

Should male consorts of women with bacterial vaginosis be treated?

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SUMMARY Nitroimidazoles have been shown to be the drugs of choice to treat women with bacterial vaginosis, but the recurrence rate is high. Some workers have suggested that the recurrence of symptoms may in fact be reinfection by male consorts, but no controlled studies have been undertaken to confirm this. In an international, multicentre, randomised, double blind trial, the recurrence rate was studied in 241 women with a clinical diagnosis of bacterial vaginosis. All women were treated with 2 g metronidazole twice at an interval of two days. The patients were randomly allocated to two groups, one contained 123 women, whose consorts were given the same dose of metronidazole, the other consisted of 118 women whose consorts were given inert but identical placebo tablets. The women were evaluated at weeks 1, 4, and 12 after treatment. At week 1, the cure rate was 97% (115/119) in women whose consorts had been treated and 98% (111/113) in the others. At week 4 bacterial vaginosis had recurred in 17% (19/112) of women whose consorts had been treated and in 13% (14/106) of those whose consorts had received placebo. At week 12 the recurrence rates were 21% (20/95) in women with treated consorts, and 16% (15/95) in the others. The differences in recurrence rates between the two groups of women were not significant. In conclusion, treating the sexual partners of women with bacterial vaginosis does not seem to increase the cure rate.

Bacterial vaginosis is a common condition in women.¹ This clinical syndrome is characterised by malodorous vaginal discharge that has decreased acidity and contains clue cells.² Microbiological characteristics are "replacement of the lactobacilli of the vagina by characteristic groups of bacteria accompanied by changed properties of the vaginal fluid".³ There is generally no vaginal irritation, soreness, or other sign of inflammation, and few white blood cells are found in a wet smear of the discharge. Bacterial vaginosis

may, however, coexist with infection of the vagina and cervix uteri, with bacteria such as *Chlamydia trachomatis*, protozoa such as *Trichomonas vaginalis*, or fungi such as *Candida albicans*, which may cause an inflammatory reaction.

Nitroimidazoles have been shown to be the drugs of choice in treating women with bacterial vaginosis.⁴ Some workers have suggested that the recurrence of symptoms may be caused by reinfection by their male consorts and that treating their sexual partners may decrease the recurrence rate.^{4,5} Until recently, no controlled studies had been undertaken to confirm or reject this theory.

The purpose of the present study was to investigate the recurrence rate of bacterial vaginosis in women in relation to concomitant treatment of their consorts. The study was designed as a long term international multicentre double blind trial. The dose of metronidazole was chosen according to the recommendations of a Norwegian multicentre study, which showed a cure rate of 94% after four weeks.⁶

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Patients and methods

PATIENTS

The study comprised non-pregnant sexually active women aged 17–56 (median 32) years with a diagnosis of bacterial vaginosis who attended one of the four clinics participating in the study. To be included, each patient had to have at least three of the four following symptoms or signs: (a) thin, greyish, sticky vaginal discharge; (b) pH of the vaginal discharge 4.5 or more; (c) a fishy amine odour after mixing 10% potassium hydroxide with the discharge on a glass slide; and (d) clue cells in a wet smear of the vaginal discharge. At least two symptoms or signs had to have resolved for bacterial vaginosis to be considered cured, but in general all symptoms and signs had resolved in cured patients.

Each patient included had one male consort with whom she had sexual intercourse, without using a condom, at least once a week during the study period. Few of the men were circumcised, as circumcision is rare in the Nordic countries. The men were not examined, except those attending one centre (Sweden).

Criteria for exclusion were pregnancy or lactation, hematological or neurological disease, a history of allergy to metronidazole, or antibiotic treatment in the preceding week.

