METRONIDAZOLE TO PREVENT PRETERM DELIVERY IN PREGNANT WOMEN WITH ASYMPTOMATIC BACTERIAL VAGINOSIS

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Abstract

Background Bacterial vaginosis has been associated with preterm birth. In clinical trials, the treatment of bacterial vaginosis in pregnant women who previously had a preterm delivery reduced the risk of recurrence.

Methods To determine whether treating women in a general obstetrical population who have asymptomatic bacterial vaginosis (as diagnosed on the basis of vaginal Gram's staining and pH) prevents preterm delivery, we randomly assigned 1953 women who were 16 to less than 24 weeks pregnant to receive two 2-g doses of metronidazole or placebo. The diagnostic studies were repeated and a second treatment was administered to all the women at 24 to less than 30 weeks' gestation. The primary outcome was the rate of delivery before 37 weeks' gestation.

Results Bacterial vaginosis resolved in 657 of 845 women who had follow-up Gram's staining in the metronidazole group (77.8 percent) and 321 of 859 women in the placebo group (37.4 percent). Data on the time and characteristics of delivery were available for 953 women in the metronidazole group and 966 in the placebo group. Preterm delivery occurred in 116 women in the metronidazole group (12.2 percent) and 121 women in the placebo group (12.5 percent) (relative risk, 1.0; 95 percent confidence interval, 0.8 to 1.2). Treatment did not prevent preterm deliveries that resulted from spontaneous labor (5.1 percent in the metronidazole group vs. 5.7 percent in the placebo group) or spontaneous rupture of the membranes (4.2 percent vs. 3.7 percent), nor did it prevent delivery before 32 weeks (2.3 percent vs. 2.7 percent). Treatment with metronidazole did not reduce the occurrence of preterm labor, intraamniotic or postpartum infections, neonatal sepsis, or admission of the infant to the neonatal intensive care unit.

Conclusions The treatment of asymptomatic bacterial vaginosis in pregnant women does not reduce the occurrence of preterm delivery or other adverse perinatal outcomes. (N Engl J Med 2000;342:534-40.)

PRETERM birth is a common cause of neonatal morbidity and mortality. An extensive body of evidence indicates that infection is associated with preterm delivery and with low birth weight of the infant.[1] Chorioamnionitis is strongly correlated with preterm delivery[2,3] and the failure of tocolytic-drug therapy.[4] Evidence of infection, manifested by the presence of organisms or inflammatory cytokines in the amniotic fluid or chorioamniotic membranes,[3-5] commonly accompanies preterm labor and preterm premature rupture of membranes, particularly at the earliest gestational ages. Most microorganisms found in the amniotic fluid and placenta are thought to come from the vagina, especially among women with bacterial vaginosis.[3]

Bacterial vaginosis affects approximately 800,000 pregnant women per year in the United States, and women with bacterial vaginosis are more likely than women without bacterial vaginosis to have a preterm delivery or a low-birth-weight infant.[6-10] If the treatment of bacterial vaginosis were to reduce this risk, as many as 80,000 preterm births, leading to 4000 perinatal deaths and 4000 infants with neurologic abnormalities, might be prevented in the United States each year.[9] Among women with bacterial vaginosis who had a prior preterm delivery, the use of metronidazole alone[11,12] or metronidazole plus erythromycin[13] reduced the risk of recurrent preterm delivery. However, the treatment of bacterial vaginosis with vagi-

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nal clindamycin cream in pregnant women at lower risk for preterm delivery did not reduce the incidence of preterm delivery.[14,15] To determine whether screening for bacterial vaginosis and systemic treatment of the condition would reduce the risk of preterm delivery, we conducted a trial of metronidazole therapy in pregnant women with asymptomatic bacterial vaginosis.

