous low-birth-weight infant	17.5	3.1*‡	20.4	15.6*
Loss of an earlier pregnancy§	5.3	3.1*‡	14.9	15.6
Cigarette smoking	6.0	4.2*	16.1	15.7
Alcohol consumption	4.8	4.9	16.3	14.4
Age <15 yr at first sexual contact	4.7	4.9	17.2	15.7*
≥4 Lifetime partners	5.2	4.8	15.4	16.0
Urinary tract infection during pregnancy	6.1	4.7*	15.0	16.0
Antibiotic use before enrollment	5.8	4.6*	19.0	15.1*
Genital flora at enrollment				
Lactobacillus	4.5	5.6*	9.9	32.2*
<i>Gardnerella vaginalis</i>	5.3	4.2*	27.2	1.2*
Bacteroides	6.1	4.5*	38.0	10.9*
<i>Mycoplasma hominis</i>	5.7	4.4*	34.8	6.7*
<i>Ureaplasma urealyticum</i>	5.2	3.8*	18.8	7.7*
Group B streptococci	6.1	4.6*	13.4	16.3*
<i>Neisseria gonorrhoeae</i>	5.4	4.8	27.9	15.6*
<i>Chlamydia trachomatis</i>	6.8	4.7*	28.4	14.8*
<i>Trichomonas vaginalis</i>	7.1	4.5*	17.7	15.5*
Candida	5.3	4.8	6.8	16.8*

\*P<0.05 for the comparison with women with the specified characteristic.

†As compared with white women.

‡As compared with women who had earlier pregnancies that resulted in the live birth of infants weighing 2500 g or more.

§Includes abortions (spontaneous or induced) and stillbirths.

women who did not use antibiotics and women without yeast vaginitis.

At enrollment, colonization with *G. vaginalis*, bacteroides, or *M. hominis* was associated with bacterial vaginosis (Table 1), as was colonization with *U. urealyticum*, *C. trachomatis*, or *Neisseria gonorrhoeae*. Colonization with lactobacilli, group B streptococci, or *Candida albicans* was inversely associated with the presence of bacterial vaginosis.

Because the use of antibiotics could either eliminate bacterial vaginosis or modify its effect on the outcome of pregnancy, outcome data were restricted to women who did not use antibiotics during the period after their enrollment and before 37 weeks' gestation. Outcome data on women who used oral metronidazole, ampicillin, amoxicillin, or intravaginal sulfa cream were not used, because these antibiotics are considered effective against bacterial vaginosis.

The outcomes of pregnancy among women with bacterial vaginosis who did not receive metronidazole, ampicillin, amoxicillin, or intravaginal sulfa cream are shown in Table 2. Bacterial vaginosis was associated with an increased risk of preterm delivery of an infant with low birth weight (odds ratio, 1.5; 95 percent con-

fidence interval, 1.2 to 1.9). Bacterial vaginosis was also related to a birth weight below 2500 g (odds ratio, 1.5) and a significantly reduced mean birth weight. Women who received antimicrobial agents from their primary care providers that were effective against bacterial vaginosis had the same incidence of preterm delivery of infants with low birth weight as women without bacterial vaginosis (8 of 187, or 4.3 percent). There was no association between bacterial vaginosis and premature rupture of membranes (Table 2). A trend toward increased preterm delivery of infants with low birth weights among women with bacterial vaginosis was observed at all study centers. If bacterial vaginosis was diagnosed on the basis of Gram's staining alone, the increase in the risk of preterm delivery of a low-birth-weight infant (odds ratio, 1.4; 95 percent confidence interval, 1.2 to 1.7) was similar to that found when both pH and Gram's staining were used. A vaginal pH above 4.5 was associated with the preterm delivery of an infant with low birth weight only among women with bacterial vaginosis.