We enrolled into the study 241 women who fulfilled the criteria given above, and their male consorts (table 1). They consisted of 100 women attending the department of obstetrics and gynaecology of University Central Hospital, Turku, Finland, 70 attending the department of gynaecology of Ullevål University Hospital, Oslo, Norway, 35 attending a private clinic for gynaecology in Odense, Denmark, and 36 attending the outpatient clinics for gynaecology and for sexually transmitted diseases at Örebro Medical Center Hospital, Örebro, Sweden. The trial was approved by the local ethical committees, and informed consent was given by the patients and their consorts.

DESIGN OF THE STUDY

All the 241 women with bacterial vaginosis were treated with an initial dose of 2 g metronidazole that

was repeated two days later. They were randomly allocated to one of two groups for a double blind trial. One group consisted of 123 women (median age 31 years) whose male consorts were given the same dose of metronidazole as the women. The other group consisted of 118 (median age 33 years) whose male consorts were given inert but identical placebo tablets.

CLINICAL EVALUATION

The women were examined at weeks 1, 4, and 12 after treatment. They and their consorts were asked about compliance and they were asked about symptoms of bacterial vaginosis. Replies were recorded on a standardised questionnaire. Each patient was subjected to a thorough pelvic examination, and the following tests were performed. The amount of vaginal discharge was recorded as being normal, subnormal, or increased. The odour of the undiluted discharge was recorded as being normal, weak, or strong. The pH of the vaginal discharge was recorded by dipping a colour-fixed indicator stick, pH 3.6–6.1 (Macherey-Nagel, Germany) into the vaginal discharge that collected on a speculum, or by exposing to a pH indicator stick discharge, but not cervical secretion, taken from the lateral vaginal fornix with a plastic loop. The amine test was performed by adding one drop of a 10% potassium hydroxide solution to the vaginal discharge to identify a fishy amine odour; weak or strong odour was categorised showing as a positive result. Vaginal discharge was wet mounted, with or without staining according to the routine of the clinic, and the smear was examined under an ordinary light microscope with substage illumination or under a phase contrast microscope at a $\times 400$ magnification to identify clue cells, *T vaginalis*, white blood cells, or yeasts. At one of the participating centres (Örebro, Sweden), an additional smear of vaginal discharge was taken for Gram staining.

Patients whose signs of bacterial vaginosis had recurred at follow up visits were asked about symptoms. Those who had symptoms were treated with metronidazole and withdrawn from the study, as were women who had received other antibiotics during the study period.

MICROBIOLOGICAL EXAMINATION

Material for cultures for *C trachomatis* and for *Neisseria gonorrhoeae* was taken at the first and last visits, and patients with gonorrhoea or chlamydial infection were withdrawn from the study because they received additional antibiotic treatment. The routines for each of the clinics were followed. At one of the participating centres (Örebro, Sweden), vaginal specimens from 31 women and specimens from the urethra and the preputial cavity from 22 male consorts were collected with cotton tipped swabs and trans-

Table 1 Distribution of 241 women with bacterial vaginosis whose consorts were randomised for treatment

	No whose consort received:		Total
	Metronidazole	Placebo	
Sweden	19	17	36
Denmark	18	17	35
Finland	50	50	100
Norway	36	34	70
Total	123	118	241

ported to the laboratory in modified Stuart's medium.⁷ The samples were inoculated on to selective differential bilayer HB agar (human blood bilayer agar containing 15 mg colistin and 10 mg nalidixic acid/ml) for semiquantitative cultures for *Gardnerella vaginalis*.⁸ The strains isolated were characterised by oxidase, catalase, β glucosidase, hippurate, and α glucosidase tests.⁸ Growth on the agar plates was graded as moderate, abundant, or none. At the Örebro clinic, specimens were taken from the women and their male consorts for anaerobic culture of *Mobiluncus* spp using supplemented brain heart infusion agar.⁹ Strains isolated were characterised by morphology (Gram stain), sensitivity to metronidazole, and biochemical (hippurate, oxidase, and catalase) tests.¹⁰ Material was also taken from each man for culture for *C trachomatis* and for *N gonorrhoeae*.