METHODS

Subjects and Screening

We screened women who had completed between 8 weeks 0 days of gestation and 22 weeks 6 days of gestation for bacterial vaginosis and *Trichomonas vaginalis* infection. Women were ineligible for screening if they reported any of the following: increased vaginal discharge with itching, burning, or odor; an allergy to metronidazole; current abuse of ethanol; antibiotic therapy within the previous 14 days; an intention to receive antenatal care or to deliver the infant at a location where the follow-up visit could not be completed or from which information on delivery could not be obtained; planned antibiotic therapy before delivery (excluding intrapartum antibiotic prophylaxis); current or planned cervical cerclage; preterm labor before screening; current or planned tocolytic-drug therapy; fetal death or known life-threatening fetal anomaly; multifetal gestation; or medical illnesses (such as hypertension, preexisting diabetes mellitus, or asthma) that required long-term or intermittent drug therapy.

One Dacron swab, 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 pH stick (ColorpHast pH stick, Curtin Matheson, Grand Prairie, Tex.). The slides from women whose vaginal pH was higher than 4.4 were shipped to the laboratory of one of the authors, where they underwent Gram's staining, with the results interpreted according to the criteria of Nugent et al.[16] The scoring system is detailed in Table 1. In accordance with our previous work,[8] we defined bacterial vaginosis as a Gram's-staining score of 7 or higher in conjunction with a vaginal pH higher than 4.4. Slides from women with a vaginal pH of 4.4 or lower were discarded, because, according to our definition, these women did not have bacterial vaginosis. An additional swab was inoculated into Diamond's medium for the isolation of *T. vaginalis.*

Women who had bacterial vaginosis on screening were considered for randomization. Those who had both bacterial vaginosis and *T. vaginalis* were ineligible for the trial and instead were assigned to a parallel, ongoing trial of the treatment of *T. vaginalis* infection. Women were eligible for randomization if they had pregnancies that were between 16 weeks 0 days and 23 weeks 6 days and had none of the exclusion criteria. Women were ineligible if they had received any antibiotics since screening, if the time between screening and randomization exceeded eight weeks, or if their tests for syphilis or gonorrhea (or *Chlamydia trachomatis,* if testing was done routinely at that time of gestation) were positive. The study was approved by the institutional review boards of the clinical sites, and all the women gave written informed consent before randomization.

Randomization and Follow-up Visits

The women underwent ultrasonography, if they had not already done so, to confirm the gestational age of the fetus, as estimated from the last menstrual period. At randomization, vaginal samples were obtained for measurement of pH, for Gram's staining, and for *T. vaginalis* cultures; the results were reported to the biostatistical coordinating center but not to the clinical site.

After these specimens were obtained, the women were randomly assigned in a double-blind manner to receive eight capsules, each of which contained either 250 mg of metronidazole or a lactose placebo. The capsules were prepared by placing either a generic metronidazole tablet or a placebo tablet in a capsule and filling the remainder with lactose, so that they were identical in appearance. The capsules were ingested in the presence of study personnel. The women were given an additional eight capsules that contained the same substance as previously assigned, to be taken 48 hours later. In a meta-analysis, a similar two-dose regimen was found to have an effectiveness similar to that of the standard seven-day regimen of metronidazole,[17] and in a pilot study we found that this regimen reduced the Gram's-staining score to less than 7 in 100 percent of 33 women and to 4 or less in 89 percent of the women. The urn method of randomization,[18] with stratification according to clinical center, was used to create the computer-generated randomization sequence.

One follow-up visit was scheduled between 24 weeks 0 days of gestation and 29 weeks 6 days of gestation, at least 14 days after the initial visit. The types of specimens that were collected at the base-line visit were collected again at the follow-up visit. The personnel in the clinic were again unaware of the results of the assays. All women were treated again with the same two-dose regimen received initially, regardless of the results of follow-up Gram's staining. Study personnel questioned the women about whether they had taken the second dose, which was to be taken 48 hours after the initial dose; about any side effects of the first two doses; and about whether they had received clinically indicated antibiotics after randomization.

