

## REDUCED INCIDENCE OF PRETERM DELIVERY WITH METRONIDAZOLE AND ERYTHROMYCIN IN WOMEN WITH BACTERIAL VAGINOSIS

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**Abstract Background.** Pregnant women with bacterial vaginosis may be at increased risk for preterm delivery. We investigated whether treatment with metronidazole and erythromycin during the second trimester would lower the incidence of delivery before 37 weeks' gestation.

**Methods.** In 624 pregnant women at risk for delivering prematurely, vaginal and cervical cultures and other laboratory tests for bacterial vaginosis were performed at a mean of 22.9 weeks' gestation. We then performed a 2:1 double-blind randomization to treatment with metronidazole and erythromycin (433 women) or placebo (191 women). After treatment, the vaginal and cervical tests were repeated and a second course of treatment was given to women who had bacterial vaginosis at that time (a mean of 27.6 weeks' gestation).

**Results.** A total of 178 women (29 percent) delivered infants at less than 37 weeks' gestation. Eight women were lost to follow-up. In the remaining population, 110 of the 426 women assigned to metronidazole and erythromycin (26 percent) delivered prematurely, as compared with 68 of the 190 assigned to placebo (36 percent,

$P=0.01$ ). However, the association between the study treatment and lower rates of prematurity was observed only among the 258 women who had bacterial vaginosis (rate of preterm delivery, 31 percent with treatment vs. 49 percent with placebo;  $P=0.006$ ). Of the 358 women who did not have bacterial vaginosis when initially examined, 22 percent of those assigned to metronidazole and erythromycin and 25 percent of those assigned to placebo delivered prematurely ( $P=0.55$ ). The lower rate of preterm delivery among the women with bacterial vaginosis who were assigned to the study treatment was observed both in women at risk because of previous preterm delivery (preterm delivery in the treatment group, 39 percent; and in the placebo group, 57 percent;  $P=0.02$ ) and in women who weighed less than 50 kg before pregnancy (preterm delivery in the treatment group, 14 percent; and in the placebo group, 33 percent;  $P=0.04$ ).

**Conclusions.** Treatment with metronidazole and erythromycin reduced rates of premature delivery in women with bacterial vaginosis and an increased risk for preterm delivery. (N Engl J Med 1995;333:1732-6.)

PRETERM delivery is the primary cause of perinatal mortality in the United States. To date, no effective means of preventing spontaneous preterm delivery has been identified. At least in some cases, however, microbial colonization of the fetal membranes or the amniotic fluid, or alterations in the vaginal flora such as are seen in patients with bacterial vaginosis, have been associated with spontaneous labor and preterm delivery.<sup>1-10</sup>

We undertook a prospective, double-blind trial to address three questions. First, does antimicrobial therapy reduce the incidence of preterm delivery in women at risk for preterm delivery? Second, does antimicrobial therapy reduce the incidence of preterm delivery in women with bacterial vaginosis? Finally, in women who are already at risk for preterm delivery, does bacterial vaginosis increase the risk even further?

### METHODS

#### Study Subjects

We identified for inclusion in the study otherwise healthy women between 22 and 24 weeks of gestation who had previously had a spontaneous preterm delivery or who weighed less than 50 kg before pregnancy. These two characteristics are associated with risks of preterm delivery of 26 percent and 16 percent, respectively (odds ratios, 2.9 and 2.7, as compared with the risk in women without these characteristics).<sup>11</sup> Among women with either risk factor, bacterial vaginosis is present in more than 40 percent and the risk of preterm delivery is 35 percent. Women were excluded from the study if they had known allergies to metronidazole or erythromycin, an uncertain length of gestation, a multiple gestation, prior vaginal bleeding, or a medical complication of pregnancy, such as diabetes mellitus or chronic renal

disease. Women were screened and treated for asymptomatic bacteriuria. Only women who had not received antimicrobial therapy for at least four weeks were enrolled.