STATISTICS

Differences between the treatment groups were tested statistically using the χ^2 test with Yates's correction and a two sided significance level of 5%. Statistical tests were performed on numbers including patients who had dropped out or had been withdrawn (according to the principle of intention to treat) and without including such patients. In general, the differences between these numbers were small.

Results

Table 2 summarises the relative occurrence of each of the individual criteria for diagnosing bacterial vaginosis in the 241 women enrolled in the study. The findings in the two groups were similar. Clue cells showed the best correlation with a diagnosis of bacterial vaginosis and were documented in 98%

Table 2 Findings in 241 women with bacterial vaginosis at randomisation

Diagnostic criteria	No* (%) whose consort received:	
	Metronidazole (n = 123)	Placebo (n = 118)
Increased vaginal discharge:		
Noted by patient	112/123 (91)	100/116 (86)
Noted by doctor	109/122 (89)	100/118 (85)
Abnormal odour of the discharge:		
Noted by patient	114/122 (93)	109/115 (95)
Noted by doctor	110/122 (90)	111/117 (95)
pH > 4.5	117/123 (95)	108/117 (92)
Amine test positive	117/121 (97)	112/116 (97)
Microscopy of wet smear:		
Clue cells	121/123 (98)	114/117 (97)
<i>Trichomonas vaginalis</i>	0/122 (0)	1/115 (1)
Yeast	3/103 (3)	4/ 99 (4)
Culture:		
<i>Gardnerella vaginalis</i>	62/ 72 (86)	60/ 66 (91)
<i>Candida albicans</i>	6/ 60 (10)	4/ 55 (7)

*No of women fulfilling criterion/No for whom information was given on questionnaire.

Table 3 Findings after one week in 232 women who attended first follow up

Diagnostic criteria	No* (%) whose consort received:	
	Metronidazole (n = 119)	Placebo (n = 113)
Symptoms had improved	107/117 (91)	96/112 (86)
Increased vaginal discharge	10/116 (9)	12/113 (11)
pH > 4.5	10/113 (9)	8/112 (7)
Amine test positive	14/115 (12)	11/113 (10)
Microscopy of wet smear:		
Clue cells	7/115 (6)	3/113 (3)
Yeast	6†/101 (6)	5†/ 96 (5)
Treatment failures	4/119 (3)	2/113 (2)

*See table 2.

†None of these women had treatment failures.

(235/240) of the patients, followed by a positive amine test in 97% (229/237) and a pH of 4.5 or more in 94% (225/240). Increased vaginal discharge was noted by 89% (212/239) of the women and observed by the doctor in 87% (209/240). *G vaginalis* was cultured in 88% (122/138) specimens from women. *C trachomatis* was cultured in six (5%) of 121 patients who were therefore withdrawn from the study after the first follow up visit. None of the patients yielded *N gonorrhoeae* on culture. Trichomoniasis was found by microscopy in one patient, but not in any of the 65 for whom culture for *T vaginalis* was carried out.

The figure and tables 3–5 summarise the results at weeks 1, 4, and 12 after treatment. In the group of women whose male consorts were treated with metronidazole, 97% (115/119) were cured after one week, but relapse had occurred in 17% (19/112) after four weeks and in 21% (20/95) after 12 weeks. In the group of women whose male partners had received placebo 98% (111/113) were cured at week 1 but 13% (49/106) and 16% (15/95) respectively, had had relapses at weeks 4 and 12. The differences between the two groups of women were thus not significant.

Table 4 Findings after four weeks in 218 women who attended second follow up

Diagnostic criteria	No* (%) whose consort received:	
	Metronidazole (n = 112)	Placebo (n = 106)
Subjective symptoms of relapse	30/107 (28)	22/105 (21)
Increased vaginal discharge	28/106 (26)	14/105 (13)
pH > 4.5	25/104 (24)	17/105 (16)
Amine test positive	28/100 (28)	21/102 (21)
Microscopy of wet smear:		
Clue cells	23/105 (22)	18/104 (17)
Yeast	11†/94 (12)	11†/92 (12)
Relapses between first and second follow up	19/112 (17)	14/106 (13)

*See table 2.

