การสวนล้างช่องคลอดด้วยไฮโดรเจนเพอร์ออกไซด์ครั้งเดียว เปรียบเทียบกับการรับประทานยาเมโทรนิดาโซลครั้งเดียว ในการรักษาภาวะแบคทีเรียลวาไจโนสิส

นายสุรสิทธิ์ ชัยทองวงศ์วัฒนา

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SINGLE HYDROGEN PEROXIDE VAGINAL DOUCHING VERSUS SINGLE-DOSE ORAL METRONIDAZOLE FOR THE TREATMENT OF BACTERIAL VAGINOSIS

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สุรสิทธิ์ ชัยทองวงศ์วัฒนา : การสวนล้างช่องคลอดด้วยไฮโดรเจนเพอร์ออกไซด์ครั้งเดียวเปรียบเทียบกับการรับประทานยาเมโทรนิดาโซลครั้งเดียวในการรักษาภาวะแบคทีเรียลวาไจโนสิส (Single hydrogen peroxide vaginal douching versus single-dose oral metronidazole for the treatment of bacterial vaginosis) อาจารย์ที่ปรึกษา : ศ.นพ.จิตร สิทธิอมร, อาจารย์ที่ปรึกษาร่วม : รศ.นพ. สมภพ ลิ้มพงศานุรักษ์ 48 หน้า ISBN 974-347-071-9

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รูปแบบการวิจัย : การทดลองทางคลินิกแบบสุ่มทดลองโดยมีกลุ่มเปรียบเทียบ

สถานที่ทำการวิจัย : คลินิกผู้ป่วยนอก โรงพยาบาลจุฬาลงกรณ์

กลุ่มตัวอย่าง : ผู้ป่วยสตรีอายุระหว่าง 15 ถึง 45 ปี ซึ่งได้รับการวินิจฉัยเป็นภาวะแบคทีเรียลวาไจโนสิส จำนวน 142 ราย

การกระทำ : แบ่งผู้ป่วยโดยการสุ่มเป็น 2 กลุ่ม กลุ่มแรกได้รับการรักษาโดยการสวนล้างช่องคลอดด้วยไฮโดรเจนเพอร์ออกไซด์ความเข้มข้นร้อยละ 3 ปริมาณ 20 มิลลิลิตร และรับประทานยาหลอกครั้งเดียว กลุ่มที่สองได้รับการรักษาโดยการสวนล้างช่องคลอดด้วยยาหลอกและรับประทานยาเมโทรนิดาโซลขนาด 2 กรัมครั้งเดียว

การวัดผล : อัตราการหาย ประเมินโดยใช้ Amsel's criteria

ผลการศึกษา : อัตราการหายในผู้ป่วยที่ได้รับการรักษาด้วยการสวนล้างช่องคลอดด้วยไฮโดรเจนเพอร์ออกไซด์ครั้งเดียว ต่ำกว่าในผู้ป่วยที่รับประทานยาเมโทรนิดาโซลครั้งเดียว (62.5% ต่อ 78.6%, p value = 0.036) และพบอัตราผลข้างเคียงต่อระบบทางเดินอาหารในผู้ป่วยที่รับประทานยาเมโทรนิดาโซลสูงกว่า (48.6% ต่อ 13.9% , p value < 0.001)

สรุป : การสวนล้างช่องคลอดด้วยไฮโดรเจนเพอร์ออกไซด์ครั้งเดียว มีประสิทธิผลในการรักษาภาวะแบคทีเรียลวาไจโนสิส ต่ำกว่าการรับประทานยาเมโทรนิดาโซลครั้งเดียว

หลักสูตร.....การพัฒนาสุขภาพ..... **ลายมือชื่อนิสิต**.....

สาขาวิชา.....การพัฒนาสุขภาพ..... **ลายมือชื่ออาจารย์ที่ปรึกษา**.....

ปีการศึกษา.....2543..... **ลายมือชื่ออาจารย์ที่ปรึกษาร่วม**.....

4175388130 : MAJOR HEALTH DEVELOPMENT
KEYWORD : HYDROGEN PEROXIDE/ METRONIDAZOLE/ BACTERIAL VAGINOSIS
SURASITH CHAITHONGWONGWATTHANA : SINGLE HYDROGEN PEROXIDE VAGINAL DOUCHING VERSUS SINGLE-DOSE ORAL METRONIDAZOLE FOR THE TREATMENT OF BACTERIAL VAGINOSIS. THESIS ADVISOR : PROFESSOR CHITR SITTHI-AMORN, M.D., M.Sc., Ph.D., THESIS CO-ADVISER : ASSOCIATE PROFESSOR SOMPOP LIMPONGSANURAK, M.D., M.P.H. 48 pp. ISBN 974-347-071-9

Objective : To compare the effectiveness of hydrogen peroxide single vaginal douching and single-dose oral metronidazole for the treatment of bacterial vaginosis.

