Should sexual partners of women with bacterial vaginosis receive treatment?

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SUMMARY

Bacterial vaginosis is the most prevalent infectious cause of vaginitis. It is associated with significant morbidity, particularly in pregnant women and following gynaecological operations. Cure is difficult. There is some controversy over whether treating sexual partners of affected women can improve cure rates. This paper provides a critical appraisal of the evidence for simultaneously treating the male partner of women affected by bacterial vaginosis. Unfortunately, no evidence was found supporting the treatment of partners of women affected by bacterial vaginosis.

Keywords: bacterial vaginosis; vaginitis; sexual partners.

Introduction

BACTERIAL vaginosis is currently the most prevalent infectious cause of vaginitis.[1] Prevalence varies between 10 and 15%.[2-6] Half of all women with bacterial vaginosis will have no symptoms but there are definite sequelae associated with infection. There is an association between pelvic inflammatory disease and bacterial vaginosis. Postoperative pelvic infections are more common in infected women. In pregnancy there is an association with preterm labour, premature rupture of membranes, chorioamnionitis, and postcaesarean and postpartum endometritis. Post abortion pelvic inflammatory disease is decreased threefold if infected women are treated with metronidazole.[1]

The current first-line treatment of symptomatic bacterial vaginosis is either oral metronidazole or topical clindamycin, and bacterial vaginosis will recur in over half of women in whom initial treatment appears effective.[8]

There is some evidence that bacterial vaginosis is sexually transmitted in that the bacteria associated with bacterial vaginosis have been cultured from male partners of women sufferers.[9-13] In addition, the risk of bacterial vaginosis is increased with multiple sexual partners. Conversely, most trials have found no improvement in cure rate when sexual partners are treated, bacterial vaginosis has been identified in 12% of virginal women, and the bacteria associated with bacterial vaginosis do not persist in male sexual partners.[1] However, two authors have suggested that a beneficial effect of treating the male partner cannot be discounted.[8,14]

The aim of this paper was to assess the evidence for treatment of the sexual partner of a woman with symptomatic bacterial vaginosis.

Method

Search methodology

MEDLINE, Cochrane, and EMBASE databases were searched using the keywords sexual partner(s), vaginitis, haemophilus vaginitis, gardnerella vaginitis, and non-specific vaginitis. A shortened Cochrane search strategy was employed for MEDLINE and EMBASE[15] to identify randomized controlled trials, and was then combined with the previous searches. Five trials of treatment of sexual partners[16-20] were identified using this technique; a further trial[21] was identified from scrutinizing references in the identified papers.

The evidence

The four trials not discussed in depth are summarized in Table 1.[16,18,19,21] None of them support treatment of the male partner, but all have methodological problems. The remaining two trials are examined in depth, one because it is the only trial to suggest there may be an advantage in treating male partners,[17] and the other[20] because it is methodologically the most rigorous.

Trial 1: Mengel *et al*[17]

Description

This study was a randomized, double blind trial of treating the sexual partner of women with symptomatic bacterial vaginosis. There were two aims:

1. To test the effectiveness of a single dose of metronidazole for sexual partners of patients with bacterial vaginosis.
2. To test the effectiveness of single dose metronidazole therapy compared with seven-day courses.

Women aged 18 to 40 years with bacterial vaginosis were randomized into one of four groups as shown in Figure 1.

Diagnosis of bacterial vaginosis was based on Amsel's clinical criteria:[2] three out of four being present of (i) increased vaginal discharge, (ii) vaginal pH >4.5, (iii) detection of clue cells, (iv) positive amine test. Eligible women were randomized in blocks. Physicians, patients, and partners were unaware of the treatment arm to which patients were randomized.

Follow-up examination was performed at two weeks on the female subjects, and telephone contact was used for follow-up at five and eight weeks. During the telephone contact, patients were asked about symptoms in themselves and their partners, and were asked to obtain a slide of vaginal fluid and return it. At five and eight weeks, recurrence of bacterial vaginosis was based on Gram-stained smears that were all interpreted by one 'blinded' medical laboratory scientific officer (MLSO).