†None of these women had relapse of bacterial vaginosis.

‡Two of these women had relapse of bacterial vaginosis; one of the two gave negative culture for *Candida albicans*.

Table 5 Findings after 12 weeks in 190 women who attended third follow up

Diagnostic criteria	No* (%) whose consort received:	
	Metronidazole (n = 95)	Placebo (n = 95)
Subjective symptoms of relapse	22/94 (23)	24/95 (25)
Increased vaginal discharge	23/90 (26)	16/94 (17)
pH > 4.5	23/90 (26)	19/94 (20)
Amine test positive	23/85 (27)	19/93 (20)
Microscopy of wet smear:		
Clue cells	22/90 (24)	19/94 (20)
Yeast	5†/82 (6)	7‡/84 (8)
Relapses between second and third follow up	20/95 (21)	15/95 (16)

*See table 2.

†None of these women had relapse of bacterial vaginosis.

‡One of these women had relapse of bacterial vaginosis.

BACTERIOLOGICAL EVALUATION

In the extended bacteriological evaluation of 31 women (table 6) at one of the clinics (Örebro, Sweden), two strains of *M. curtisii* and one strain of *M. mulieris* were isolated from the vaginal walls of three patients at their first visits. Curved rods, however, were observed in Gram stained vaginal smears from 12 (39%) women. Cultures of vaginal specimens for *G. vaginalis* showed abundant growth in 24 women and moderate growth in one. Of the six women who did not yield *G. vaginalis*, three showed abundant growth of bacteria morphologically similar to that of *G. vaginalis* but gave negative results in the Hippurate test.

One week after treatment, the extended culture of samples from 16 women whose consorts had been treated showed abundant growth of *G. vaginalis* in two, moderate growth in three, and no growth in 11. Of the

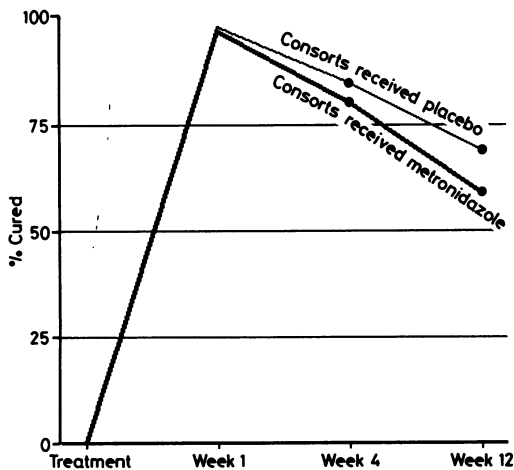


Figure Cure at 1, 4, and 12 weeks after treating women with bacterial vaginosis.

15 whose consorts had received placebo, six had abundant, two moderate, and seven no growth. One patient, from whom *M. mulieris* had been isolated on day 1, still had signs of bacterial vaginosis and yielded *M. curtisii* on this occasion as well as an abundant growth of *G. vaginalis*. She received no additional treatment, but was free from signs of bacterial vaginosis at weeks 4 and 12.

Four weeks after treatment, two patients were withdrawn from the study because of chlamydial infection and one had dropped out. In the remaining 28 patients recurrence was diagnosed in four whose consorts had received metronidazole (three of whom received additional treatment and were withdrawn) and in one of the others (who was withdrawn from the study because of receiving additional treatment). Vaginal culture from the remaining 13 women whose consorts had received metronidazole showed abundant growth of *G. vaginalis* in eight and no growth in five samples; of the 15 women whose consorts had received placebo, seven had abundant and eight no growth. *M. curtisii* was isolated from one woman in whom recurrence was diagnosed.