Design : A randomized double-blind controlled trial.

Setting : Outpatient gynecologic clinic, King Chulalongkorn Memorial Hospital.

Subjects : 142 female patients aged between 15 to 45 years who were diagnosed as having bacterial vaginosis.

Intervention : The eligible patients were randomly allocated into either hydrogen peroxide or metronidazole group. The hydrogen peroxide group were douched with 20 milliliters of 3% hydrogen peroxide and received oral placebo. The metronidazole group received oral metronidazole 2 grams and were douched with placebo.

Main outcome measurement : Cure rate in each group was assessed by using Amsel's criteria

Results : Cure rate in hydrogen peroxide group is lower than in metronidazole group (62.5% versus 78.6%, p value = 0.036). Rate of gastro-intestinal side effects in metronidazole group is higher than in hydrogen peroxide group (48.6% versus 13.9% , p value < 0.001).

Conclusion : Hydrogen peroxide single vaginal douching has less effectiveness than single-dose oral metronidazole in treatment of bacterial vaginosis.

Program.....Health Development..... **Student's signature**.....
Field of study.....Health Development..... **Advisor's signature**.....
Academic year.....2000..... **Co-advisor's signature**.....

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CHAPTER 1

BACKGROUND AND RATIONALE

Bacterial vaginosis is the most common cause of abnormal vaginal discharge in reproductive age women.[1] It results from a shift of bacteria in vagina from the normal peroxide-producing lactobacilli to a polymicrobial group consisting of anaerobes, *Gardnerella vaginalis* and *Mycoplasma hominis.*[2,3] Recent studies have confirmed its association with several obstetrics and gynecologic complications, including acute pelvic inflammatory disease, postoperative infection following hysterectomy and preterm labor.[4-10]

The major clinical feature of bacterial vaginosis is the presence of a thin malodorous homogeneous gray-white vaginal discharge.[1] Diagnosis of bacterial vaginosis was considered if three of the four following criteria are found: (1) homogeneous vaginal discharge, (2) vaginal pH greater than 4.5, (3) fishy amine odor with mixture of discharge with 10% potassium hydroxide (KOH), called positive "whiff" test, and (4) the presence of more than 20% of epithelial cells classified as clue cells (vaginal epithelial cells with adherent bacteria) on saline wet mount or Gram stain.[11,12]

Standard treatment regimens for bacterial vaginosis include 7 days course or single-dose oral metronidazole, oral clindamycin, clindamycin vaginal cream and metronidazole vaginal gel.[1,13] Topical formulations have the

advantage of reduced systemic side effects but are significantly more expensive, as compared to metronidazole[13], and are not available in Thailand.

Hydrogen peroxide (H_2O_2) production has been proposed as a mechanism by which lactobacilli may inhibit the growth of other vaginal organisms.[14] Studies about association between vaginal microflora and bacterial vaginosis supported the hypothesis that H_2O_2-producing vaginal lactobacilli protect against acquisition of bacterial vaginosis.[15] From this evidence, there is a question that whether H_2O_2 is effective for treatment of patients with this condition or not. If it is effective in the treatment of bacterial vaginosis, it might be widely applicable in clinical practice because it is cheap, easily available and amendable to topical use.

There is one study that reported the efficacy of using a single vaginal washout with 3% H_2O_2 for treatment of bacterial vaginosis[16], however, it was not a controlled trial. For testing the effectiveness of single vaginal douching with 3% H_2O_2 in the treatment of bacterial vaginosis, this randomized study was conducted to compare the effectiveness between single vaginal douching with 3% H_2O_2 and single-dose oral metronidazole.

