

FAILURE OF METRONIDAZOLE TO PREVENT PRETERM DELIVERY AMONG PREGNANT WOMEN WITH ASYMPTOMATIC *TRICHOMONAS VAGINALIS* INFECTION

MARK A. KLEBANOFF, M.D., M.P.H., J. CHRISTOPHER CAREY, M.D., JOHN C. HAUTH, M.D., SHARON L. HILLIER, PH.D.,
ROBERT P. NUGENT, PH.D., M.P.H., ELIZABETH A. THOM, PH.D., J.M. ERNEST, M.D., R. PHILLIP HEINE, M.D.,
RONALD J. WAPNER, M.D., WAYNE TROUT, M.D., ATEF MOAWAD, M.D., KENNETH J. LEVENO, M.D.,
AND THE NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT NETWORK
OF MATERNAL-FETAL MEDICINE UNITS*

ABSTRACT

Background Infection with *Trichomonas vaginalis* during pregnancy has been associated with preterm delivery. It is uncertain whether treatment of asymptomatic trichomoniasis in pregnant women reduces the occurrence of preterm delivery.

Methods We screened pregnant women for trichomoniasis by culture of vaginal secretions. We randomly assigned 617 women with asymptomatic trichomoniasis who were 16 to 23 weeks pregnant to receive two 2-g doses of metronidazole (320 women) or placebo (297 women) 48 hours apart. We treated women again with the same two-dose regimen at 24 to 29 weeks of gestation. The primary outcome was delivery before 37 weeks of gestation.

Results Between randomization and follow-up, trichomoniasis resolved in 249 of 269 women for whom follow-up cultures were available in the metronidazole group (92.6 percent) and 92 of 260 women with follow-up cultures in the placebo group (35.4 percent). Data on the time and characteristics of delivery were available for 315 women in the metronidazole group and 289 women in the placebo group. Delivery occurred before 37 weeks of gestation in 60 women in the metronidazole group (19.0 percent) and 31 women in the placebo group (10.7 percent) (relative risk, 1.8; 95 percent confidence interval, 1.2 to 2.7; $P=0.004$). The difference was attributable primarily to an increase in preterm delivery resulting from spontaneous preterm labor (10.2 percent vs. 3.5 percent; relative risk, 3.0; 95 percent confidence interval, 1.5 to 5.9).

Conclusions Treatment of pregnant women with asymptomatic trichomoniasis does not prevent preterm delivery. Routine screening and treatment of asymptomatic pregnant women for this condition cannot be recommended. (N Engl J Med 2001;345:487-93.)
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INFECTION with *Trichomonas vaginalis* has been associated with an increase in adverse outcomes of pregnancy. In the Vaginal Infections and Prematurity Study, pregnant women colonized with *T. vaginalis* had a 30 percent higher risk of delivering an infant with low birth weight or delivering before term, a 40 percent higher risk of giving birth to an infant who was both preterm and of

low birth weight, and nearly twice the risk of stillbirth or neonatal death, as compared with women without *T. vaginalis* colonization.¹ Eleven percent of preterm deliveries among African-American women have been considered potentially attributable to trichomoniasis.¹ Trichomoniasis during pregnancy has been associated with reduced infant birth weight and preterm delivery among pregnant adolescents² and with preterm rupture of the amniotic membranes.^{3,4}

It is not known whether treatment of asymptomatic trichomoniasis during pregnancy reduces the occurrence of preterm delivery or other adverse outcomes. One observational study noted similar rates of preterm delivery among 597 pregnant women with trichomoniasis, regardless of whether they were treated with a 7- or 10-day course of metronidazole or were not treated⁵; however, untreated women were more likely to be asymptomatic than treated women. Although there have been no large, randomized clinical trials of treatment of trichomoniasis during pregnancy, screen-