Results

One hundred and sixty-one women with symptomatic bacterial vaginosis were enrolled in the study; 21 were 'dropped' from the study after randomization, leaving 140 who were analysed, indicating 'on treatment' rather than the preferred 'intention-to-treat' analysis. Ninety-eight partners (70%) of the 140 women consented to participate. The study found statistically significant benefits of partner treatment in the cure rate at two weeks assessed by Gram-stained smears, and in the percentage of women with symptoms eight weeks after treatment. Recurrence rates after eight weeks assessed by Gram-stained smear were not significantly different for women whose partners received treatment.

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Table 1. Characteristics of studies not discussed in depth.

Study	Method	Participants	Interventions	Outcomes	Notes
1. Moi et al[18]	Randomization; no method given. Intention-to-treat analysis and on treatment analysis.	Scandinavian women aged 17–56 years; international long-term trial. Amsel's criteria for bacterial vaginosis (BV). One male consort. One hundred women from a gynaecology clinic in Finland, 70 from a gynaecology clinic in Norway, 35 from a private gynaecology clinic in Denmark, and 36 from a gynaecology clinic in Sweden.	All women treated with 2 g metronidazole repeated after two days. Half of consorts were given the same, the other half were given identical inert placebo.	Cure as defined by absence of two or more of Amsel's criteria at one, four, and 12 weeks Result: A 21% (20/95) recurrence in the group with treated consorts and 16% (15/95) in the placebo group. No significant difference	Difficult to follow patients through the study as recurrence is repeatedly reported instead of reporting those still cured at each milestone. No precision analysis (power calculation or confidence intervals); it would be good to simply report those cured at different milestones with the difference between the two treatment groups and a 95% confidence interval. Evidence for not treating the partner.
2. Swedberg et al[21]	Randomized, no method described. Clinical practitioner and laboratory personnel blind to treatment group assignation.	USA Non-pregnant women aged 18–45 years with symptomatic BV. Amsel's clinical criteria used.	Two groups: 1. Single 2 g metronidazole 2. 500 mg metronidazole BD ´ seven days. Half of each group was then selected (randomly, no method) for treatment of the partner with the same dose regimen as the patient. No placebo for partners.	Cure at one and three weeks. Cure based on *G. vaginalis* not isolated on culture and marked improvement in symptoms.	One hundred and two women enrolled, only 64 completed the protocol. Very small numbers, on treatment analysis only. No precision calculations. Authors admit that this study does not answer the question of whether or not to treat sexual partners of women with BV.
3. Colli et al[16]	Randomized, no method described. Follow-up at one, four, and 12 weeks. Intention-to-treat analysis. Planned to recruit 150 patients and, with a decreased probability of recurrence from 30% in women whose partner received placebo to 10% in those whose partner was given clindamycin, this would give a power of 80%.	Italy Sexually active women, 18–45 years with a current sexual partner who agreed to be treated. Fourteen hospital outpatient clinics. Diagnosis based on Clue cells plus two of the other three of Amsel's criteria.	All women treated with clindamycin cream daily for seven days. Partners randomized to receive either clindamycin 150 mg qds for seven days or placebo.	Cure = absence of clue cells and at least two of the other three criteria. Follow-up to 12 weeks Result: No significant difference in cure rate between women whose partner received clindamycin or placebo.	Only 139 patients recruited. Therefore precision much less than 80%. Rather difficult treatment to take; clindamycin four times daily for seven days. Slightly odd variation of Amsel's criteria. No evidence for treating the sexual partner of women with bacterial vaginosis with clindamycin.
4. Vejtorp et al[19]	Randomization of partners in blocks of four. Investigators blinded. Alpha = <0.05. Beta = 95% for not detecting a 20% increase in subjective improvement in the metronidazole group (calculated after the trial).	Denmark One hundred and twenty-six monogamous women attending general practice or gynaecology clinic with BV, diagnosed by Amsel's criteria	All women received metronidazole 2 g stat plus 2 g on day three. Partners received the same or placebo.	Symptom and cure at five weeks. Results: 95% CI for difference in proportion of women symptom free or improved at five weeks = -14% to 19% 95% CI for difference on cure rates at five weeks = -13% to 20%.	One hundred and twenty-six women entered, 19 'excluded' on treatment analysis, which would tend to exaggerate the effect of treatment. No evidence for treating the sexual partner with metronidazole.