TABLE 1. SCORING OF GRAM'S STAINS.*

MORPHOLOGIC TYPE†	QUANTITY‡	SCORE
Large gram-positive rods	4+	0
	3+	1
	2+	2
	1+	3
	0	4
Small gram-variable or gram-negative rods	0	0
	1+	1
	2+	2
	3+	3
	4+	4
Long, curved gram-variable rods	0	0
	1+ or 2+	1
	3+ or 4+	2

*The method used was that described in Nugent et al.[16]

†A gram-variable rod is a bacterial morphotype that is not consistently gram-positive or gram-negative.

‡Five oil-immersion fields were examined. The score 4+ denotes more than 30 per oil-immersion field, 3+ denotes 5 to 30 per oil-immersion field, 2+ denotes 1 to 4 per oil-immersion field, 1+ denotes fewer than 1 per oil-immersion field, and 0 denotes none seen.

Assessment of Outcome

The gestational age of the fetus at the time of randomization was determined from the last menstrual period, provided that the estimate based on the last menstrual period and the estimate based on the ultrasound results agreed within 7 days, if ultrasonography was performed at less than 20 weeks' gestation, or within 14 days, if it was performed at or after 20 weeks' gestation. When there was disagreement between the two estimates, gestational age at randomization was determined from the results of the first ultrasonographic study performed during pregnancy, and gestational age at delivery was determined from the length of time between randomization and delivery. Preterm birth was defined as delivery at less than 37 completed weeks (259 days) of gestation.

In addition to the base-line and follow-up visits, the women received the usual prenatal care at their institutions. After delivery,