From the National Institute of Child Health and Human Development, Bethesda, Md. (M.A.K., R.P.N.); the Department of Obstetrics and Gynecology, University of Oklahoma, Oklahoma City (J.C.C.); the Department of Obstetrics and Gynecology, University of Alabama at Birmingham, Birmingham (J.C.H.); the Department of Obstetrics, Gynecology, and Reproductive Sciences, University of Pittsburgh, Pittsburgh (S.L.H., R.P.H.); the Biostatistics Center, George Washington University, Rockville, Md. (E.A.T.); the Department of Obstetrics and Gynecology, Wake Forest University School of Medicine, Winston-Salem, N.C. (J.M.E.); the Department of Obstetrics and Gynecology, Thomas Jefferson University, Philadelphia (R.J.W.); the Department of Obstetrics and Gynecology, Ohio State University, Columbus (W.T.); the Department of Obstetrics and Gynecology, University of Chicago, Chicago (A.M.); and the Department of Obstetrics and Gynecology, University of Texas Southwestern Medical Center, Dallas (K.J.L.). Address reprint requests to Dr. Klebanoff at the National Institute of Child Health and Human Development, 6100 Executive Blvd., Rm. 7B05, MSC 7510, Bethesda, MD 20892-7510, or at mk90h@nih.gov.

Other authors were Menachem Miodovnik, M.D., Department of Obstetrics and Gynecology, University of Cincinnati, Cincinnati; Baha M. Sibai, M.D., Department of Obstetrics and Gynecology, University of Tennessee, Memphis; J. Peter Van Dorsten, M.D., Department of Obstetrics and Gynecology, Medical University of South Carolina, Charleston; Mitchell P. Dombrowski, M.D., Department of Obstetrics and Gynecology, Wayne State University, Detroit; Mary J. O'Sullivan, M.D., Department of Obstetrics and Gynecology, University of Miami, Miami; Michael Varner, M.D., Department of Obstetrics and Gynecology, University of Utah, Salt Lake City; Oded Langer, M.D., Department of Obstetrics and Gynecology, University of Texas, San Antonio; Donald McNellis, M.D., National Institute of Child Health and Human Development, Bethesda, Md.; and James M. Roberts, M.D., Department of Obstetrics, Gynecology, and Reproductive Sciences, University of Pittsburgh, Pittsburgh.

*Other members of the Network of Maternal-Fetal Medicine Units are listed in the Appendix.

ing and treatment for this infection during pregnancy have been recommended.⁶ We conducted a randomized clinical trial of metronidazole in pregnant women with asymptomatic trichomoniasis to assess whether therapy would reduce the risk of preterm delivery.

METHODS

Subjects and Screening

At 15 participating sites, we screened women from 8 weeks, 0 days, to 22 weeks, 6 days, of gestation for bacterial vaginosis and *T. vaginalis*. Women were excluded who reported any of the following: increased vaginal discharge with itching, burning, or vaginal odor; allergy to metronidazole; current ethanol abuse; antibiotic therapy within the previous 14 days; an intention to receive antenatal care or give birth at a location where the follow-up visit could not be completed or information on the delivery could not be obtained; a language barrier precluding informed consent; 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 the presence of a known life-threatening congenital anomaly; multifetal gestation; or medical illness (such as hypertension, preexisting diabetes mellitus, or asthma) requiring long-term or intermittent drug therapy.

Because it is more sensitive than a wet preparation of vaginal secretions, culture was used to screen for *T. vaginalis*.⁷ A Dacron swab was placed at the junction of the upper one third and the lower two thirds of the lateral vaginal wall and was used to inoculate modified Diamond's medium (PML Microbiologicals, Warwick, R.I.) for the isolation of *T. vaginalis*. After inoculation, the specimens were left at room temperature for up to eight hours before placement in an incubator at 37°C. A drop of the medium was evaluated microscopically each day for motile trichomonads until a positive result was obtained or for up to five days. A second swab was evaluated for bacterial vaginosis by pH and Gram's staining.^{8,9}

Women were eligible for randomization if they had a positive culture for *T. vaginalis*; if they were between 16 weeks, 0 days, and 23 weeks, 6 days, of gestation; and if they met none of the exclusion criteria. Women were ineligible for randomization if they had received any antibiotics since screening, if the time between screening and randomization exceeded eight weeks, or if they were positive for syphilis or gonorrhea (or for *Chlamydia trachomatis* if the test was routinely performed at their stage of gestation). The study was approved by the institutional review boards of the clinical sites, and all women gave written informed consent before randomization.