Candidates for our study were women who had been pregnant for less than 24 weeks who were identified between May 1989 and December 1993 from among the 5000 women who receive antepartum care at public health clinics in Jefferson County, Alabama, each year. At the initial visit to the research clinic, each woman's week of gestation was determined from the timing of the last menses and was confirmed by ultrasonography. Written informed consent was obtained before randomization. The study was approved by the institutional review board.

#### Laboratory Tests

Each woman underwent the following tests: a cervical enzyme immunoassay (Chlamydiazyme, Abbott Laboratories, Chicago), cervical cultures for group B streptococci (*Streptococcus agalactiae*) and *Neisseria gonorrhoeae*, and a urine culture. Patients with *N. gonorrhoeae* and symptomatic vaginal yeast infections or *Trichomonas vaginalis* received appropriate antibiotic therapy. These conditions had to be eliminated before a woman was considered for participation in this clinical trial. A vaginal washing with 2 ml of sterile normal saline was performed to collect secretions for analysis by gas-liquid chromatography in order to detect volatile and nonvolatile short-chain organic acids and determine the succinate:lactate ratio (ratios of 0.4 or higher were considered abnormal).<sup>12-14</sup>

For the diagnosis of bacterial vaginosis, three of the following four criteria had to be met<sup>15</sup>: (1) the determination of a vaginal pH greater than 4.5 with pH strips or a pH meter, (2) the presence of an amine odor (trimethylamine) when 10 percent potassium hydroxide was applied to vaginal secretions,<sup>16</sup> (3) the detection in vaginal fluid of vaginal epithelial cells heavily coated with bacilli ("clue cells"), and (4) the presence of a thin vaginal secretion of uniform consistency. In addition, the diagnosis was based on the detection of few white cells and a mixed flora (as compared with the normal predominance of lactobacilli) on Gram's staining of vaginal fluid.<sup>17,18</sup> We found a 90 percent correlation between the clinical findings and the results of Gram's staining.

#### Randomization, Treatment, and Compliance

Our Investigational Drug Service generated a blocked randomization scheme in a ratio of 2:1 (i.e., two women were assigned to the

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study treatment for every one woman assigned to placebo), with blocks of randomly chosen sizes. At 22 to 24 weeks' gestation (mean, 22.9), each woman was assigned to take either metronidazole (250 mg three times a day for 7 days) and erythromycin base (333 mg three times a day for 14 days) or an identical-appearing placebo containing a lactose filler. Two to four weeks after treatment, the vaginal and cervical tests were repeated and a second course of the initially assigned treatment was given to women who had bacterial vaginosis at that time (at a mean of 27.6 weeks of gestation). All the women were seen every two weeks for antepartum care by the same nursing team, and the importance of adherence to treatment was emphasized. Pills were counted at each visit, and each woman kept a log of medications. If a woman's compliance was less than 80 percent, she was counseled again about the importance of taking the pills. All follow-up visits were scheduled for the same day of the week, but women who presented at unscheduled times still received care from the same nursing team. Patients who missed their regular clinic visits were called on the telephone and seen at the next convenient time.

### Rationale for Antimicrobial Therapy

When the study protocol was being developed in 1988, published data indicated that a seven-day course of oral metronidazole was more efficacious in treating bacterial vaginosis than amoxicillin, doxycycline, ampicillin, or a vaginal cream containing three sulfa drugs.<sup>19-21</sup> Moreover, metronidazole was the therapy recommended for this condition by the Centers for Disease Control.<sup>22</sup> Hence, we elected to use metronidazole and obtained the approval of the institutional review board for the use of this category B drug in pregnant women.<sup>23,24</sup> Recently, a meta-analysis confirmed the safety of metronidazole in pregnancy.<sup>25</sup> Other reasons for choosing metronidazole were the following: metronidazole does not eradicate lactobacillus, as does amoxicillin<sup>26</sup>; allergy to penicillin would not exclude otherwise eligible patients from participation in the study; and metronidazole is resistant to inactivation by beta-lactamases (which are produced by 50 percent of vaginal organisms). We included erythromycin as adjunctive treatment because of data (evolving in 1988) on the association of *Chlamydia trachomatis* and *Ureaplasma urealyticum* with preterm delivery or premature rupture of membranes.<sup>27-30</sup>

