Randomised treatment trial of bacterial vaginosis to prevent post-abortion complication

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Objective To evaluate the efficacy of metronidazole to reduce post-abortion complications among women with bacterial vaginosis.

Design A randomised, double-blind placebo-controlled trial.

Setting An American outpatient abortion facility between April 1999 and June 2000.

Sample Women presenting for surgical abortion were screened for bacterial vaginosis using a pH and amines card test.

Methods Women positive for elevated pH and amines on a self-collected vaginal discharge sample were randomised to 1000 mg oral metronidazole before abortion followed by 500 mg twice daily or placebo. All randomised women were also dispensed 100 mg doxycycline to take twice daily for seven days.

Main outcome measures Data were collected by phone, daily diary or visit and scored from 0 to 7 for post-abortion complications. Intention-to-treat analyses were completed prior to unblinding.

Results Of 1764 women screened by card test, 638 (36%) were positive. Of these, 393 were randomised. Follow up data were available for 253 (64%) of these women. A complication score of 3 or more occurred in 21% of women assigned to metronidazole, compared with 19% in those assigned placebo (RR 1.1, 95% CI 0.7–1.9). Among 153 women with Gram stain confirmation for bacterial vaginosis, there was a similar lack of benefit with treatment (RR 1.6, 95% CI 0.9–3.0). No individual symptom or sign was statistically different between groups even for second trimester procedures.

Conclusion Among women undergoing abortion and diagnosed with bacterial vaginosis, oral metronidazole, in conjunction with doxycycline, did not reduce post-abortion complications.

INTRODUCTION

In the United States, over a million women annually undergo voluntary termination of pregnancy or abortion. Because many women travel outside their county of residence to obtain an abortion, the time to screen and treat infections prior to instrumentation is limited. The incidence of infectious complications after elective surgical abortion can approach 12% and infection is responsible for 16% of abortion mortality.

A recent meta-analysis recommended universal antibiotic prophylaxis at the time of induced abortion. However, the optimal antibiotic and dosing regimen remain unclear. In the UK, it has been recommended that women either be screened or given prophylactic antibiotics for both Chlamydia trachomatis and bacterial vaginosis. Still, most women in the United States are not screened for any infection and receive only prophylactic doxycycline following abortion. While C. trachomatis screening or prophylaxis is efficacious, it is unknown if screening or prophylaxis for bacterial vaginosis provides additional benefit.

In one randomised, placebo-controlled trial, metronidazole treatment of bacterial vaginosis a week prior to abortion reduced post-abortion infectious complications from 12.2% to 3.8%. A more recent trial found that a single dose of 200 mg metronidazole administered on the day of first trimester surgical abortion reduced post-abortion symptoms and antibiotic prescription. In these trials, diagnosis of bacterial vaginosis was based on either wet mount or Gram stain, and women with C. trachomatis were either excluded or treated prior to the procedure.

We randomised women with elevated vaginal pH and amines detected in their vaginal discharge into a double-blind treatment trial. We wished to determine whether seven days of oral metronidazole, started on the day of the procedure, in addition to standard doxycycline prophylaxis, would reduce signs and symptoms of post-abortion infectious complications.
METHODS

The institutional review board of the University of Washington approved the study. All women presenting for surgical abortion at a single facility between May 1999 and June 2000 were given an information sheet about the study at registration. Interested women were administered a standardised verbal consent to test for bacterial vaginosis. Women planning a medical abortion, abortion under general anaesthesia or with current vaginal bleeding (since cervical mucus, macroscopic blood and urine can cause false card test results) were excluded from screening. To identify women with bacterial vaginosis prior to the abortion procedure, women were given a sterile cotton swab and instructed both verbally and by restroom poster to collect a vaginal specimen prior to urination. Women were instructed to place the swab into the vagina approximately 3 in., turned the swab three complete revolutions (avoiding contact with the cervix) and place it into a clean, single-use plastic test tube. The swab was applied to the FemExam (Cooper Surgical, Trumbull, Connecticut, USA) card test to identify women with bacterial vaginosis.