Randomization and Follow-up Visits

Women underwent ultrasonography, if they had not already done so, to confirm the gestational age of the fetus as estimated on the basis of the last menstrual period. At randomization, vaginal samples were obtained again for Gram's staining, culture for *T. vaginalis*, and measurement of pH. A urine sample was obtained for the detection of *C. trachomatis* by the ligase chain reaction. The results of these tests were reported to the biostatistical coordinating center, but not to the clinical sites, and they did not influence randomization.

After specimens were obtained, the women were randomly assigned in a double-blind manner to receive eight capsules containing either 250 mg of generic metronidazole each or a lactose placebo. The capsules were prepared by placing either a metronidazole 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, containing the same substance as previously assigned, to take 48 hours later. The sexual partners of the women in both the treatment and the placebo groups were pre-

scribed a single 2-g dose of metronidazole, and the women were given a supply of condoms and instructed to have their partners use them for the duration of the treatment regimen (i.e., until the second dose had been taken). The urn method of randomization,¹⁰ with stratification according to clinical center, was used to create the computer-generated randomization sequence.

One follow-up study visit was completed between 24 weeks, 0 days, and 29 weeks, 6 days, of gestation and at least 14 days after the initial visit. At this visit, the specimens were collected in the same way as at the first visit. To maintain blinding, the clinic staff were kept unaware of the results of the assays. Study personnel asked the women about their adherence to the instructions for the second dose (at 48 hours after randomization), whether they had side effects from the first dose, and whether they had taken other antibiotics after randomization. All the women were treated again with the same two-dose regimen received initially.

Assessment of Outcomes

The length of gestation at randomization was determined from the last menstrual period, provided that ultrasonography confirmed that estimate within 7 days if it was performed at less than 20 weeks of gestation, or within 14 days if it was performed at or after 20 weeks of gestation. When there was discordance between the menstrual and sonographic estimates, the duration of gestation at randomization was determined from the first sonogram. The duration of gestation at delivery was determined calculating the elapsed time from randomization to delivery. Preterm birth was defined as delivery at less than 37 completed weeks (259 days) of gestation.

With the exception of the two extra visits for randomization and follow-up, women received the usual prenatal care at their institutions. After delivery, study personnel reviewed prenatal, delivery, and postpartum medical records for the following information: date of delivery; infant's birth weight; any antibiotics prescribed after randomization through the postpartum period, and the dates and indications for therapy; any hospital visits and admissions for preterm labor not resulting in delivery; any use of tocolytic drugs; presence or absence of preterm rupture of the membranes (membrane rupture at least one hour before the onset of labor and before 37 weeks of gestation); any occurrence of clinical intraamniotic infection (indicated by fever and uterine tenderness without other known infection); any occurrence of postpartum endometritis; and any suspected or confirmed neonatal sepsis.

Statistical Analysis

Continuous variables were compared with use of the Wilcoxon rank-sum test, and categorical variables with use of the chi-square or Fisher's exact test. Prolongation of pregnancy was assessed by life-table methods. Data were included from the time of randomization until the women gave birth, were lost to follow-up, or reached 37 weeks of gestation. Event-free survival curves were estimated by the Kaplan-Meier method, with adjustment for the duration of gestation at entry.¹¹ The statistical significance of this comparison 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 to adjust the significance level of interim analyses.¹² Four interim analyses were performed, on data sets corresponding to 4.3 percent, 15.7 percent, 24.8 percent, and 27.2 percent of the total planned sample size of 1900. This sample size was calculated on the basis of an 80 percent power to detect a reduction of 30 percent or more in the rate of preterm delivery with active treatment. According to this monitoring plan, the critical z score for stopping the study at the fourth analysis was 4.17, which corresponds to a P value of 0.00002. However, the independent data and safety monitoring committee reviewed the interim results and recommended that recruitment cease in January 1999, before the planned enrollment target was reached. This recommendation was based on the slow rate of accrual of subjects and the unexpected but consistent increase in the risk of preterm delivery in the metronidazole group. The Biostatistics Center of George Wash-

ington University maintained the data and performed the statistical analyses.