Logistic regression was used to study the association between bacterial vaginosis and the preterm delivery of an infant with low birth weight independently of other variables associated with such a delivery (Table 3). Bacterial vaginosis remained independently associated with the preterm delivery of a low-birth-weight infant (odds ratio, 1.4; 95 percent confidence interval, 1.1 to 1.8) after adjustment for smoking, race, any previous delivery of a low-birth-weight infant, any loss of an earlier pregnancy, gravidity, maternal age, marital status, any use of antibiotics, and any colonization with *C. trachomatis*, *N. gonorrhoeae*, *T. vaginalis*, or group B streptococci. The excess risk of preterm delivery of a low-birth-weight infant among women with bacterial vaginosis was unchanged in that model and was similar to the risks associated with cigarette smoking and black race. Delivery of a low-birth-weight infant in the woman's preceding pregnancy was the factor most strongly associated with the premature delivery of such an infant in the current pregnancy. In addition, having lost an earlier pregnancy (because of either stillbirth or abortion, spontaneous or induced) and being a primigravida were also significantly associated with the preterm delivery of a low-birth-weight infant.

*G. vaginalis*, bacteroides, and *M. hominis* were the microorganisms most strongly associated with the pres-

ence of bacterial vaginosis. To evaluate the role of individual species in the association between bacterial vaginosis and the preterm delivery of an infant with low birth weight, we analyzed the incidence of such deliveries in women with bacteroides and *M. hominis* after the women were classified as either having or not having bacterial vaginosis (Fig. 1). The recovery of *G. vaginalis* had no effect on the incidence of preterm delivery of a low-birth-weight infant independently of the presence of bacterial vaginosis (data not shown). In the absence of bacteroides and *M. hominis*, women with bacterial vaginosis had no greater risk of giving birth prematurely to low-birth-weight infants than the reference group of women who did not have bacterial vaginosis or either microorganism (odds ratio, 0.8; 95 percent confidence interval, 0.4 to 1.6). In contrast, women with bacterial vaginosis, bacteroides, and *M. hominis* had the highest incidence of preterm delivery of an infant with low birth weight (odds ratio, 2.1; 95 percent confidence interval, 1.5 to 3.0) relative to the reference group. The presence of either bacteroides or *M. hominis* was associated with preterm delivery of a low-birth-weight infant (odds ratios, 1.5 and 1.6, respectively), even in the absence of bacterial vaginosis.

### DISCUSSION

In this study, women with bacterial vaginosis diagnosed during the second trimester of pregnancy were 40 percent more likely to give birth to a premature, low-birth-weight infant than women without bacterial vaginosis. The relation between bacterial vaginosis and such births remained unchanged after adjustment for confounding variables, which suggests that bacterial vaginosis is an independent risk factor for the preterm delivery of an infant with low birth weight. The evidence that bacterial vaginosis may cause such births is strong. Criteria for assessing the causal contributions of associated factors include the consistency of the association among studies conducted under different circumstances; the magnitude of the relative risk; the demonstration that the exposure occurs before the outcome, showing a biologic gradient in which an increased exposure is associated with an in-

Table 2. Association of Bacterial Vaginosis with Outcomes of Pregnancy among Women without *Trichomonas* Who Did Not Receive Antibiotics between the Time of Enrollment in the Study and Delivery or 37 Weeks' Gestation.

OUTCOME	BACTERIAL VAGINOSIS	NO BACTERIAL VAGINOSIS	ODDS RATIO (95% CI)*
Mean birth weight (g)	3204±618	3294±576†	—
	<i>no. with outcome/total no. (%)</i>		
Low birth weight	118/1218 (9.7)	459/6978 (6.6)	1.5 (1.2–1.7)
Preterm delivery	77/1218 (6.3)	291/6978 (4.2)	1.5 (1.2–1.9)
Delivery at term	41/1218 (3.4)	168/6978 (2.4)	1.4 (1.0–2.0)
Premature rupture of membranes	35/1132 (3.1)	182/6617 (2.8)	1.1 (0.8–1.6)

\*CI denotes confidence interval.