The FemExam card test is a flat plastic card with two clearly marked circles where vaginal secretions are applied and observed for two minutes. The FemExam test is approved by the American FDA to detect abnormal amine concentration or pH ≥ 4.7 in vaginal fluid. A blue ‘plus’ sign signifies a pH ≥ 4.7, the presence of volatile amines >0.50 mM concentrations or both when plus signs are present in both windows. A study assistant applied the swab to the card per the package labelling and recorded the card test results. Following the card test, the same swab was rolled on to a glass slide, air-dried, labeled, stored in a dark slide box and sent for Gram stain at our research microbiology laboratory. The slides were interpreted using Nugent criteria by a single experienced microbiologist blinded to the card test results and randomisation assignment. All card test positive slides were stained and scored, but because of cost, only every third negative card test slide was analysed.

Women with a positive card test were offered enrolment into the randomised treatment trial following a written informed consent. Exclusions were (1) non-English speaking, (2) metronidazole allergy, (3) alcohol dependence, (4) current antibiotic use within five days of enrolment, (5) refusal of the verbal consent for bacterial vaginosis screening and/or the written consent for treatment study randomisation, (6) unwilling or unable to be contacted by phone in 7–10 days to answer questions about symptoms, (7) history of a heart murmur, as these women received amoxicillin or other streptococcal antibiotic coverage prior to the procedure, (8) doxycycline allergy necessitating the use of a different C. trachomatis antibiotic prophylactic, (9) inability to swallow gelatine capsules, (10) bleeding or a bloody card test specimen limiting test accuracy, and (11) planned medical abortion.

A self-administered questionnaire was used to ascertain demographics, prior diagnosis of bacterial vaginosis, douching habits and other risk factors. Routine counselling, ultrasound, other laboratory testing and the abortion procedures were carried out by regular clinic staff. All procedures were performed by one of two providers. Aspiration was used up to 12 weeks of gestation, whereas dilation and evacuation following one or two days of hygroscopic dilators was used for later gestations. Intrafetal digoxin injection 24 hours prior to the procedure was used after 18 weeks of gestation. All women were given C. trachomatis prophylaxis beginning after the procedure unless a history was given of C. trachomatis infection or pelvic inflammatory disease within the prior 12 months, in which case, the antibiotic was begun 1 hour prior to the procedure.

An off-site institutional pharmacy (Harborview Medical Center, Seattle, Washington, USA) supplied study medications, the randomisation schedule and allocation verification. Placebo tablets identical in appearance to metronidazole were not available, so gelatine capsules were used to dispense pulverised study medication. A computerised random number generator program was used to generate a single, balanced block of 310 subjects. Subsequently, with additional funding, 90 more subjects were randomised in blocks of 10. The resulting assignment schedule of 400 subjects was concealed throughout the duration of the study period and it was not broken until data analysis was complete.

Approximately 60 minutes prior to the surgical procedure, the woman was randomised by dispensing a sequentially numbered (1–400) prescription bottle containing identical gelatine capsules of either 250 mg of metronidazole or placebo. The woman was instructed to take four capsules orally and to continue taking two capsules twice a day for seven days. Women assigned to active drug took 1000 mg of metronidazole prior to the procedure and 500 mg twice a day for the following week. In addition, at discharge the woman was dispensed fourteen 100 mg doxycycline capsules, to be taken twice a day for the same week. No information was collected regarding the post-abortion prescription or actual use of hormonal contraceptive or pain medication. Additional information was abstracted by the study assistant from the clinic chart. If a clinic physician prescribed metronidazole because of concerns about infection, the woman was discontinued from study medication but was followed and included in all analyses as assigned.