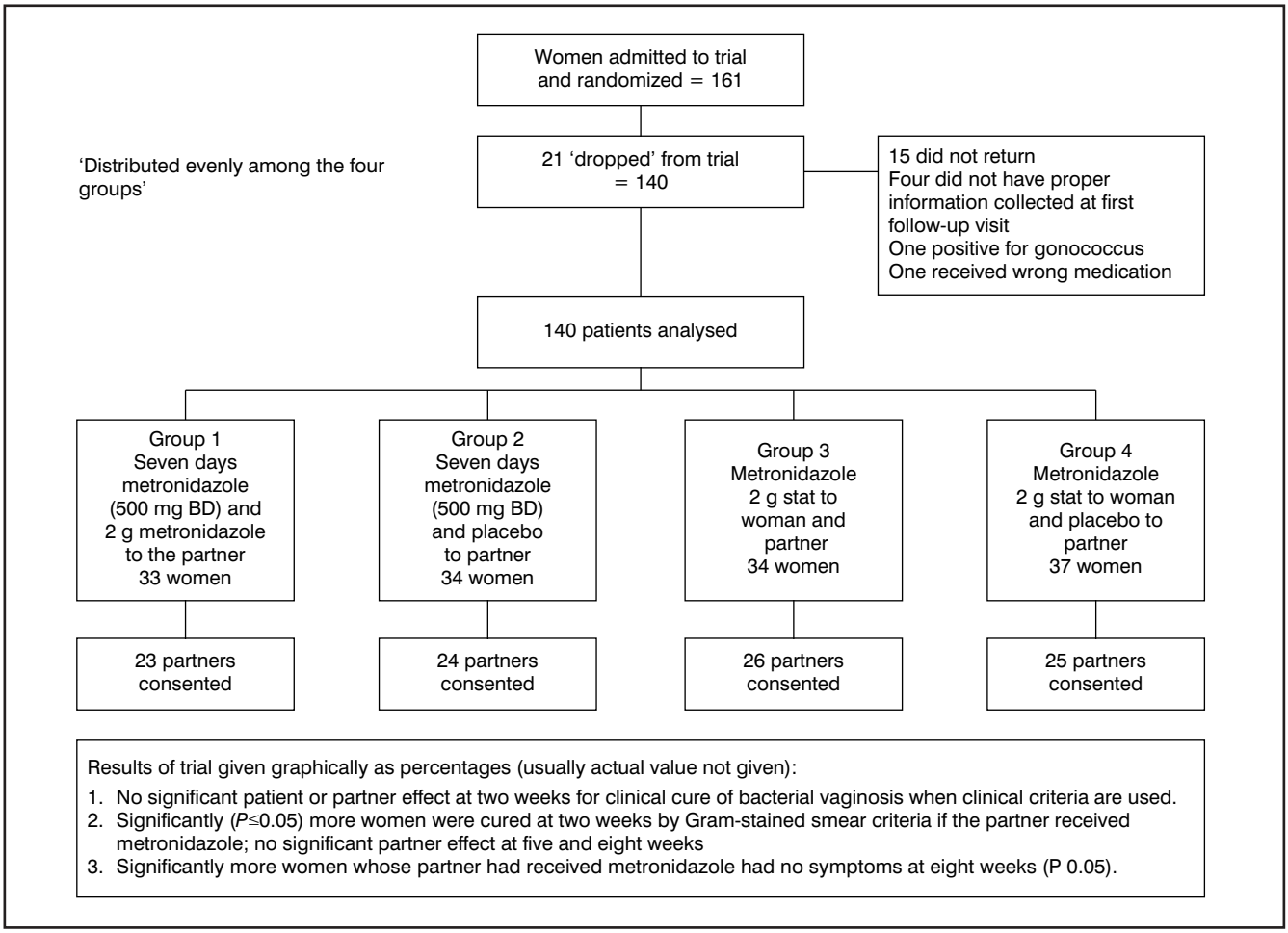

Figure 1. Graphic of clinical trial Mengel et al.[17]

Possible sources of bias in this study

1. Recruitment. Women with a clinical diagnosis of bacterial vaginosis were recruited after having been examined by one of the 12 practitioners comprising the Bacterial Vaginosis Study Group. There is no information as to inter-examiner reliability.