†P<0.001 for the comparison with women who had bacterial vaginosis.

Table 3. Multivariate Analysis of Risk Factors for the Preterm Delivery of an Infant with Low Birth Weight among the 10,397 Women Enrolled in the Study.

COVARIATE	ADJUSTED ODDS RATIO (95% CI)*
Bacterial vaginosis	1.4 (1.1–1.8)
Cigarette smoking	1.4 (1.1–1.7)
Black race	1.4 (1.1–1.7)
Previous low birth weight†	6.2 (4.6–8.4)
Loss of an earlier pregnancy‡	1.7 (1.3–2.2)
Primigravidity†	1.6 (1.1–1.9)

\*Odds ratios are for the preterm delivery of an infant with low birth weight after adjustment for age; marital status; gravidity; any use of antibiotics; any colonization with *C. trachomatis*, *N. gonorrhoeae*, *T. vaginalis*, or group B streptococci; and the covariates shown. CI denotes confidence interval.

†As compared with women who had previously given birth to an infant at term who did not have low birth weight.

‡Includes abortions (spontaneous or induced) and stillbirths.

creased risk of the abnormal outcome; and biologic plausibility. The results of this study together with those of other published studies of bacterial vaginosis in pregnancy support a causal role for this infection in prematurity.

Over the past decade, six studies have reported an increased risk of preterm delivery among women with bacterial vaginosis.<sup>5–10</sup> The appearance of this finding in case-control<sup>6,10</sup> and cohort<sup>5,7–9</sup> studies, conducted in the United States, Scandinavia, the United Kingdom, and Indonesia, meets the criterion of consistency. The risk of preterm delivery among women with bacterial vaginosis, which was found to be 1.4 in our study, ranged from 2.0 to 2.8 in four other studies<sup>5,6,8,10</sup> and was 3.5 and 6.9 in two additional ones.<sup>7,9</sup> The highest risks were reported in cohort studies in which bacterial vaginosis was identified early in pregnancy. In our study, women were not enrolled until late in the second trimester, a fact that precluded the analysis of very early loss of pregnancy among women with bacterial vaginosis, which may account for the lower estimate of risk that we found.

Our study controlled for other risk factors for prematurity and simultaneously examined the roles of individual bacterial species and of bacterial vaginosis as risk factors for the preterm delivery of an infant with low birth weight. Like earlier studies reporting links between bacteroides, *M. hominis*, and preterm birth,<sup>15–17</sup> this study documented an increased risk of preterm delivery of low-birth-weight infants among women colonized by these microorganisms. In addition, we demonstrated that women with bacterial vaginosis and both pathogens are at the highest risk for the preterm delivery of such infants (Fig. 1).

The mechanism by which bacterial vaginosis causes the preterm birth of an infant with low birth weight is not known, but there is evidence that it causes infection of the upper genital tract, which in turn causes premature birth. In other studies, bacterial vaginosis has been associated with two- to threefold increases in infection