Twelve weeks after treatment, four women were withdrawn from the survey because they had been treated for relapse, and two had dropped out. Of the remaining nine women whose consorts had received metronidazole, four had relapsed and had abundant growth of *G. vaginalis* in vaginal fluid (one negative in the Hippurate test). Of the five women without signs of bacterial vaginosis, two had abundant growth, one had a moderate growth, and one had no growth of *G. vaginalis*, and culture failed in one. Of the remaining 13 women whose consorts had received placebo, two had relapses and abundant growths of *G. vaginalis* in vaginal fluid, as did six other women without signs of bacterial vaginosis. Five women who were free from signs of bacterial vaginosis had no growth of *G. vaginalis*. Four patients whose consorts had received metronidazole and 11 of the others were still cured according to the composite clinical criteria. A long curved rod was isolated, but not typed because of weak growth, from one woman whose partner had yielded *M. curtisii* on day 1.

MALE CONSORTS

Of the 22 male consorts examined at Örebro, Sweden, seven (32%) yielded *G. vaginalis* from the urethra at the first visit, none had signs of urethritis in stained urethral smears, and two yielded *M. curtisii* from the preputial sack. Of 13 men followed up one week after treatment, three yielded *G. vaginalis*. These three men had all been treated with metronidazole. No significant correlation was seen between finding *G. vaginalis* in a man and the recurrence of bacterial vaginosis in his female consort.

Table 6 Extended semiquantitative culture for *Gardnerella vaginalis* in 31 Swedish women with bacterial vaginosis

	No of women in week 0 whose consort received:		No of women in week 1 whose consort received:		No of women in week 4 whose consort received:		No of women in week 12 whose consort received:	
	Metronidazole (n = 16)	Placebo (n = 15)	Metronidazole (n = 16)	Placebo (n = 15)	Metronidazole (n = 13)	Placebo (n = 15)	Metronidazole (n = 9)*	Placebo (n = 13)
Growth of <i>G vaginalis</i> :								
Abundant	13	11	2	6	8	7	6	8
Moderate	1	0	3	2	0	0	1	0
None	2	4	11	7	5	8	1	5
<i>Mobiluncus</i> spp isolated	2	1	0	1	1	0	1	0

*Culture not performed for one patient.

CONTRACEPTION

Information about contraceptive methods was available for 77 (63%) women whose consorts received metronidazole and 80 (68%) whose consorts received placebo. Twenty five women in each group used oral contraception, and 47 and 48 women respectively used interuterine contraceptive devices. Seven treated consorts and five consorts who received placebo used condoms, but not regularly. No significant correlation was seen between cure rates and contraceptive methods used.

Discussion

Nitroimidazoles are the drugs of choice for treating bacterial vaginosis as they give initial cure rates of 90% or more.^{4,6,11,12} This high initial cure rate with metronidazole was confirmed by the cure rate of 97% after one week in the study published here. Recurrence rates may be high, however, between 14% and 41%, as shown in the present study and by others.^{4,11,13} The possible role of sexual transmission to explain the high recurrence rates has therefore been proposed by several authors,^{4,5,11-14} and treating partners has been discussed.^{4,13,15} Studies by Eschenbach et al¹⁶ and Swedberg et al,¹⁷ in which the sexual partners of women with bacterial vaginosis were treated, did not show improved cure rates or reductions in recurrence rates in the women. Those studies, however, were not designed to elucidate the question of treating partners. Weaver and Mengel found significantly better cure rates, as diagnosed by Gram stained slides, but not by clinical criteria, two weeks after treatment if men were treated.¹⁸ Eight weeks after treatment, however, no significant difference was seen.