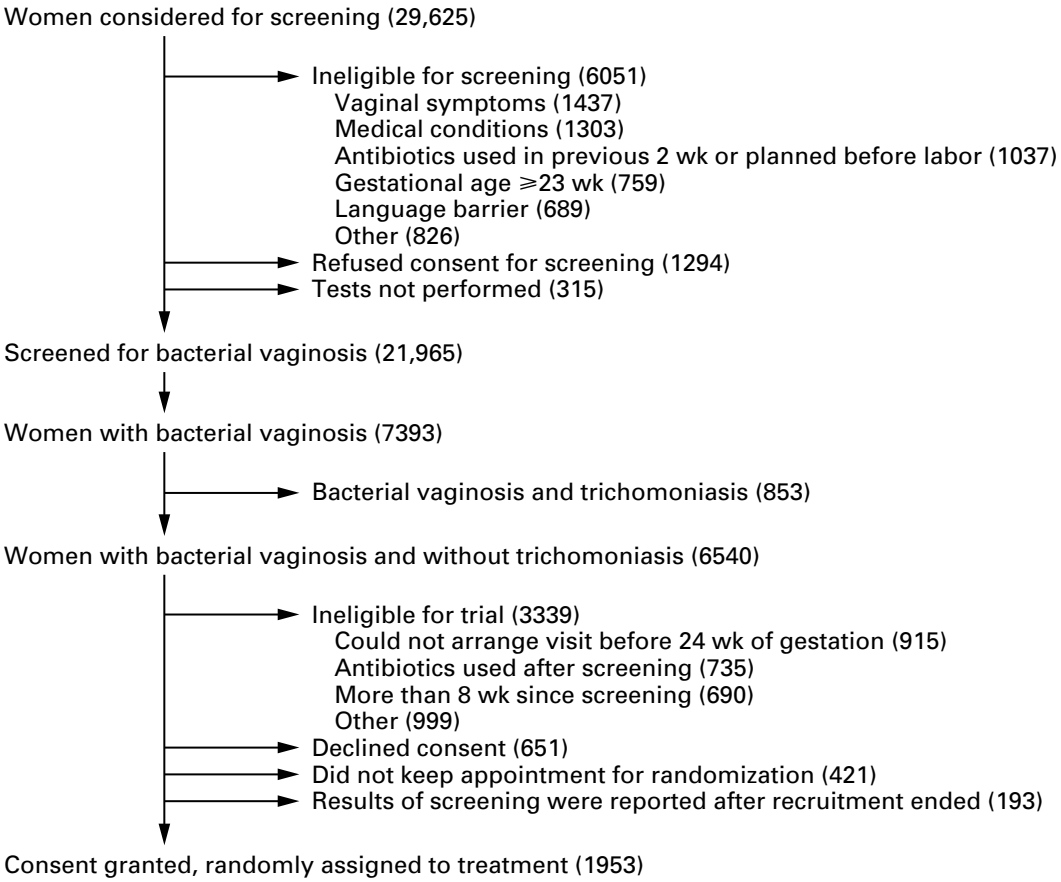

Figure 1. Summary of Screening and Randomization.

The number of women who granted consent and were randomly assigned to treatment (1953) includes 17 women who underwent randomization in error: 10 who did not have bacterial vaginosis and 7 who had both bacterial vaginosis and trichomoniasis at screening.

study personnel reviewed all prenatal, delivery, and postpartum records and abstracted the date of delivery, birth weight of the infant, and details of any antibiotic therapy received after randomization through the postpartum period and the dates of and indications for the therapy. Also noted were visits and admissions to the hospital, preterm labor, the use of tocolytic drugs, preterm premature rupture of the membranes (at least one hour before the onset of labor and before 37 weeks' gestation), clinical intraamniotic infection, postpartum endometritis, and neonatal sepsis.

Statistical Analysis

We compared continuous variables using the Wilcoxon rank-sum test and compared categorical variables using chi-square or Fisher's exact tests. Prolongation of pregnancy was assessed by life-table methods, with women entering the life table at the gestational age at randomization and continuing until they gave birth, were lost to follow-up, or reached 37 weeks' gestation, whichever came first. Event-free survival curves were estimated with use of the Kaplan–Meier method, with adjustment to account for differing gestational ages at entry.[19] The statistical significance of the difference between the survival curves was assessed with use of the proportional-hazards-model score function test. Before the study started, the group sequential method of Lan and DeMets with the modified O'Brien–Fleming spending function was chosen for the adjustment of the significance level in interim analyses.[20] Two interim analyses were performed, with data corresponding to 14 percent and 49 percent of the total planned sample. Therefore, in the final analysis of preterm delivery, two-tailed P values of 0.049 or less, rather than 0.05 or less, were considered significant. For other comparisons, a P value of 0.05 or less was considered significant. An independent data and safety monitoring committee reviewed the interim results.

RESULTS

A total of 29,625 women were considered for a screening examination from May 30, 1995, through January 5, 1998 (Fig. 1). Of these, 21,965 women completed the screening examination, 6540 had bacterial vaginosis without trichomoniasis, and 1953 were randomly assigned to receive placebo or metronidazole. The characteristics of the women in the two groups were similar (Table 2). Data on the week of gestation at delivery were missing for 34 women (1.7 percent), 13 in the metronidazole group and 21 in the placebo group ($P=0.19$).

Compliance and Side Effects

A full course of treatment consisted of 32 capsules divided into four doses; women who did not com-

TABLE 2. BASE-LINE CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	METRONIDAZOLE GROUP (N=966)	PLACEBO GROUP (N=987)
Gram's-staining score at screening — no. (%)		
<7†	5 (0.5)	5 (0.5)
7	124 (12.8)	113 (11.4)
8	355 (36.7)	392 (39.7)
9	132 (13.7)	125 (12.7)
10	350 (36.2)	352 (35.7)
Race or ethnic group — no. (%)		
Black	678 (70.2)	679 (68.8)
Non-Hispanic white	144 (14.9)	146 (14.8)
Hispanic and other	144 (14.9)	162 (16.4)
Marital status — no. (%)		
Never married	596 (61.7)	587 (59.5)
Married or living with partner	317 (32.8)	342 (34.7)
Divorced, widowed, or separated	53 (5.5)	58 (5.9)
Nulliparous — no. (%)	436 (45.1)	407 (41.2)
Previous preterm delivery — no. (%)	103 (10.7)	110 (11.1)
Prepregnancy weight <50 kg — no. (%)‡	99 (10.3)	117 (12.1)
Smoking during pregnancy — no. (%)	176 (18.2)	193 (19.6)
Bacterial vaginosis persisted until randomization — no. (%)	728 (75.4)	771 (78.1)
Trichomonas vaginalis infection at randomization — no. (%)	40 (4.1)	41 (4.2)
Age — yr	23±6	23±5
Prepregnancy weight — kg	70.7±18.9	70.6±20.0
Educational level — yr	12±2	12±2
Week of gestation at randomization	19.5±2.5	19.8±2.6