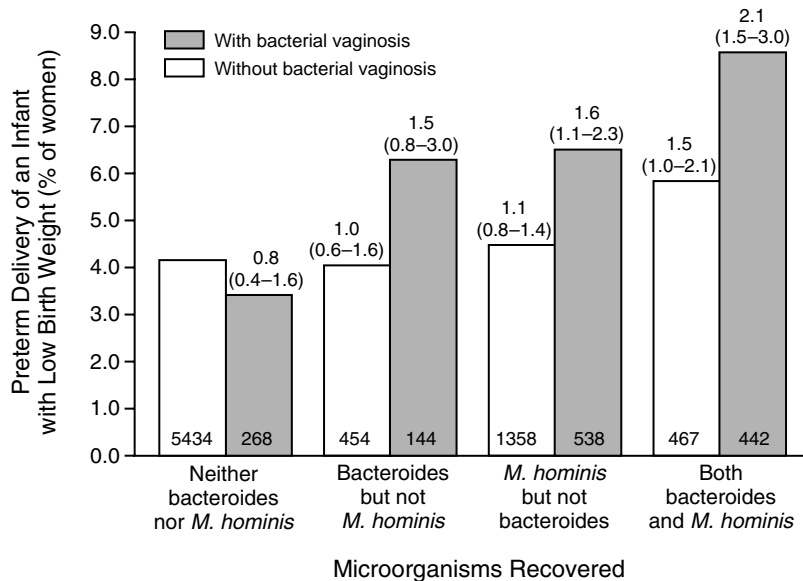


Figure 1. Frequency of Preterm Delivery of an Infant with Low Birth Weight, According to Whether Bacterial Vaginosis Was Present and Whether Bacteroides and *Mycoplasma hominis* Were Recovered from the Mother's Vagina.

Odds ratios, followed in parentheses by 95 percent confidence intervals, are shown above each bar. The bar at the far left represents the reference group. The numbers inside the bars are the numbers of women in the groups. Women who received antibiotics were excluded from this analysis.

of amniotic fluid,<sup>5,14,24</sup> infection of the chorion and amnion,<sup>11</sup> and histologic chorioamnionitis.<sup>11</sup> Pregnant women with bacterial vaginosis have elevated vaginal or cervical levels of endotoxin,<sup>25</sup> mucinase,<sup>26</sup> sialidase,<sup>26</sup> and interleukin-1 $\alpha$ ,<sup>25</sup> suggesting that microorganisms that cause bacterial vaginosis stimulate the production of cytokines. A relative reduction in the number of vaginal lactobacilli is one characteristic of this syndrome. It is noteworthy that the presence of vaginal lactobacilli appeared to protect against preterm delivery in this study and an earlier one,<sup>15</sup> further supporting the biologic plausibility of the hypothesis that bacterial vaginosis causes an increase in the preterm delivery of infants with low birth weight.

Bacterial vaginosis is one of the most common genital infections in pregnancy. From 12 to 22 percent of pregnant women have this syndrome<sup>7,9</sup>; it was present in 16 percent of our study population, with a range of 9 to 28 percent among centers. Currently, pregnant women with asymptomatic bacterial vaginosis are not routinely screened or treated for this syndrome. Given the high frequency of bacterial vaginosis, its treatment could have a substantial effect on the incidence of preterm delivery of infants with low birth weight. Although there is some concern about the use of systemic metronidazole because of potential carcinogenicity,<sup>27,28</sup> a recent analysis of seven studies suggested that there was no increase in birth defects among infants exposed to metronidazole during the first trimester.<sup>29</sup>

The population attributable risk for the preterm delivery of infants with low birth weight that was account-

ed for by bacterial vaginosis in this observational study was 6 percent. The best method of demonstrating a causal relation between bacterial vaginosis and such deliveries would be to conduct a randomized clinical trial. In our study, bacterial vaginosis was related to very premature birth at a mean gestational age of 32 weeks and a mean birth weight of 1827 g. The prevention of even a small proportion of such births could translate into large monetary savings and a decrease in neonatal morbidity and mortality.

## APPENDIX

In addition to the study authors, the following investigators and institutions participated in the Vaginal Infections and Prematurity Study Group: S.J. Yaffe, C.S. Catz, G.G. Rhoads, and H.W. Berendes (National Institute of Child Health and Human Development, Bethesda, Md.); W.C. Blackwelder, R.A. Kaslow, and G.F. Reed (National Institute for Allergy and Infectious Diseases, Bethesda, Md.); E. Greenberg (Columbia University, New York); C. Cammarata (Louisiana State University, New Orleans); P. Sommers (Tulane University, New Orleans); P. Rettig and R. Wilkerson (University of Oklahoma, Oklahoma City); P. St. Clair (University of Texas, San Antonio); and W.K. Poole (Research Triangle Institute, Research Triangle Park, N.C.).

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