RESULTS

From May 1995 to January 1999, 40,857 women were considered for a screening examination at the 15 centers participating in the study. Of these, 7768 women were ineligible, 1711 refused consent, and tests were not performed on 221, so that 31,157 were screened. There were 2377 women found to have *T. vaginalis* infection (7.6 percent); 617 were eligible and consented to participate, of whom 320 were randomly assigned to receive metronidazole and 297

to receive placebo. Details of the screening are provided in Figure 1. The characteristics of the two groups of women are presented in Table 1. The groups were similar in terms of all characteristics listed in Table 1. Information on the length of gestation at delivery was missing for 13 women (2.1 percent): 5 in the metronidazole group and 8 in the placebo group (P=0.33).

Compliance and Side Effects

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

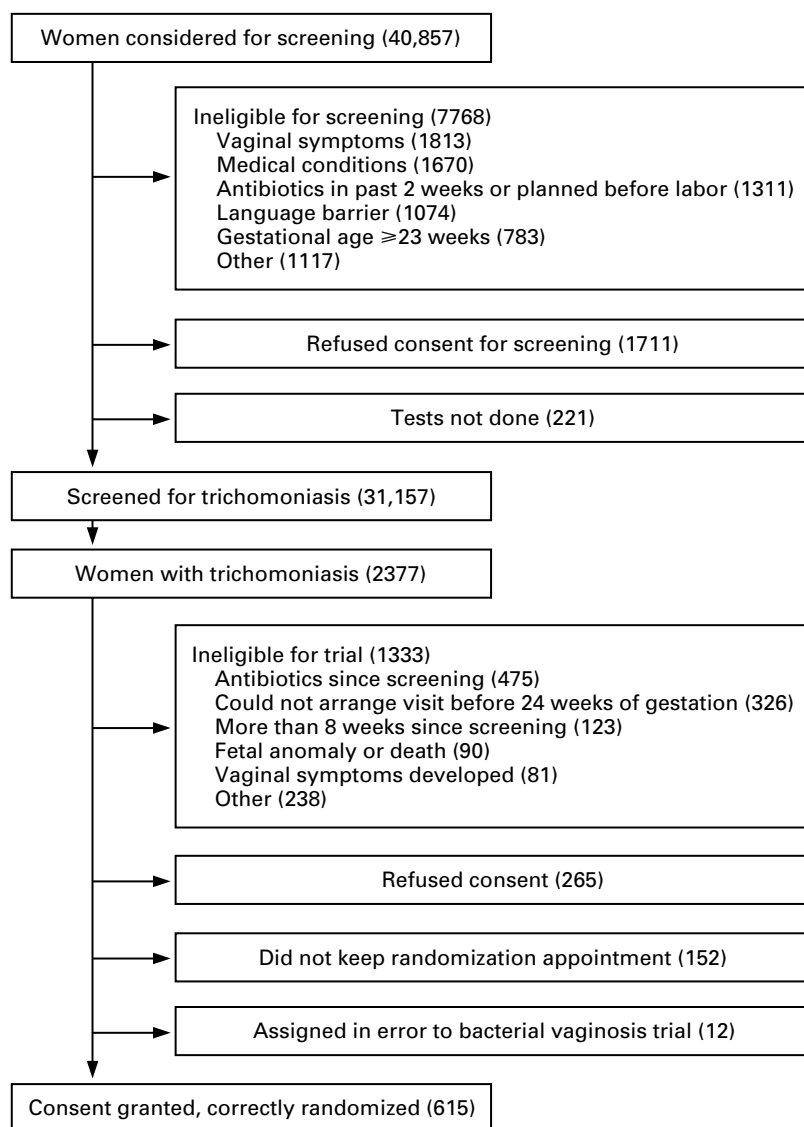


Figure 1. Women Screened and Randomly Assigned to Metronidazole or Placebo. A total of 617 women underwent randomization, including 2 who did not actually have trichomoniasis and were enrolled in error.