### Statistical Analysis

All outcome data were collected after delivery and included in a relational data base before the double-blind code was broken. We report the results of an intention-to-treat analysis of the efficacy of treatment with metronidazole and erythromycin in reducing the rate of delivery before 37 weeks' gestation. Student's t-test, chi-square tests of proportion, and two-tailed Fisher's exact tests<sup>31</sup> were used in the analysis where appropriate.

## RESULTS

A total of 624 women were enrolled; 433 were randomly assigned to active treatment and 191 were assigned to placebo. The women in the two groups were similar with respect to selected characteristics (Table 1). They were also similar with respect to substance abuse: 29.7 percent of the treatment group used alcohol, tobacco, or illegal drugs, as compared with 30.3 percent of the placebo group. The percentage of pills taken was also similar in both groups during both the first and the second treatment. These 624 women had been screened and treated for asymptomatic bacteriuria at least four weeks before randomization. Therefore, at randomization only 11 of the 433 women assigned to the treatment group (2.5 percent) and 7 of the 191 women assigned to the placebo group (3.7 percent) had positive urine cultures. These 18 patients received oral nitrofurantoin therapy.

The effect of treatment with metronidazole and erythromycin on selected markers of altered vaginal flora is compared with the effects of placebo in Table 2.

**Table 1. Characteristics of the Women in the Study at the Time of Randomization to Treatment with Metronidazole and Erythromycin or to Placebo.\***

CHARACTERISTIC	TREATMENT GROUP (N = 433)	PLACEBO GROUP (N = 191)
Weight <50 kg	156 (36)	77 (40)
Prior preterm delivery	277 (64)	114 (60)
Black race	309 (71)	150 (79)
Primiparity	84 (19)	30 (16)
Preceding pregnancy		
Spontaneous preterm delivery	127 (29)	62 (32)
Preterm rupture of membranes	85 (20)	31 (16)
Any other pregnancy		
Spontaneous preterm delivery	36 (8)	12 (6)
Preterm rupture of membranes	31 (7)	11 (6)
Compliance (%)		
First treatment	65.2±38.7	72.1±34.1
Second treatment	70.5±31.3	75.4±33.3
Body-mass index†	23.2±7.2	24.0±7.8
Age (yr)	23.7±4.9	23.6±4.8
Weeks of gestation		
First examination	23.0±2.3	22.9±2.5
Second examination	27.6±2.6	27.6±2.7

\*Numbers followed by a number in parentheses are numbers of women and percentages of the group. Plus-minus values are means ±SD. There were no significant differences between the groups.

†Calculated as the weight in kilograms divided by the square of the height in meters.

Before treatment, the percentage of women with each marker was similar in the two groups. At the time of the follow-up examination, the percentage of women with each marker (except group B streptococci and *Candida albicans*) decreased significantly in the treatment group, but not in the placebo group. With the study treatment, bacterial vaginosis disappeared in 70 percent of the affected women ( $P<0.001$ ), whereas it appeared in only 5 percent of those who initially did not have bacterial vaginosis. In the placebo group, 18 percent of women who initially had bacterial vaginosis were found no longer to have it, whereas the reverse was true of 13 percent of initially negative women. Between the first and second examinations (performed at a mean of 22.9 and 27.6 weeks' gestation, respectively), markers of altered vaginal flora remained remarkably constant in the women assigned to placebo.