When measuring outcomes, the authors use both clinical criteria and Gram-stained smear; at inclusion, these symptomatic women, all with positive clinical criteria, were Gram-stained positive in each group as follows: 72%, 91%, 63%, and 58% respectively. The authors state that excluding the women without bacterial vaginosis on Gram-stained smear produced little change in the subsequent analysis. (Remember that Gram-stained smear is the preferred method of diagnosis of bacterial vaginosis in the United Kingdom.) They give a table of the ability of clinical criteria to assess care as judged by Gram-stained smear. The data can be used to produce a 2×2 table[23] using Gram-stained smear as the gold standard for the diagnosis of bacterial vaginosis (Table 2).

We would be unlikely to accept a test into clinical practice with such a poor positive predictive value and sensitivity as this clinical test. It seems that, with these researchers and this MLSO, Gram-stained smear and clinical criteria have very poor agreement for what is bacterial vaginosis.

2. Blinding. The authors admit that patients were able to guess which regimen they were taking, which may have influenced their reporting of symptoms and therefore biased the results at eight weeks where fewer women whose partners received treatment had no symptoms. Reporting by clinicians could similarly have been affected.

3. Attrition bias. The dropout rate from randomization was 40% and, from those who started the study, was 31% at eight weeks. Sackett[24] states that it would be unusual for a trial to survive a worse case analysis if it lost more than 20% of its patients.

4. Outcome measures. The diagnostic criteria for bacterial vaginosis were changed in mid trial. The authors admit there was no difference between treatment groups when clinical criteria were used for outcome assessment, nor was there a significant difference in cure rates for Gram-stained smear at five or eight weeks. Only one MLSO assessed all smears, which may have helped reliability of the results, but validity may have been improved if a second technician had assessed a proportion of the slides.

Precision of the study

It would be ideal if, before this study, the authors had done a precision analysis, having first been clear of the desired outcomes. They have produced a power calculation from the results, stating that the study had an 85% power to detect a 25% difference in bacterial vaginosis cure rates by Gram-stained smear between seven days and single-dose metronidazole therapy at the first follow-up visit. Such a power is reasonable; however, the calculation does not appear to have been extended to the arm of the study involved with treatment of the partner, nor have the results

Table 2. 2 ´ 2 table for clinical criteria as a test for bacterial vaginosis, using Gram-stained smear as the gold standard.[23]

	Gram-stained smear positive for bacterial vaginosis	Gram-stained smear negative for bacterial vaginosis
Clinical criteria positive for bacterial vaginosis	8	11
Clinical criteria negative for bacterial vaginosis	17	76
Positive predictive value	42%	
Negative predictive value	82%	
Sensitivity	32%	
Specificity	87%	

been presented in the most useful format, which would be as a difference between the two groups expressed as a percentage with 95% confidence intervals. It is not possible to reproduce this calculation from the figures presented. It is likely that, with the high dropout rates and low numbers, that the power of this study to show a difference for treating the sexual partner would be very low, and any confidence intervals produced would be wide and crossing zero.

It is unlikely that the finding of decreased symptoms at eight weeks would have clinical significance as there was no difference in bacterial vaginosis rates at five and eight weeks, and most women had guessed which treatment group they were in.

Summary

A number of potential sources of bias have been identified, in particular in the method of diagnosing bacterial vaginosis and cure. The high dropout rate and relatively low numbers of patients and consenting partners in each of the four groups will have had a deleterious effect on the precision of the study. In retrospect, more useful evidence would have been gained if the trial had been restricted to a single aim. It is difficult to recommend simultaneous treatment of sexual partners of women with bacterial vaginosis on this evidence.