TABLE 1. CHARACTERISTICS OF THE 617 WOMEN AT RANDOMIZATION.*

CHARACTERISTIC	METRONIDAZOLE (N=320)	PLACEBO (N=297)
Race or ethnic group — no. (%)†		
Black	289 (90.3)	267 (89.9)
Non-Hispanic white	15 (4.7)	18 (6.1)
Hispanic and other	16 (5.0)	12 (4.0)
Marital status — no. (%)		
Never married	247 (77.2)	225 (75.8)
Married, living with partner	61 (19.1)	56 (18.9)
Divorced, widowed, or separated	12 (3.8)	16 (5.4)
Nulliparous — no. (%)	154 (48.1)	137 (46.1)
Previous preterm delivery — no. (%)	34 (10.6)	30 (10.1)
Weight before pregnancy <50 kg — no. (%)	36 (11.2)	30 (10.1)
Smoked during pregnancy — no. (%)	59 (18.4)	57 (19.2)
Bacterial vaginosis present — no. (%)‡	120/318 (37.7)	114/294 (38.8)
<i>Trichomonas vaginalis</i> present — no. (%)‡	229/319 (71.8)	209/296 (70.6)
<i>Chlamydia trachomatis</i> present — no. (%)‡	41/294 (13.9)	33/266 (12.4)
Age — yr	22.9±5.4	22.7±5.8
Weight before pregnancy — kg	71.2±19.0	72.7±20.9
Years of education	11.6±1.6	11.5±1.6
Length of gestation — wk	19.6±2.5	19.8±2.6

*Plus-minus values are means ±SD.

†Information on race or ethnic group was abstracted from medical records in almost all cases; in the remainder the women themselves were asked.

‡Denominators indicate the number of women in whom the given test was performed.

plete the follow-up visit were assumed to have taken no doses beyond the first. Since women were not contacted after the follow-up visit, information was not collected regarding compliance with the final (fourth) 2-g dose. The mean number of capsules taken of the maximum of 24 for which information was collected was 21.2 in the metronidazole group and 21.9 in the placebo group ($P=0.21$). All 24 capsules were taken by 79.7 percent of women in the metronidazole group and 83.2 percent of women in the placebo group; two women in the metronidazole group and none in the placebo group did not take any capsules.

In this study, 544 of the 617 women (88.2 percent) returned for the follow-up visit and provided information on side effects. The reasons for failure to return were loss of contact (47 women), delivery before the scheduled visit (16 women), refusal to continue in the study (8 women), and other reasons (2 women); there was no significant difference between the groups in the proportion of women who did not return for a follow-up visit. Side effects were significantly more common in the metronidazole

group (14.1 percent) than in the placebo group (6.4 percent, $P=0.003$). This difference was attributable primarily to an increase in gastrointestinal symptoms in the metronidazole group (13.0 percent vs. 5.2 percent).

Occurrence of Preterm Delivery

Outcome data, shown in Table 2, were available for 604 of the 617 women who underwent randomization (97.9 percent). Delivery before 37 weeks of gestation was more common among women assigned to metronidazole (relative risk, 1.8; 95 percent confidence interval, 1.2 to 2.7; $P=0.004$). Most of the difference between the groups was due to an increase in the rate of spontaneous preterm labor among women assigned to metronidazole (Table 2). A survival analysis comparing the week of gestation at delivery for women in the placebo and metronidazole groups is presented in Figure 2. Differences in the occurrence of preterm birth became most apparent for women in whom gestation lasted 34 to 36 weeks.

The association between metronidazole use and preterm delivery was consistent across many subgroups (Table 3), with the exception of women who had positive tests for *C. trachomatis* at randomization, among whom preterm delivery was nonsignificantly reduced with metronidazole treatment. Among women whose cultures for trichomoniasis were still positive at randomization, 46 of 226 in the metronidazole group and 22 of 204 in the placebo group gave birth at less than 37 weeks of gestation (relative risk, 1.9; 95 percent confidence interval, 1.2 to 3.0).

There were 544 women who completed the follow-up visit (88.2 percent of the women who underwent randomization), 529 of whom had follow-up cultures for *T. vaginalis*. The organism persisted in 64.6 percent of women assigned to placebo (168 of 260) and 7.4 percent of women assigned to metronidazole (20 of 269).