CHAPTER 2

LITERATURE REVIEW

2.1 Epidemiology

2.1.1 Prevalence

Bacterial vaginosis is the most common cause of vaginal discharge in reproductive age women.[1] The prevalence of bacterial vaginosis varies widely among the different populations studied. Women seen in sexually transmitted disease clinics have the highest prevalence of bacterial vaginosis ranging up to 61%.[17-20] For college students, estimates of prevalence is 5% if totally without symptoms to 25% for those with gynecologic symptoms.[21] Among women attending family planning clinics and gynecologic clinics, the prevalence of bacterial vaginosis also varies from 7% to 39%.[22-24]

Studies of pregnant women demonstrate prevalence for bacterial vaginosis similar to those found among the nonpregnant population. Among pregnant research volunteer in U.S. studies, the prevalence of bacterial vaginosis varies from 10% to 32%.[21] The prevalence in Thai pregnant women was 15.9%.[2]

2.1.2 Risk factors

2.1.2.1 Race

When groups of U.S. women are examined in greater detail, the prevalence of bacterial vaginosis is highest among African American women. However, in the study of Gravett, et al.[25] of 534 pregnant women, bacterial vaginosis was diagnosed in 17% of white patients and 25% of non-white patients, a statistically insignificant different.

2.1.2.2 Sexual activity

Whether bacterial vaginosis is sexually transmitted continued to be debated. There are a number of factors that link bacterial vaginosis to sexual activity. Bacterial vaginosis most often occurs among sexually active women and may be related to acquiring a new male partner.[26] In general, bacterial vaginosis occurs more frequently among women who have initiated sexual activity at earlier ages, among women reporting more sexual partners, and among women with concurrent or prior sexually transmitted infections.[26,27]

Conversely, detection of bacterial vaginosis among virginal women and children, although the occurrence is low, weighs against sexual transmission as the exclusive means for acquisition of bacterial vaginosis.[28] Strong evidence contradicting exclusive heterosexual transmission of bacterial

vaginosis comes from a number of randomized controlled trials demonstrating the recurrence of bacterial vaginosis among women despite the treatment of male contacts.[29,30]

2.1.2.3 Contraceptive techniques

Bacterial vaginosis has been detected more often among women not using any method of contraception and among women using an intrauterine contraceptive device.[11,31] Bacterial vaginosis has not been related to oral contraceptive use. The incidence of bacterial vaginosis is reduced among women using the spermicide nonoxinol 9.[26]

2.2 Microbiology

Microbiologically, bacterial vaginosis is characterized by a shift of the vaginal flora from the normal peroxide-producing lactobacilli to a polymicrobial group consisting of anaerobes (*Bacteroides* species, *Prevotella* species, *Porphyromonas* species, *Peptostreptococcus* species, *Mobiluncus* species), *Gardnerella vaginalis* and *Mycoplasma hominis.*[2,3]

The production of H_2O_2 by lactobacilli has been proposed to represent a nonspecific antimicrobial defense mechanism of the normal vaginal ecosystem. In one study, the vagina of 96% of normal women contained H_2O_2-producing lactobacilli, and 4% contained anaerobic lactobacilli that did

not produce H_2O_2. In contrast, 6% of women with bacterial vaginosis contained H_2O_2-producing lactobacilli in their vagina, while 36% contained H_2O_2-nonproducing lactobacilli.[14] In vitro study, H_2O_2-producing lactobacilli were shown the bactericidal effect to both *Gardnerella vaginalis* and *Bacteroides bivius.*[32] A study in Japanese and Thai pregnant women found the association between *Prevotella* species, *Porphyromonas* species, *Peptostreptococcus* species, *Mobiluncus* species, *Gardnerella vaginalis*, H_2O_2-nonproducing lactobacilli and bacterial vaginosis. These organisms were less associated with H_2O_2-producing lactobacilli, with were predominant in women with normal flora.[2] Another cohort study of 182 women attending a sexually transmitted disease clinic also supported the hypothesis that H_2O_2-producing vaginal lactobacilli protect against acquisition of bacterial vaginosis, however, do not protect against vulvovaginal candidiasis and vaginal trichomoniasis.[15]

2.3 Clinical Implications and Morbidity

Bacterial vaginosis is associated with an increased risk of several gynecologic conditions, including postoperative infection following hysterectomy and postabortion pelvic inflammatory disease.[4] The risk of plasma cell endometritis in women with bacterial vaginosis has been reported to be 15 times higher than the risk in women without bacterial vaginosis.[33]

In pregnant women, bacterial vaginosis is associated with the presence of fetal fibronectin. Women with fetal fibronectin have a 16-fold increase in

clinical chorioamnionitis and a sixfold increase in neonatal sepsis.[8] The microorganisms found in bacterial vaginosis are also commonly found in the amniotic fluid of women with amniotic fluid infection.[34] The odds ratio for premature rupture of the membranes is 7.3 in women with bacterial vaginosis.[35] Bacterial vaginosis has been associated with low birth weight[9] and preterm birth, with odds ratios for preterm birth estimated to be 1.84.[10]