All women were asked to telephone the clinic after the procedure if they experienced symptoms including fever, excessive bleeding or pain. A telephone appointment was made for 7–10 days post-procedure and a standardised follow up questionnaire was administered. Information on compliance, side effects and symptoms of infection (including days of bleeding, abnormal vaginal discharge, fever, feeling unwell or ill (malaise), abdominal or pelvic pain) and interim clinic visit(s) were collected.

Women returning to the clinic for a routine or non-routine post-abortion visit because of suspected infection within 12 weeks following the procedure were asked standardised questions identical to those administered by phone. The woman’s temperature was recorded and a pelvic exam was performed to assess cervical mucopurulence and tenderness, uterine examination finding (tender, boggy, enlarged or normal), adnexal masses or tenderness and whether and why antibiotics were prescribed. If hospitalisation or a post-abortion visit occurred elsewhere, records or information about the visit were sought and abstracted using the standardised visit form.

Two study protocol changes occurred during the study. The first was designed to improve follow up data collection. Beginning with the 124th randomised woman, a 28-day diary was provided to the subject to record pill compliance, amount of bleeding and symptom information. Diaries were returned by mail and women were compensated $20 upon receipt. The second protocol change was designed to increase the enrolment of women with Gram stain confirmed bacterial vaginosis. Beginning with the 235th randomised woman, the research assistant was instructed to enrol only women with bright blue coloration of the plus sign for amines on the card test.

Twelve weeks after study completion, study data forms were reviewed by the principal investigator (L.M.) and post-abortion complication scores were assigned according to pre-defined criteria derived from a previous study. The score ranged from 0 to 10 and consisted of the sum of the following, weighted as one point each: (1) vaginal discharge or odor ≥ 7 days after abortion; (2) purulent cervical discharge on examination ≥ 7 days after abortion; (3) tenderness of the uterus or adnexae on pelvic examination; (4) abnormally heavy bleeding of ≥3 days or continued bleeding ≥ 7 days after abortion; (5) palpable adnexal masses on pelvic examination; (6) self-report of pain, excessive tiredness or feeling unwell ≥7 days after abortion; and weighted as two points each: (1) temperature greater than 38°C reported for ≥24 hours or measured on examination; (2) antibiotics given for pelvic infection at a follow up visit. Thus, eight symptoms or signs were measured from study chart documentation that may have included a post-abortion visit, a telephone follow up questionnaire, a self-administered diary mailed back and/or outside records. A priori, we decided that scores of 3 and 5 were clinically relevant cut-points for analysing the post-abortion complication score.

The pre-study power calculation indicated that 186 subjects were needed in each arm to achieve 80% power to detect a decrease in infectious complications as large as that reported by Larsson et al. from 12.2% to 3.8%. All data recorded on standardised data forms were entered centrally, double entry verified and analysed off site. Categorical variables were compared using Fisher’s exact test.
test. Continuous variables were compared using t tests. Two-tailed P values of ≤0.05 were considered statistically significant. Analyses were by intent-to-treat, meaning that subjects were analysed according to the randomised group assignment regardless of compliance with treatment. All analyses were completed before unblinding.

**RESULTS**

Of 2522 women seeking surgical abortion under local anaesthesia, 1764 (70%) were screened for bacterial vaginosis using the pH and amine card test (Fig. 1). The screening could not be performed on the following women: 471 who refused specimen collection, 168 who did not speak English, 62 in whom the swab was contaminated with blood or urine or was too dry to perform the card test, 18 who decided to choose medical abortion and 39 with a reason not recorded for failing to perform the card test. Bacterial vaginosis was suspected in 683 (39%) women based on a positive card test (elevated pH and amines).

Of women with a positive card test, 400 (58% of those eligible) gave written informed consent for randomisation to placebo or metronidazole, but 7 were not randomised because 1 could not swallow the gelatine capsules, 3 withdrew consent and 4 did not have the procedure. Of the 393 women randomised, 236 (60%) had bacterial vaginosis confirmed by a Gram stain score of 7–10 on their pre-procedure vaginal discharge sample, whereas 151 (38%) had normal Gram stain scores (0–3) or an intermediate score of 4–6 and 6 (2%) had no Gram stain score determined (slide lost or broken).