Other Pregnancy-Related and Neonatal Complications

Information on other pregnancy-related and neonatal complications is presented in Table 4. There were no significant differences between the metronidazole and placebo groups in the rates of hospital admission for preterm labor or membrane rupture, receipt of tocolytic drugs, clinical intraamniotic infection, or postpartum endometritis. There were also no significant differences between the groups in the rates of stillbirth or neonatal death during the nursery stay, admission to the neonatal intensive care unit, or neonatal sepsis.

Antimicrobial drugs, including topical vaginal antifungal drugs, were used before 37 weeks of gestation significantly less frequently by women in the metronidazole group than by those in the placebo group (31.6 percent vs. 46.2 percent, $P<0.001$). This difference was largely attributable to the use of metro-

TABLE 2. OUTCOMES OF PREGNANCY ACCORDING TO TREATMENT GROUP.

OUTCOME	METRONIDAZOLE (N=315)	PLACEBO (N=289)	RELATIVE RISK (95% CONFIDENCE INTERVAL)
	no. (%)		
Delivery at <37 wk*	60 (19.0)	31 (10.7)	1.8 (1.2–2.7)
Due to preterm labor	32 (10.2)	10 (3.5)	3.0 (1.5–5.9)
Due to membrane rupture	14 (4.4)	12 (4.2)	1.1 (0.5–2.3)
By induction of labor or cesarean section without labor	11 (3.5)	8 (2.8)	1.3 (0.5–3.1)
Delivery at <35 wk	27 (8.6)	19 (6.6)	1.3 (0.7–2.3)
Delivery at <32 wk	16 (5.1)	11 (3.8)	1.3 (0.6–2.8)
Infant's birth weight <2500 g	51 (16.2)	34 (11.8)	1.4 (0.9–2.1)
Infant's birth weight <1500 g	17 (5.4)	11 (3.8)	1.4 (0.7–3.0)

*The reason for preterm delivery was unknown for four women (three in the metronidazole group and one in the placebo group).

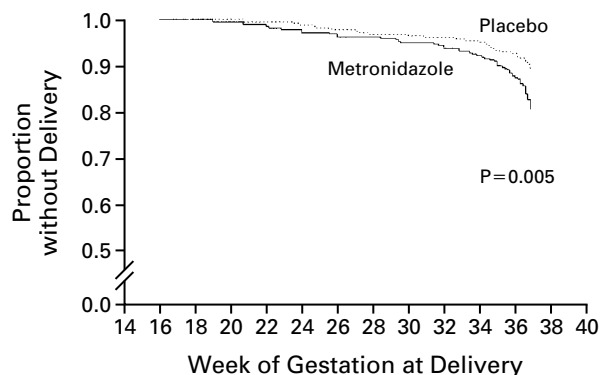


Figure 2. Length of Gestation at Delivery According to Treatment Group.

nidazole, which was administered for various clinical indications outside the study to 11.9 percent of women assigned to metronidazole and 26.2 percent of women assigned to placebo ($P < 0.001$); 7.7 percent of women in the metronidazole group and 22.7 percent of women in the placebo group were treated specifically for trichomoniasis ($P < 0.001$). There was a trend toward more treatment for vaginal fungal infections in the metronidazole group (10.3 percent) than in the placebo group (6.6 percent, $P = 0.11$).

DISCUSSION

Treatment of asymptomatic pregnant women colonized with *T. vaginalis* effectively eliminated the or-

ganism, but it was ineffective in preventing preterm delivery and may have increased the risk as compared with that in the placebo group. Although this unanticipated result had a nominal P value of considerably less than 0.05, the test statistic did not cross pre-defined stopping boundaries and is equivalent to a final alpha level of 0.20. Nevertheless, the data and safety monitoring board was sufficiently concerned about this increased risk to recommend cessation of recruitment.

One possible explanation for our findings is that dying *T. vaginalis* organisms elicit an inflammatory response that triggers preterm labor. The last treatment was administered at less than 30 weeks of gestation, and the greatest increase in preterm delivery was at 35 and 36 weeks. The apparent absence of an immediate effect suggests that this mechanism is unlikely, however, and also suggests it is unlikely that metronidazole itself triggers preterm labor. Lysis of *T. vaginalis* might release a pathogenic virus. Some strains of *T. vaginalis* have been reported to carry viruses, and herpes simplex virus type 2 has been shown to survive within *T. vaginalis* organisms.¹³ However, the relation between genital viral infections and preterm delivery has not been well documented.