Among all 624 women studied, 178 (29 percent) delivered infants before 37 weeks of gestation. Bacterial vaginosis was present in 258 women (41 percent) at the base-line examination. Eight women were subsequently lost to follow-up. Of the remaining women, 110 of the 426 assigned to metronidazole and erythromycin (26 percent) delivered before 37 weeks, as compared with 68 of the 190 assigned to placebo (36 percent,  $P=0.01$ ) (Table 3). However, the association between the study treatment and a lower rate of delivery before 37 weeks' gestation was observed only among the 258 women who had bacterial vaginosis (rate of preterm delivery, 31 percent with treatment vs. 49 percent in the placebo group;  $P=0.006$ ). Among the 358 women who did not have bacterial vaginosis at the time of their initial examinations, 22 percent of those assigned to the study treatment and 25 percent of those assigned to placebo delivered before 37 weeks. Assignment to the study treatment resulted in a significantly lower rate of deliv-

Table 2. Markers of Altered Vaginal Flora in the Women Assigned to Treatment with Metronidazole and Erythromycin or to Placebo.\*

MARKER	TREATMENT GROUP (N = 433)			PLACEBO GROUP (N = 191)		
	BASE LINE	FOLLOW-UP	P VALUE	BASE LINE	FOLLOW-UP	P VALUE
	no. (%) of women			no. (%) of women		
Bacterial vaginosis	176 (40.7)	53 (15.1)	<0.001	87 (45.6)	71 (43.6)	0.71
<i>T. vaginalis</i>	27 (6.2)	6 (1.7)	0.002	11 (5.8)	8 (4.9)	0.72
<i>C. trachomatis</i> †	52 (12.0)	26 (7.4)	0.03	33 (17.3)	25 (15.3)	0.61
Group B streptococci	17 (3.9)	13 (3.7)	0.88	4 (2.1)	2 (1.2)	0.69
Candida	84 (19.4)	65 (18.6)	0.77	40 (20.9)	21 (12.9)	0.45
Vaginal pH >4.5						
Measured with pH strip	168 (38.8)	73 (20.9)	<0.001	77 (40.3)	65 (39.9)	0.93
Measured with pH meter	176 (40.7)	102 (29.9)	0.001	85 (44.5)	66 (41.8)	0.55
Volatile organic acids	122 (28.2)	29 (8.3)	<0.001	57 (29.8)	44 (27.0)	0.55
Succinate:lactate ratio ≥0.4	108 (24.9)	22 (6.5)	<0.001	56 (29.3)	41 (26.0)	0.43
Bacterial vaginosis, pH >4.5, or GLC finding‡	210 (48.5)	95 (27.1)	<0.001	101 (52.9)	81 (49.7)	0.55

\*Percentages shown for the follow-up period exclude women who had no follow-up examination.

†As detected by a cervical enzyme immunoassay.

‡GLC denotes gas-liquid chromatography; findings include the detection of volatile and nonvolatile short-chain organic acids and abnormal succinate:lactate ratios (ratios of 0.4 or above).

ery before 37 weeks of gestation among women who had bacterial vaginosis and were at increased risk, either because they had previously had a preterm delivery or because they weighed less than 50 kg before pregnancy (Table 3).

We analyzed our study population further to determine the incidence of preterm delivery due only to spontaneous preterm labor, preterm rupture of membranes, or both — that is, excluding women who had preterm deliveries because of medical or obstetrical complications involving the mother. In this analysis, we identified 228 women with bacterial vaginosis who did not have preterm deliveries due to such complications. Among these women, 151 had previously had a spontaneous preterm delivery, and 77 weighed less than 50 kg before pregnancy. Assignment to metronidazole and erythromycin resulted in a lower rate of spontaneous preterm delivery among the 228 women with bacterial vaginosis (24.5 percent, vs. 39.7 percent with placebo;  $P=0.02$ ) and also among those with a previous preterm delivery (31.1 percent vs. 46.7 percent,  $P=0.07$ ) or a prepregnancy weight of less than 50 kg (10.2 percent vs. 28.6 percent,  $P=0.04$ ).