Trial 2: Vutyavanich *et al*[20]

Description

This was a randomized, double blind trial of 250 monogamous women aged 17 to 40 with symptomatic bacterial vaginosis attending a gynaecology clinic in Thailand. All women were given a single oral dose of tinidazole and half of the women's partners given the same, the rest were given a placebo (Figure 2).

The main outcome measure was clinical cure at four weeks. No statistical difference (P>0.05) was found when treatment of the partner was compared with placebo.

The authors state that tinidazole was chosen because 'it is more effective than metronidazole *in vitro* against *gardnerella vaginalis* and certain anaerobes, especially Bacteroides'. There is no evidence of conflict of interest. Ideally, metronidazole would have been used to improve generalizability of the findings, although tinidazole appears to be equivalent.[25]

Possible sources of bias in this study

1. Selection and performance bias. This is a very simple study looking at the cure rate of women with bacterial vaginosis at one and four weeks after a single dose of tinidazole, and comparing the effect of giving either the same dose or placebo to sexual partners.

Diagnosis and cure of bacterial vaginosis was based on Amsel's clinical criteria (three out of four being present). Only two gynaecologists were used — they each examined every patient initially — and a kappa index of clinical agreement was produced (0.687): a very respectable score and a good attempt to improve the validity of the study. A table of baseline characteristics of the patients is included, and the patients in the two groups appear similar. There is no discussion on how the authors assessed monogamy or whether they assessed male partners for 'monogamy'.

All clinicians, patients, and partners were kept blind to the randomization, which was achieved using a table of random numbers. The drugs and placebos looked identical and were presented in the same packaging. Drugs were given to and taken by the women in the clinic under supervision; the women took the partners' drugs home but were asked to return the empty packets and report whether their partners had taken the drugs. They point out that they would have liked to witness the partner taking the drugs but that would have been impractical.

2. Attrition bias. Two hundred and fifty out of 726 symptomatic patients met the eligibility criteria (267 had bacterial vaginosis) and were randomized: 125 into each group. Seven were later excluded (four placebo, three treatment group): four because they did not return for follow-up visits, one was found positive for *Trichomonas vaginalis*, and two were found positive for gonococci. Of the remaining 243, 10 (four placebo and six treatment) attended the first follow-up visit and not the second, and two (placebo group) attended the second visit only. This represents a very low dropout rate. This is a remarkably different dropout rate to all other included trials, raising questions on how it was achieved.

3. Outcome assessment. As already discussed, outcomes were assessed by two 'blinded' gynaecologists who had undergone a process of assessing clinical agreement. It is difficult to imagine that they could have been more thorough in eliminating detection bias.

Precision of the study

The authors performed a calculation after the study and found a power of 95% to detect an improvement in the clinical cure rate or symptomatic improvement rate of 20% or more. The limit for type one error is the usual 0.05. Importantly, results are presented in the ideal format: percentage difference with 95% confidence intervals. This helps the reader to judge quickly whether the results are significant, and gives far more information than P-values (Figure 2).

Throughout, raw figures are given and intention-to-treat analysis is used.

Summary

This is a well-designed and executed trial, which is difficult to fault; the results concur with five out of six trials that there is no benefit in treating the sexual partner of women with bacterial vaginosis.