The main objective of this study was to elucidate the question of treating sexual partners, as no controlled studies of sexual partners have been reported.¹⁹ In our multicentre double blind trial with metronidazole and placebo we showed that treating male consorts did not influence recurrence rates. The female partners of men treated with metronidazole in fact had higher recurrence rates, though not significantly so, than those whose consorts received placebo. Multicentre trials

may often encounter various types of problems, but the clinical findings and results of treatment and follow up visits were similar for each of the clinics participating in our study. Our results were confirmed by a study by Vejtorp et al, who found that treating male partners did not affect the recurrence of subjective symptoms or clinical signs or the isolation of *G vaginalis* at weeks 1 and 5 after treatment.²⁰

Bacterial vaginosis is, by definition, a condition without inflammation but associated with various microbes. *G vaginalis* is often isolated from patients, as shown in the present and many other studies.^{4,5,11,14,21} The Gram negative or Gram labile short and long curved rods consistently found in Gram stained smears are considered to represent the *Mobiluncus* spp, *M mulieris* and *M curtisii*. The role of *G vaginalis* and *Mobiluncus* spp in sexual transmission has been discussed by several authors.^{4,5,22-24} In the limited bacteriological study that formed part of the present work, *G vaginalis* was isolated from one third of the men. Hallén could not show *Mobiluncus* spp in any partner of women with *Mobiluncus* associated bacterial vaginosis,²³ and in the present work *M curtisii* was isolated in only 9% of the male partners. *G vaginalis* was isolated at the follow up visit after treatment from three men who had received metronidazole, but their female partners had no recurrence of bacterial vaginosis. *G vaginalis* was eradicated from one, but not the other woman. The third woman was withdrawn from the study after the first follow up because of chlamydial infection. These findings thus indicate that sexual transmission, although it cannot be ruled out, seems to play a minor part in the recurrence of bacterial vaginosis.

Pseudomycelium was found on microscopy of wet smears from the vaginas of 5-12% of the patients at the follow up visits (see tables 3-5). As culture for yeasts was performed in only about half the patients, the culture results are not shown in the tables. At week 4 two (9%) of the 22 women with hyphae in their wet smears had signs of recurrence of bacterial vaginosis, but only one of the two yielded *C albicans* on culture. At week 1 after treatment none of 11 patients with evidence of vulvo-vaginal candidiasis had recurrences

of bacterial vaginosis, and at week 12 one (9%) of 12 had a recurrence. The recurrence rate of bacterial vaginosis in patients without evidence of yeast infection was twice as high or more as in those with yeast infections. The correlation of candidiasis with bacterial vaginosis has seldom been discussed previously, as patients with concomitant candidal vaginitis have been excluded from most studies of bacterial vaginosis.^{16,17} Fleury observed that concomitant candidiasis does not inhibit clue cell formation, but the amine test often gave a negative result when appreciable candidal infection was present.²⁵ This observation was not confirmed by the present study. A negative correlation of candidiasis with bacterial vaginosis, however, was also observed by Hallén *et al*,²⁶ and a possible explanation could be different environmental needs for the two conditions.

Bacteroides spp are also implicated in bacterial vaginosis.²⁷ These organisms and *M. mulieris* are highly sensitive to metronidazole, whereas *G. vaginalis* and *M. curtisii* are relatively resistant. There is, however, a discrepancy between this low sensitivity and the efficacy of metronidazole in reducing or eliminating *G. vaginalis*, as shown in the present and other studies. Active hydroxy-metabolites of metronidazole might be responsible for this.²⁸⁻³⁰ Another possible explanation may be that metronidazole does not act direct on *G. vaginalis* but on organisms that are synergistic with it. Their eradication would thus create an environment inimical to *G. vaginalis*.¹⁴

The findings of the present and other studies support the concept that bacterial vaginosis is the expression of a clinical syndrome with multifactorial and multibacterial aetiologies. The present study also shows that treating consorts is of no value in curing patients. Although sexual activity may be important in establishing bacterial vaginosis, sexual transmission of agents sensitive to metronidazole does not seem to be a major cause of recurrences.

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