*Plus–minus values are means ±SD.

†Ten women without bacterial vaginosis (five in the metronidazole group and five in the placebo group) were randomized in error.

‡Data on prepregnancy weight were available for 957 women in the metronidazole group and 970 women in the placebo group.

plete the follow-up visit were assumed to have taken no doses after the first. Because the women were not contacted after the follow-up visit, information was not collected regarding compliance with respect to the final (fourth) 2-g dose. For the first three doses, the mean number of capsules taken by the women for whom this information was available was 21.4 in the metronidazole group and 21.7 in the placebo group (P=0.12). All 24 capsules in the first three doses were taken by 78.8 percent of the women in the metronidazole group and 81.8 percent of the women in the placebo group; no women in the metronidazole group and only one in the placebo group did not take any capsules.

A total of 1757 of the 1953 women (90.0 percent) returned for the follow-up visit and provided information on side effects. The reasons for failure to return were loss of contact (114 women), a decision by the woman not to continue in the study (38 women), delivery before the scheduled visit (27 women), and miscellaneous reasons (17 women); there was no significant difference between the groups in the proportion of women who did not have a follow-up visit. Side effects were significantly more common in the metronidazole group (21.6 percent) than in the placebo group (9.1 percent). This finding was attributable primarily to a higher rate of gastrointestinal symptoms (19.7 percent vs. 7.5 percent), particularly vomiting (9.7 percent vs. 2.8 percent), in the metronidazole group. A total of 12.0 percent of the women assigned to metronidazole and 4.9 percent of those assigned to placebo were treated for vaginal yeast infections with topical antifungal drugs (P<0.001).

Occurrence of Preterm Delivery

Outcome data were available for 1919 of the 1953 women (98.3 percent) (Table 3). The frequency of delivery before 37 weeks' gestation did not differ significantly between the metronidazole group and the placebo group (relative risk in the metronidazole group, 1.0; 95 percent confidence interval, 0.8 to 1.2). Similarly, there were no significant differences between the groups in terms of the rate of delivery before 35 or 32 weeks' gestation. The two groups did not differ significantly with regard to low birth weight (<2500 g), very low birth weight (<1500 g), or preterm delivery attributable to spontaneous labor or spontaneous rupture of the membranes. The placebo group and the metronidazole group were compared in a survival analysis (Fig. 2). Additional analyses did not identify any subgroup of women in whom metronidazole significantly reduced the occurrence of preterm delivery (Table 4).

Effectiveness of Treatment

Among the women who had follow-up Gram's staining after the first course of treatment, bacterial vaginosis was still present in 188 of 845 women in the metronidazole group (22.2 percent) and 538 of 859 women in the placebo group (62.6 percent). Among the 1687 women in both groups who had follow-up Gram's staining and for whom information on delivery was available, preterm birth occurred in 77 of 718 women who had bacterial vaginosis at follow-up (10.7 percent) and 103 of 969 women whose bacterial vaginosis remitted (10.6 percent) (P=0.95), regardless of treatment.