2.4 Diagnosis

Clinical diagnosis can be performed by using the criteria proposed by Amsel and colleques.[11] It was considered present if three of the four following criteria were found: (1) homogeneous vaginal discharge, (2) vaginal pH greater than 4.5, (3) fishy amine odor with mixture of discharge with 10% KOH and (4) the presence of clue cells more than 20% of epithelial cells on saline wet mount or Gram stain. An alternative diagnostic criterion utilizes Gram staining of vaginal secretions. The loss of lactobacillus morphotypes and increase in Gardnerella and Bacteroides morphotypes and curved gram-variable rods, when combined with the pH, correlated well with Amsel's criteria.[12] Gram stain may not be useful in determining eradication of the infection because of its high proportion of intermediate results.[1]

2.5 Treatment

Oral metronidazole (500 mg twice daily for 7 days) is the preferred treatment for bacterial vaginosis. Other effective treatment regimens include single-dose metronidazole (2 g orally), oral clindamycin (300 mg twice daily for 7 days), 2% clindamycin vaginal cream (once daily for 7 days) and 0.75% metronidazole vaginal gel (twice daily for 5 days).[1,13] The rate of cure for a seven-day course of metronidazole has been reported to be from 70% to 100%.[13] Oral clindamycin results in a clinical cure rate of over 90%. In a comparative study with oral metronidazole, the corresponding cure rates were 94% for seven-day course clindamycin and 96% for seven-day course metronidazole. Adverse reactions occurred in 11% of those taking clindamycin and 15% of those taking metronidazole.[36] Single-dose metronidazole may be used to treat bacterial vaginosis especially when compliance with the seven-day regimen is poor. However, the efficacy of the single-dose regimen is slightly lower than the seven-day regimen. In a meta-analysis, the over all cure rates with the seven-day regimen is 78% and that of the single dose regimen is 72%, with no statistical difference.[37] Clindamycin vaginal cream and metronidazole vaginal gel seem to be effective treatments for this syndrome, they have the advantage of reducing systemic side effects but are significantly more expensive, as compared to oral metronidazole.[1] About sex partner, available data do not support the practice of routine treatment of male sex partners of infected females.[13,29,30]

There is one study using a single vaginal washout with 3% H_2O_2 for treatment of recurrent bacterial vaginosis. A total of 30 symptomatic women with clinically confirmed bacterial vaginosis in the absence of other genital infections were recruited. Three percent H_2O_2 was instilled into the vagina, left for 3 minutes and drained. Twenty three women who completed the study were reassessed at 3 weeks after treatment. Symptoms cleared completely in 78% (18/23), improved in 13% (3/23) and remained unchanged in 9% (2/23). All the 3 women with improved symptoms had a mild vaginal discharge, with one of them was still able to perceive the malodor. The amine test was negative in all 23 women including the 2 (9%) who felt no change in their symptoms following treatment. Mixed anaerobes isolated in all women before treatment were not re-isolated, and microscopy did not show clue cells in the vaginal discharge following treatment. Vaginal acidity was restored to normal in all but one (96%). No side-effects were observed in the treated women.[16]

CHAPTER 3

RESEARCH METHODOLOGY

3.1 Research Questions and Objectives

3.1.1 Research questions

3.1.1.1 Primary research question

In cases of symptomatic bacterial vaginosis, does a single vaginal douching with H_2O_2 result in a 25% relative difference in the cure rate compared to a single-dose oral metronidazole ?

3.1.1.2 Secondary research question

Is there any difference in the side effects between a single vaginal douching with H_2O_2 and a single-dose oral metronidazole ?

3.1.2 Research objectives

3.1.2.1 To compare the effectiveness in term of cure rate between single vaginal douching with H_2O_2 and single-dose oral metronidazole for the treatment of patients with bacterial vaginosis.

3.1.2.2 To evaluate the side effects of treatment comparing single vaginal douching with H_2O_2 and single-dose oral metronidazole.

3.2 Research Hypothesis

There is a 25% relative difference between the cure rate of a single vaginal douching with H_2O_2 compared to a single-dose oral metronidazole in the treatment of patients with bacterial vaginosis.