Follow up information was obtained for 253 (64%) of all women randomised and of these, 154 women (61%) had bacterial vaginosis by Gram stain (Fig. 1). Outcome data were obtained by phone from 205 (81%) of 253 women, by diary from 67 and by interview and examination at the clinic from 115 (some subjects had multiple sources of follow up data). The median time elapsed between abortion and follow up questionnaire administration was 10 days (range 4–99) for telephone contact (often after multiple attempts) and 12 days (range 2–90) if obtained at clinic visit.

Demographic, clinical characteristics and baseline risk factors were compared between those with and without follow up for all subjects and among those with confirmed bacterial vaginosis by Gram stain. No significant differences were found between groups (data not shown) except fewer women contributing follow up data underwent an additional suction aspiration on the day of the abortion

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**Table 2.** Symptoms, signs and post-abortion complication score* by randomisation group among all subjects with follow up. Values are given as n (%) or RR [95% CI].

<table>
<thead>
<tr>
<th>Complication symptoms or signs</th>
<th>Metronidazole (n = 131)</th>
<th>Placebo (n = 122)</th>
<th>RR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Odour/vaginal discharge for ≥7 days</td>
<td>18 (14)</td>
<td>28 (23)</td>
<td>0.6 [0.3–1.0]</td>
</tr>
<tr>
<td>2. Purulent cervical discharge on exam</td>
<td>1 (1)</td>
<td>4 (3)</td>
<td>0.2 [0.0–2.1]</td>
</tr>
<tr>
<td>3. Uterine tenderness on exam</td>
<td>6 (5)</td>
<td>11 (9)</td>
<td>0.5 [0.2–1.3]</td>
</tr>
<tr>
<td>4. Abnormal bleeding after abortion</td>
<td>81 (62)</td>
<td>75 (61)</td>
<td>1.0 [0.8–1.2]</td>
</tr>
<tr>
<td>5. Palpable adnexal masses</td>
<td>0 (0)</td>
<td>2 (2)</td>
<td>–</td>
</tr>
<tr>
<td>6. Pain/malaise/unwell for ≥7 days</td>
<td>40 (31)</td>
<td>50 (41)</td>
<td>0.7 [0.5–1.0]</td>
</tr>
<tr>
<td>7. Temperature &gt;38°C for ≥24 hours</td>
<td>13 (10)</td>
<td>6 (5)</td>
<td>2.0 [0.8–5.1]</td>
</tr>
<tr>
<td>8. Antibiotics given after exam</td>
<td>9 (7)</td>
<td>11 (9)</td>
<td>0.8 [0.3–1.8]</td>
</tr>
<tr>
<td>Total post-abortion complication score ≥3</td>
<td>28 (21)</td>
<td>23 (19)</td>
<td>1.1 [0.7–1.9]</td>
</tr>
<tr>
<td>Total post-abortion complication score ≥5</td>
<td>8 (6)</td>
<td>10 (8)</td>
<td>0.7 [0.3–1.8]</td>
</tr>
</tbody>
</table>

* The post-abortion score could range from 0 to 10 but was never higher than 7 and consisted of the sum of the symptoms or signs as listed in the table and if present; weighted as one point each (1–6) and two points each (7–8). No symptom, sign or score was statistically significantly associated with randomisation, at P < 0.05 by Fisher’s exact test. This is an intent-to-treat analysis, meaning all subjects were analysed according to the randomisation group, regardless of compliance to treatment.

procedure (5/82 vs 1/154). In addition, no differences were seen in reported baseline risk factors for either bacterial vaginosis or pelvic infection by drug assignment status (Table 1). The subject body mass index, mean gestational age and percent undergoing a second trimester procedure were also similar between the metronidazole and placebo subjects.