Other Pregnancy-Related and Neonatal Complications

Treatment with metronidazole did not reduce the occurrence of admission to the hospital for preterm labor or preterm premature rupture of membranes, receipt of tocolytic drugs, vaginal infections that required treatment, clinical intraamniotic infection, or postpartum endometritis (data not shown). The groups did not differ significantly with regard to the passage of meconium, fetal death or neonatal death during the stay in the nursery, admission to the neonatal intensive care unit, or the presence of neonatal sepsis (data not shown).

TABLE 3. PREGNANCY OUTCOMES ACCORDING TO TREATMENT GROUP.

OUTCOME*	METRONIDAZOLE GROUP (N=953)	PLACEBO GROUP (N=966)	RELATIVE RISK (95% CI)†
	no. (%)		
Delivery before 37 weeks	116 (12.2)	121 (12.5)	1.0 (0.8–1.2)
Due to spontaneous preterm labor	49 (5.1)	55 (5.7)	0.9 (0.6–1.3)
Due to spontaneous rupture of the membranes	40 (4.2)	36 (3.7)	1.1 (0.7–1.8)
Indicated because of complications	26 (2.7)	28 (2.9)	0.9 (0.6–1.6)
Reason unknown	1 (0.1)	2 (0.2)	
Delivery before 35 wk	48 (5.0)	49 (5.1)	1.0 (0.7–1.5)
Delivery before 32 wk	22 (2.3)	26 (2.7)	0.9 (0.5–1.5)
Birth weight less than 2500 g	103 (10.9)	109 (11.4)	1.0 (0.7–1.2)
Birth weight less than 1500 g	19 (2.0)	26 (2.7)	0.7 (0.4–1.3)

*Data on birth weight were available for the neonates of 943 women in the metronidazole group and 956 women in the placebo group.

†CI denotes confidence interval.

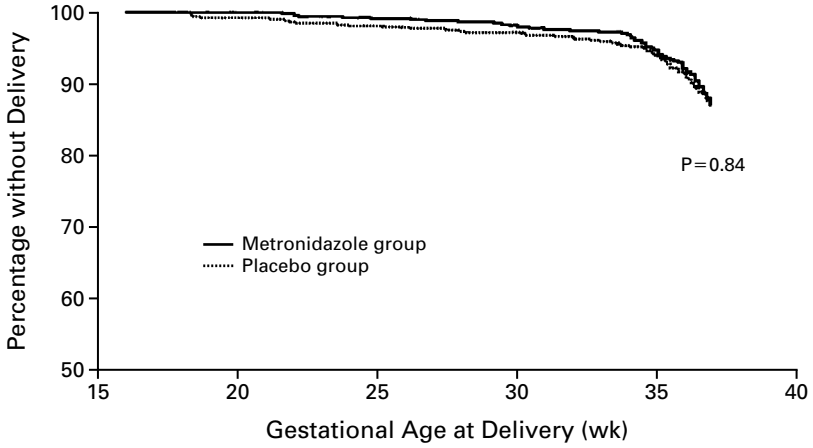

Figure 2. Gestational Age at Delivery, According to Treatment Group.

DISCUSSION

In this clinical trial, the treatment of asymptomatic bacterial vaginosis with metronidazole did not reduce the risk of preterm delivery in women at low risk for preterm delivery or women with a history of preterm delivery. Our results agree with those of McDonald et al.,[12] who also reported no reduction in the risk of preterm delivery among pregnant women with bacterial vaginosis who were treated with metronidazole. However, our results with regard to women with a prior preterm delivery disagree with those of several other studies, all of which found a lower risk of recurrent preterm delivery among women with bacterial vaginosis who were treated with metronidazole[11,12] or metronidazole and erythromycin[13] than among those who received placebo. However, our study differs from the others in several ways. Two studies were of women with previous preterm delivery,[11,13] whereas we studied a general obstetrical population; in the third study, bacterial vaginosis was diagnosed on the basis of a positive culture of *Gardnerella vaginalis* rather than Gram's staining.[12]

Several criticisms might be made of our study. The therapy consisted of a short course of metronidazole — two 2-g doses taken 48 hours apart at randomization and two more doses at 24 to less than 30 weeks' gestation. We chose this regimen to improve compliance; at least half the therapy could be given in the presence of study personnel. In contrast to our regimen of four 2-g doses, the regimens of metronidazole used in other studies were administered over four days[12] or seven days.[11,13] Our regimen was similar in efficacy to that used in the other studies in treating bacterial vaginosis, but a longer course

TABLE 4. RATE OF DELIVERY BEFORE 37 WEEKS' GESTATION ACCORDING TO SELECTED CHARACTERISTICS.