Finally, we compared the rates of preterm delivery among women who had bacterial vaginosis and among those who did not, regardless of treatment assignment. The women with bacterial vaginosis had higher rates of delivery before 37 weeks of gestation (37 percent vs. 23 percent,  $P<0.001$ ), at 34 weeks or earlier (19 percent vs. 11 percent,  $P=0.006$ ), and at 32 weeks or earlier (11 percent vs. 6 percent,  $P=0.04$ ).

It was disturbing to note that delivery at 34 weeks of gestation or earlier occurred in 34 of the 254 women (13.4 percent) who did not have bacterial vaginosis and were assigned to the study treatment, as compared with only 5 of the 104 women (4.8 percent) without bacterial vaginosis who were assigned to placebo ( $P=0.02$ ). However, among these same women without bacterial vaginosis, rates of delivery before 37 weeks in the wom-

en assigned to the study treatment (56 of 254, or 22.0 percent) as compared with placebo (26 of 104, or 25.0 percent;  $P=0.55$ ) and of delivery at 32 weeks or earlier in the women assigned to the study treatment (18 of 254, or 7.1 percent) as compared with placebo (4 of 104, or 3.8 percent;  $P=0.25$ ) were similar in both groups.

## DISCUSSION

In this study, women at increased risk for preterm delivery who were assigned to receive treatment with metronidazole and erythromycin at approximately 24 weeks' gestation had fewer preterm deliveries than women assigned to placebo. However, the benefit of treatment was observed only among the women who

had bacterial vaginosis at the time of their initial examination. Thus, our overall results do not support the use of midtrimester treatment with metronidazole and erythromycin in women at risk for preterm delivery who do not have bacterial vaginosis. The lower rates of preterm delivery found among women with bacterial vaginosis who received the study treatment occurred both among women who had previously had a spontaneous preterm delivery and among those who weighed less than 50 kg before pregnancy. We also found that the study treatment eliminated bacterial vaginosis in 70 percent of women with this condition and significantly improved other markers of adverse alterations in vaginal flora. However, the spontaneous appearance or disappearance of bacterial vaginosis may confound the results of clinical trials in which the outcome of pregnancy is found to be related to the efficacy of treatment in a single sample.

### Infection of the Upper Genital Tract and Preterm Delivery

We previously compared the frequency of cultures of amniotic fluid or chorionic or amniotic tissue that were positive for microorganisms between women who had spontaneous labor and those whose deliveries were indicated because of maternal medical or obstetrical complications.<sup>1</sup> Forty percent and 13 percent, respectively, had cultures of chorionic or amniotic tissue that were positive for one or more microorganisms ( $P<0.001$ ). Rates of positive cultures were inversely proportional to the duration of gestation in women who had spontaneous labor but not in women whose deliveries were medically or obstetrically indicated. Among women who delivered at or before 30 weeks' gestation, cultures of chorionic or amniotic tissue were positive in 73 percent of those who had spontaneous labor as compared with 21 percent of those whose deliveries were indicated ( $P<0.001$ ). Neither the duration of labor (up to 24 hours) nor the use of oxytocin to induce labor influenced the percentage of microorgan-

isms recovered from the chorion or amnion in either group.

### Bacterial Vaginosis and Its Treatment

Women were selected for our study on the basis of two established risk factors for preterm delivery: a history of spontaneous preterm delivery or a maternal weight before pregnancy of less than 50 kg.<sup>11</sup> Over 40 percent of women with one of these risk factors have bacterial vaginosis. Therefore, our selection of antimicrobial agents was primarily directed toward the eradication of bacterial vaginosis. The efficacy of metronidazole in treating bacterial vaginosis has been confirmed by McDonald et al.<sup>32</sup> and in a meta-analysis by Lugo-Miro et al.<sup>33</sup> We included treatment with erythromycin because of previous studies that suggested an association between the presence of *C. trachomatis* and *U. urealyticum* and preterm delivery. However, more recent data<sup>34,35</sup> have not supported the reports of McCormack et al.<sup>29</sup> and McGregor et al.<sup>30</sup> concerning the benefit of erythromycin in preventing preterm delivery.