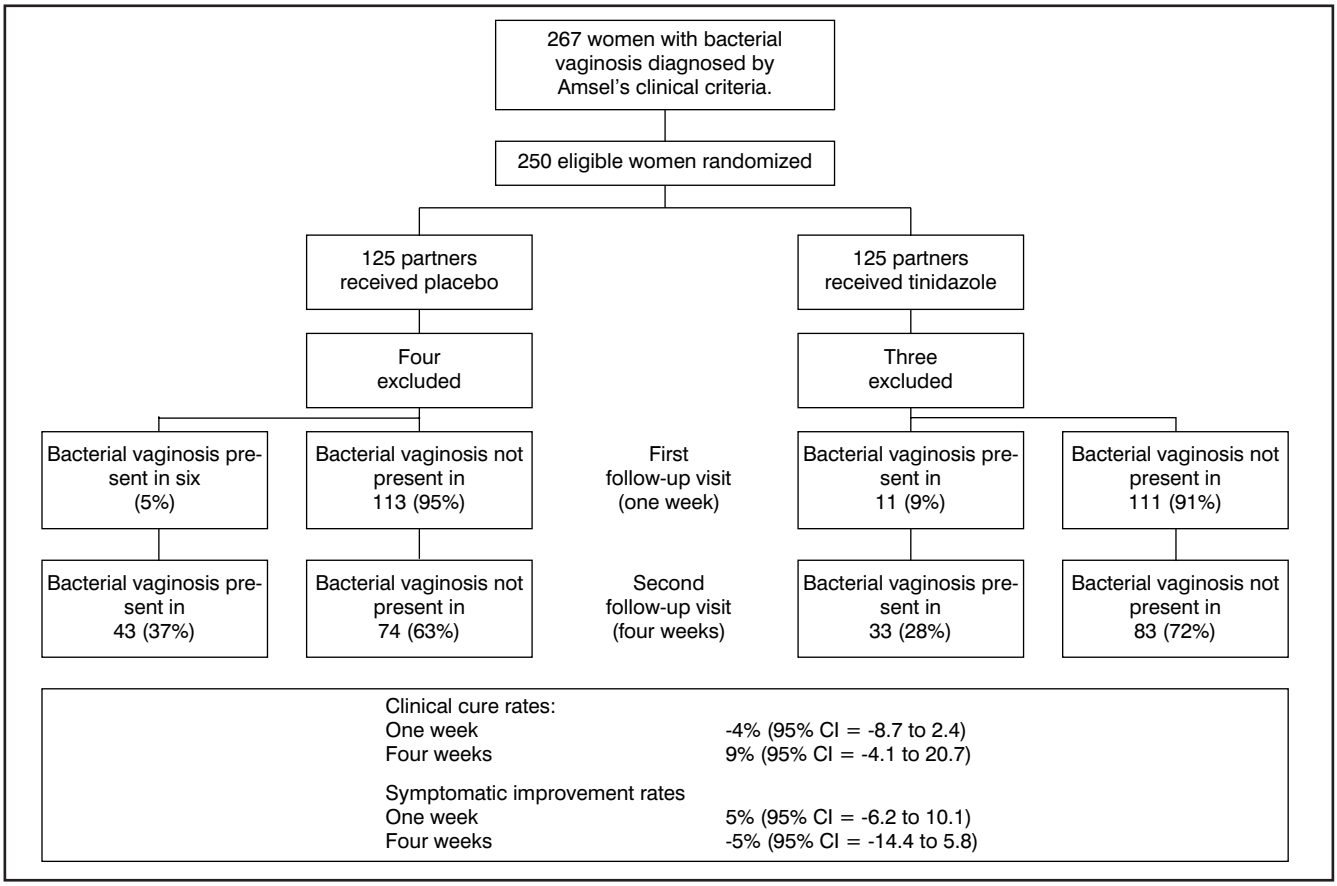

Figure 2. Graphic of clinical trial Vutyavanich et al.[20]

Conclusions

Six trials assessing the benefit of treating the sexual partner of women with bacterial vaginosis were found. None were on British patients, and two[17,21] also assessed different treatment regimes for the woman, which reduced the precision of the trials. Only two[18,19] used the same treatment regime (metronidazole 2 g repeated after two days). All used Amsel's clinical criteria for the initial diagnosis of bacterial vaginosis, and all but Mengel *et al* used the same criteria for follow-up. This raises issues of generalizability of the findings in that the preferred method of diagnosis in British general practice is Gram-stained smear. Given the debate raised by Mengel *et al*,[17] Gram-stained smears may not be identifying the same problem as Amsel's clinical criteria.

The evidence suggests that there is no benefit in treating the sexual partner of women with bacterial vaginosis with the drug regimens tested. It should be remembered however, that at least three of the trials have either very small treatment groups or large dropout rates or both.[17,18,21] No evidence of effect does not equate to evidence of no effect. On balance, however, there appears to be no justification for treating the sexual partner of a woman with bacterial vaginosis.

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