CHARACTERISTIC	METRONIDAZOLE GROUP	PLACEBO GROUP	RELATIVE RISK (95% CI)*
	no. with preterm delivery/total no. (%)		
Previous preterm delivery	30/101 (29.7)	26/109 (23.9)	1.3 (0.8–2.0)
Previous spontaneous preterm delivery	24/80 (30.0)	18/80 (22.5)	1.3 (0.8–2.3)
Duration of pregnancy at randomization			
<20 wk	71/545 (13.0)	77/522 (14.8)	0.9 (0.7–1.2)
≥20 wk	45/408 (11.0)	44/444 (9.9)	1.1 (0.8–1.7)
Race or ethnic group			
Black	87/670 (13.0)	93/668 (13.9)	0.9 (0.7–1.2)
Non-Hispanic white	19/142 (13.4)	12/142 (8.5)	1.6 (0.8–3.1)
Hispanic and other	10/141 (7.1)	16/156 (10.3)	0.7 (0.3–1.5)
Prepregnancy weight <50 kg	22/98 (22.4)	16/116 (13.8)	1.6 (0.9–2.9)
Bacterial vaginosis at randomization	86/719 (12.0)	93/757 (12.3)	1.0 (0.7–1.3)
Trichomonas vaginalis infection at randomization	10/39 (25.6)	8/41 (19.5)	1.3 (0.6–3.0)
Did not receive clinically indicated antibiotics that are effective against bacterial vaginosis†	86/795 (10.8)	86/777 (11.1)	1.0 (0.7–1.3)
Bacterial vaginosis at randomization, took 24 capsules, and did not receive clinically indicated antibiotics that are effective against bacterial vaginosis†	46/485 (9.5)	42/509 (8.3)	1.1 (0.8–1.7)

*CI denotes confidence interval.

†The antibiotics were systemic or topical metronidazole or clindamycin, systemic ampicillin or amoxicillin, or a topical sulfonamide, given for any clinical reason outside of the trial.

might be needed to eradicate organisms from the upper genital tract. Alternatively, an additional antibiotic that has antiinflammatory properties or a different spectrum of activity, such as erythromycin, might be required to reduce the risk of preterm birth.

The administration of therapy earlier or later in pregnancy might have produced different results, because the intrauterine infection associated with bacterial vaginosis may antedate the pregnancy.[21] We chose to treat early in the second trimester to avoid fetal exposure to metronidazole in the first trimester and to repeat the regimen late in the second trimester or early in the third trimester so as to spread treatment over as wide a period as practical. There was no difference in the benefit of treatment between women treated before 20 weeks' gestation and those treated at or after 20 weeks, which is when the membranes seal the uterus closed,[21] and there was no reduction in the occurrence of delivery at less than 32 weeks' gestation, which is closest to the time treatment was administered. These findings suggest that our timing of treatment was appropriate.

Our results show that screening pregnant women for asymptomatic bacterial vaginosis and treating the condition with a short course of orally administered metronidazole did not reduce the risk of preterm birth despite its effectiveness in eradicating bacterial vaginosis. Although the literature consistently indicates that intrauterine infection and bacterial vaginosis are associated with preterm delivery,[3-10] the results of our study do not support the use of metronidazole to prevent preterm delivery among pregnant women with asymptomatic bacterial vaginosis, regardless of whether they are otherwise considered at either high or low risk for preterm delivery.

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APPENDIX

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