Complication scores and individual symptoms and signs are compared by study drug assignment among those with follow up data in Table 2. Complication scores ranged from 0 to 7. Among women with bacterial vaginosis by Nugent criteria, 76 (49%) had a complication score of 7 or 1, while 35 (23%) had a score of 3 or more. Among all women with follow up, 138 (55%) had scores of 0 or 1 while a score of ≥3 was present in 28 (21%) women assigned to metronidazole and 23 (19%) assigned to placebo (RR 1.1, 95% CI 0.7–1.9, P = 0.6) (Table 3). A score of ≥3 was more common among those assigned to metronidazole (n = 22, 28%) compared with placebo (n = 13, 17%) (RR 1.6, 95% CI 0.9–3.0, P = 0.1) (Table 3) but was not statistically significant. Post-abortion complications were as common in women with abnormal Gram stain scores (scores of 4–10) as in women with normal Gram stain scores (0–3) (data not shown). No individual symptom or sign was significantly different between the two groups (Tables 2 and 3). The number of card test positive subjects reporting an abnormal vaginal odour or discharge post-abortion were fewer in the group assigned metronidazole compared with placebo, but this difference was not statistically significant. A post-abortion complication score of ≥3 occurred in 22% of women with a first trimester procedure and in 24% of women with a second trimester procedure.

We also examined the effect of drug compliance on outcome. The correct dose and duration of study drug use were reported by 178 (70%) of the 253 women while the remaining subjects reported some alteration of the planned drug dose and schedule. The study drug was terminated early by 36 (14%) and 24 (9%) women took less than two capsules each day. Only five (2%) of the women reported a discontinuation of the study drug because of side effects and typically these women also stopped taking doxycycline. Compliance with doxycycline did not appear otherwise to vary and if a subject took the study drug she also took the doxycycline in most cases. Eighteen women reported nausea and nine experienced vomiting. Women with perfect study drug compliance assigned to metronidazole had no statistically significant differences in symptoms, signs or score compared with subjects not complying with the study drug regimen (data not shown).

The charts of the nine women testing positive for bacterial vaginosis on Gram stain with complication scores of 5 or greater were reviewed in more detail. Five had first trimester procedures and eight took the study drug correctly. One had frank pelvic inflammatory disease and a positive gonorrhoea culture at follow up and two presented to local emergency rooms three weeks following a second trimester procedure and were given intravenous antibiotics, but culture or histologic confirmation of infection was not obtained. No woman had retained tissue.

**DISCUSSION**

Abortion is a common gynaecological procedure that surpasses the frequency of both caesarean section and hysterectomy. Bacterial vaginosis is considered a risk factor for post-abortion genital tract infections. Currently, screening for bacterial vaginosis requires a speculum examination and microscopic skills. Because many American women obtain abortions without a pre-operative visit, we studied, whether screening for bacterial vaginosis could be done without a speculum exam. And, if treatment with oral metronidazole starting the day of the procedure would reduce post-abortion complications among women who also receive doxycycline for *C. trachomatis* prophylaxis.

The pH and amines card test was easy to perform using a self-collected vaginal discharge sample. However, compared with Gram stain, the low positive predictive
value of the card test resulted in 60% of our randomised women not meeting accepted criteria for the diagnosis of bacterial vaginosis. Although bacterial vaginosis was common in our study, with 25% of the women screened testing positive by Gram stain, we demonstrated no reduction in post-abortion complications in women treated with metronidazole.

Our findings are limited by the absence of follow up data for 36% of the randomised women. Our follow up rates were similar in the placebo (62%) and metronidazole (67%) groups and similar to rates in prior studies. Baseline characteristics were similar among those in the two arms, giving us no reason to believe that bias arose due to a relationship between loss to follow up and treatment assignment. In addition, we could not demonstrate that compliance affected the results or that a second antibiotic compromised compliance. The slightly negative effect of metronidazole in women with Gram stain confirmation of bacterial vaginosis (RR 1.6, 95% CI 0.9–3.0) underscores the lack of benefit of the additional antibiotic. Our results also do not exclude the possibility there may be a small effect from metronidazole that could be found if a larger sample size was studied.