The risk of preterm delivery was not increased in previous clinical trials of metronidazole treatment of bacterial vaginosis during pregnancy.^{9,14-16} Our treatment regimen of 2-g doses of metronidazole given 48 hours apart is nonstandard, although it is similar to a regimen recommended for resistant cases of trichomoniasis.¹⁷ This regimen might have suppressed competing flora and allowed a particular pathogen to flourish. Because we did not see an increase in the risk of preterm delivery in our previous trial among women with bacterial vaginosis who did not also have trichomoniasis,⁹ such a pathogen would have to be associated specifically with *T. vaginalis*. We did not collect additional microbiologic data that could be used to evaluate this hypothesis.

Ninety percent of the women in this study were black, reflecting the quadrupled prevalence of trichomoniasis among black women, as compared with women of other racial or ethnic groups.¹⁸ We found a similar relative risk of preterm delivery among women of other groups who were randomly assigned to metronidazole, but our study included relatively small numbers of nonblack women.

Our results are consistent with the results of our previous clinical trial of metronidazole therapy for bacterial vaginosis⁹; in each of these studies, preterm delivery was more frequent among women with both bacterial vaginosis and trichomoniasis who were randomly assigned to receive metronidazole. An increase in the risk of preterm delivery has also been observed among pregnant women who had a prior preterm delivery¹⁹ or who had bacterial vaginosis^{20,21} and were treated with clindamycin cream, as compared with

TABLE 3. DELIVERY AT <37 WEEKS OF GESTATION ACCORDING TO TREATMENT GROUP AND SELECTED BASE-LINE CHARACTERISTICS.*

CHARACTERISTIC	PRETERM DELIVERY		RELATIVE RISK (95% CONFIDENCE INTERVAL)
	METRONIDAZOLE	PLACEBO	
	no./total no. (%)		
Previous preterm delivery	16/32 (50.0)	7/27 (25.9)	1.9 (0.9–4.0)
Previous spontaneous preterm delivery	15/26 (57.7)	6/21 (28.6)	2.0 (0.95–4.3)
No previous preterm delivery	44/283 (15.5)	24/262 (9.2)	1.7 (1.1–2.7)
Length of gestation at randomization			
<20 wk	35/171 (20.5)	16/150 (10.7)	1.9 (1.1–3.3)
≥20 wk	25/144 (17.4)	15/139 (10.8)	1.6 (0.9–2.9)
Race			
Black	55/287 (19.2)	28/262 (10.7)	1.8 (1.2–2.7)
Other	5/28 (17.9)	3/27 (11.1)	1.6 (0.4–6.0)
Weight before pregnancy			
<50 kg	13/35 (37.1)	1/28 (3.6)	10.4 (1.4–74.8)
≥50 kg	46/272 (16.9)	30/256 (11.7)	1.4 (0.9–2.2)
Bacterial vaginosis			
Present	31/119 (26.1)	16/113 (14.2)	1.8 (1.1–3.2)
Absent	29/194 (14.9)	15/173 (8.7)	1.7 (0.96–3.1)
<i>Chlamydia trachomatis</i>			
Present	5/39 (12.8)	7/33 (21.2)	0.6 (0.2–1.7)
Absent	49/251 (19.5)	22/227 (9.7)	2.0 (1.3–3.2)

*Denominators indicate the number of women for whom data on preterm delivery were available.