When this study protocol was established, published data suggested an association between infections of both the upper and the lower genital tracts with numerous organisms and preterm labor and delivery. However, we were and still are not certain that any particular microorganism or condition, such as bacterial vaginosis, is solely responsible for the premature onset of labor. The range of microorganisms isolated both from amniotic fluid and from the chorion and amnion in our previous observational study of 609 women<sup>1</sup> and in studies by Hillier et al.<sup>6</sup> and Watts et al.<sup>7</sup> lends further support to our belief that a variety of microorganisms may be involved in this process. The combination of metronidazole and erythromycin would be expected to be effective against most organisms identified in the upper genital tracts of women in these observational trials.<sup>6,7,36</sup>

We should emphasize that although lower rates of preterm delivery were observed among women with bacterial vaginosis who were treated with metronidazole and erythromycin than among those given placebo, it does not necessarily follow that eradicating bacterial vaginosis will reduce the incidence of preterm delivery. It is very possible, for example, that at midpregnancy bacterial vaginosis is a marker for or is associated with colonization of the fetal membranes by organisms such as *U. urealyticum*. Treatment with metronidazole and erythromycin, though it eradicated bacterial vaginosis, may also have eradicated early colonization of the upper genital tract. Therefore, a clinical trial in which the selection of antimicrobial agents depends solely on the eradication of bacterial vaginosis, such as a trial of single-dose metronidazole or topical clindamycin, may not result in a reduction in preterm delivery. That this may be the case is suggested by studies that compare the in-

Table 3. Rates and Risks of Delivery before 37 Weeks of Gestation among the Women Assigned to Treatment with Metronidazole and Erythromycin or to Placebo.\*

GROUP OF WOMEN	TREATMENT GROUP (N = 426)	PLACEBO GROUP (N = 190)	P VALUE	RELATIVE RISK (95% CI)
	<i>no. delivering before 37 wk/total no. (%)</i>			
All studied	110/426 (26)	68/190 (36)	0.01	1.4 (1.1–1.8)
Without bacterial vaginosis	56/254 (22)	26/104 (25)	0.55	1.1 (0.8–1.7)
With bacterial vaginosis	54/172 (31)	42/86 (49)	0.006	1.6 (1.1–2.1)
And previous preterm delivery	47/121 (39)	32/56 (57)	0.02	1.5 (1.1–2.0)
And weight <50 kg before pregnancy	7/51 (14)	10/30 (33)	0.04	2.4 (1.0–5.7)

\*Eight women were lost to follow-up after randomization. CI denotes confidence interval.

cidence of bacterial vaginosis with that of infections of the upper genital tract in nonpregnant women.<sup>37</sup>

Recently, Morales et al.<sup>38</sup> also found that metronidazole treatment in women with bacterial vaginosis and previous preterm delivery due to spontaneous labor significantly reduced the rate of recurrence of preterm delivery. In both our study and that of Morales et al.,<sup>38</sup> the women who had a lower rate of preterm delivery after treatment had both bacterial vaginosis and a risk factor for a preterm delivery. We have no data to suggest that treating low-risk pregnant women with bacterial vaginosis will decrease rates of prematurity. Randomized trials of antibiotic therapy in such women are therefore indicated.

### Preterm Delivery Attributable to Bacterial Vaginosis

Recently, it has become apparent from many studies that bacterial vaginosis approximately doubles the risk of spontaneous preterm delivery.<sup>8-10,28,39,40</sup> Furthermore, this disease is more common in some populations than in others. For example, using data from the Vaginal Infections in Prematurity Study, we have shown that pregnant black women had nearly three times as much bacterial vaginosis as pregnant white women.<sup>41</sup> Meis et al.<sup>42</sup> have also confirmed that the rate of bacterial vaginosis in black women is at least double the rate in white women.

In summary, women with bacterial vaginosis and an increased risk of preterm delivery have significantly lower rates of delivery before 37 weeks of gestation when they are treated with metronidazole and erythromycin.

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