The possibility that bacterial vaginosis is not a risk factor for post-abortion complication is unlikely because of prior links between bacterial vaginosis and signs of post-abortion infection and the absence of these signs when bacterial vaginosis was treated a week prior to the procedure. Interestingly, these studies utilised culture or clinical criteria and not solely the Gram stain score as we did for the diagnosis of bacterial vaginosis. Whether it is possible to identify the women seeking abortion who might benefit from antimicrobial coverage against anaerobes remains unclear. In one randomised trial, universal prophylactic administration of rectal metronidazole, in addition to post-operative doxycycline, was most beneficial to the women testing negative for all infections at a screening visit. A significant reduction in post-caesarean endometritis was attained with the use of vaginal metronidazole at the time of surgery without any pre-operative screening for bacterial vaginosis. Some investigators recently demonstrated that the vaginal flora can vary from one day to the next when measured by Gram stain and suggest transient flora changes may be normal. We did not study symptomatic women or women with bacterial vaginosis diagnosed by clinical criteria and there is still the possibility metronidazole prophylaxis could benefit that population.

We chose metronidazole because of its anaerobic coverage and ability to treat bacterial vaginosis. A 500 mg oral dose taken 1 hour prior to the procedure produces therapeutic serum levels including placental tissue levels. In our study, the procedure usually occurred less than an hour following ingestion of 1000 mg of metronidazole and therapeutic tissue levels may not have been achieved for many women prior to instrumentation. However, we found no evidence metronidazole benefited the women who underwent a second trimester procedure and began study medication at the time of hygroscopic dilator placement at least 24 hours prior to uterine evacuation. In our study, almost half of the women underwent second trimester procedures, and yet the percent of women with a post-abortion complication score of 3 or greater were similar after first trimester (22%) and second trimester (24%) procedures.

One randomised controlled trial that diagnosed bacterial vaginosis using clinical criteria demonstrated a significant benefit of oral metronidazole prophylaxis when the antibiotic or placebo was begun at least four days prior to first trimester surgical abortion. By contrast, two more recent trials did not observe a significant reduction in post-abortion infectious complications in women meeting Gram stain criteria for bacterial vaginosis. The first trial compared vaginal clindamycin or placebo used days prior to abortion, and the second trial randomised women to a single rectal dose of metronidazole or placebo administered the day of the procedure. Of importance, in all three trials, there was no concurrent use of doxycycline and women screened positive for C. trachomatis were either excluded or included only after treatment.

The routine administration of doxycycline for C. trachomatis prophylaxis is effective in reducing post-abortion morbidity. Doxycycline use may have reduced the incidence and severity of post-abortion complications among women with bacterial vaginosis. Our study was conducted within a typical American abortion practice without a pre-procedure visit, C. trachomatis screening is not routine and all women randomised also received a seven-day course of doxycycline. Although doxycycline is not highly active against many of the bacteria contributing to the overgrowth of vaginal flora in women with bacterial vaginosis, successful antibiotic prophylaxis for a surgical procedure may be achieved by inhibition of only a portion of the contaminating bacteria.

A problem in studies of infectious complications of abortion is the lack of standardisation and specificity of the clinical signs and symptoms used for ascertainment of complications. The rates of individual post-abortion clinical signs and symptoms in this report are consistent with prior reports, including prescribing of antibiotics, but the absence of a standardised early post-abortion exam may have minimised detection of early or mild endometritis. Without histology to confirm a pathologic diagnosis, it is possible the constellation of signs and symptoms we call complications are mostly within the natural history following abortion.

We began with the a priori hypothesis that identification and the treatment of bacterial vaginosis would reduce endometritis. Although bacterial vaginosis was highly prevalent in women seeking surgical abortion in our study, metronidazole prophylaxis was of no additional benefit for these women who also receive doxycycline.
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