TABLE 4. COMPLICATIONS OF PREGNANCY AND NEONATAL COMPLICATIONS ACCORDING TO TREATMENT GROUP.*

OUTCOME	METRONIDAZOLE	PLACEBO	RELATIVE RISK (95% CONFIDENCE INTERVAL)
	no./total no. (%)		
	Maternal		
Hospitalized for preterm labor	41/311 (13.2)	43/287 (15.0)	0.9 (0.6–1.3)
Hospitalized for preterm membrane rupture	8/311 (2.6)	7/287 (2.4)	1.1 (0.4–2.8)
Received tocolytic drugs	11/311 (3.5)	15/287 (5.2)	0.7 (0.3–1.4)
Cesarean delivery	53/313 (16.9)	44/289 (15.2)	1.1 (0.8–1.6)
Received antimicrobial therapy			
Any antimicrobial agent	98/310 (31.6)	132/286 (46.2)	0.7 (0.6–0.8)
Metronidazole, for any indication	37/310 (11.9)	75/286 (26.2)	0.5 (0.3–0.7)
Treated specifically for trichomoniasis	24/310 (7.7)	65/286 (22.7)	0.3 (0.2–0.5)
Clinical intraamniotic infection	24/309 (7.8)	24/286 (8.4)	0.9 (0.5–1.6)
Postpartum endometritis			
Vaginal delivery	4/257 (1.6)	3/240 (1.2)	1.2 (0.3–5.5)
Cesarean delivery	9/52 (17.3)	9/44 (20.5)	0.8 (0.4–1.9)
Fetal or neonatal			
Passage of meconium	69/308 (22.4)	59/284 (20.8)	1.1 (0.8–1.5)
Stillbirth or neonatal death†	11/308 (3.6)	8/287 (2.8)	1.3 (0.5–3.1)
Admission to neonatal intensive care unit	54/301 (17.9)	48/283 (17.0)	1.1 (0.7–1.5)
Neonatal sepsis (suspected or proved)	36/299 (12.0)	29/282 (10.3)	1.2 (0.7–1.9)

*Denominators indicate the number of women for whom outcome data were available.

†There were seven stillbirths in the metronidazole group at 20, 22 (two cases), 24, 26, 38, and 40 weeks of gestation.

women treated with placebo. In a previous clinical trial, a regimen of metronidazole and erythromycin increased the occurrence of delivery at less than 34 weeks of gestation among women who did not have bacterial vaginosis.¹⁵ The results of the present trial, along with previous studies, suggest that there may be a group of women in whom the risk of adverse outcomes of pregnancy is increased by antibiotic treatment.

Our results present a clinical dilemma. *T. vaginalis* is often noted in Papanicolaou smears obtained from asymptomatic pregnant women,⁷ and fewer than 20 percent of pregnant women with trichomoniasis report lower genital tract symptoms in response to direct questioning.²² Because *T. vaginalis* is a sexually transmitted pathogen, treatment of both infected women and their sexual partners is recommended as a public health measure.^{7,17} Our findings that metronidazole therapy for asymptomatic trichomoniasis in pregnancy does not reduce the rate of preterm delivery, and may increase the risk of this complication, suggest that such treatment cannot be recommended.

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APPENDIX

Other members of the Maternal-Fetal Medicine Units Network are as follows: **University of Alabama at Birmingham** — R.L. Copper, A. Northen, and W.W. Andrews; **University of Chicago** — P. Jones and M.D. Lindheimer; **University of Cincinnati** — N. Elder and T.A. Siddiqi; **George Washington University Biostatistics Center** — C. MacPherson, S. Leindecker, and M.L. Fischer; **Magee Women's Hospital, Pittsburgh** — S.N. Caritis, M. Cotroneo, and T. Camon; **University of Miami** — S. Beydoun, C. Alfonso, and F. Doyle; **National Institute of Child Health and Human Development** — C. Catz and S.J. Yaffe; **Ohio State University** — J.D. Iams, F. Johnson, and M.B. Landon; **University of Oklahoma** — G. Thurnau and A. Meier; **Medical University of South Carolina** — B.A. Collins, F. LeBoeuf, and R.B. Newman; **University of Tennessee** — B.M. Mercer and R. Ramsey; **University of Texas at San Antonio** — M. Berkus and S. Nicholson; **University of Texas Southwestern Medical Center** — M.L. Sherman and S. Bloom; **Thomas Jefferson University** — M. DiVito and J. Tolosa; **University of Utah** — D. Dudley and L. Reynolds; **Wake Forest University** — P. Meis, E. Mueller-Heubach, and M. Swain; **Wayne State University** — S.F. Bottoms (deceased) and G.S. Norman.

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