3.3 Keywords

Hydrogen peroxide, metronidazole, bacterial vaginosis, randomized controlled trial

3.4 Operational Definition

- Diagnostic criteria for bacterial vaginosis (Amsel's criteria)[11]

At least three of the following four signs required for diagnosis

1. Homogeneous vaginal discharge
2. pH of vaginal discharge greater than 4.5
3. Fishy amine odor with mixture of discharge with 10% KOH
4. Presence of clue cells more than 20% of epithelial cells on saline wet mount

- Criteria for cure[38]

The absence of at least three of Amsel's criteria defined as "cure".

- Homogeneous discharge

The characteristic of vaginal discharge in bacterial vaginosis is a homogeneous, noninflammatory discharge that adheres to the vaginal wall. The color and amount of discharge varies greatly from patient to patient.

- Vaginal pH

The pH of vaginal secretion that adheres to the vaginal wall will be determined by using a cotton swab taking the secretion applied to a strip of pH paper.

- Positive whiff test

An amine or “fishy” odor is smelt when 10% KOH solution is added to vaginal secretions.

- Clue cell

Vaginal epithelial cells that have a stripped appearance due to adherent coccobacilli. The edges of the cells are obscured and appear fuzzy compared with the normally sharp edges of vaginal epithelial cells.

- Gastro-intestinal side effects

Including nausea, vomiting and unpleasant taste.

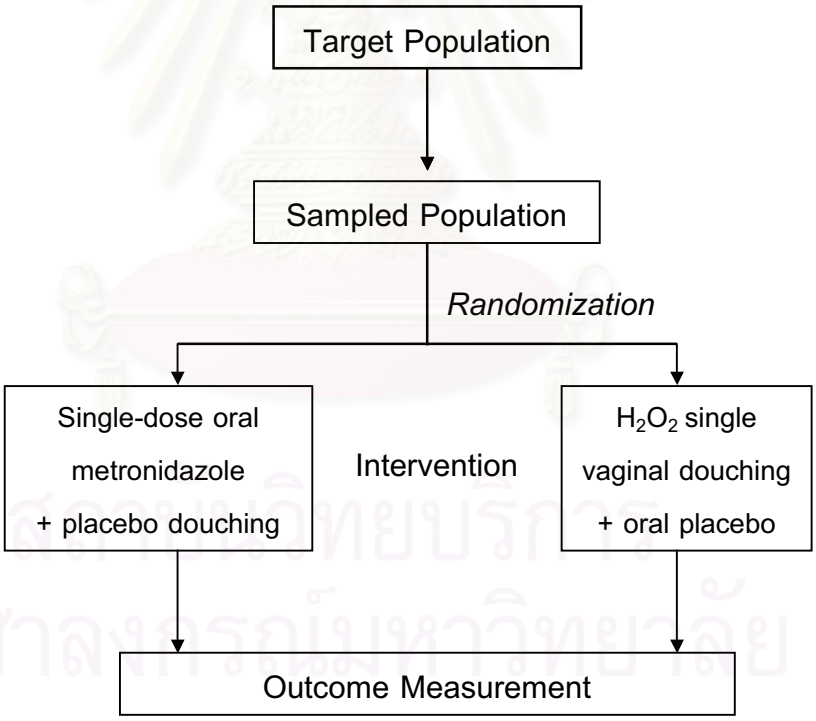
- Vaginal irritation

Including vaginal itching, burning, irritation and soreness.

3.5 Research Design

This study was carried out as a randomized double-blind controlled trial. Because of a difference in route of drug administration, the double dummies were used for blinding the treatment arm. The randomization can avoid allocation bias, tends to produce comparable groups and assures the validity of statistical tests of significance.

Figure 1 Research design model



3.6 The Sample

3.6.1 Target population

The patients with symptomatic bacterial vaginosis.

3.6.2 Sample population

The patients diagnosed as having bacterial vaginosis at outpatient gynecologic clinic in King Chulalongkorn Memorial Hospital and met the eligibility criteria.

3.6.3 Eligibility criteria

3.6.3.1 Inclusion criteria

The patients who satisfied all of the following criteria were enrolled into the study :

(1) Age between 15 and 45 years

(2) Diagnosed as having bacterial vaginosis by Amsel's criteria

(3) Informed about the study and having signed the informed consent form

3.6.3.2 Exclusion criteria

The patients who met one or more of the following criteria were excluded :

(1) History of H_2O_2 or metronidazole allergy

(2) Having taken antibiotic treatment within the two weeks prior to trial entry or need to receive antibiotics for other diseases

(3) Pregnancy

(4) Immuno-compromised host included HIV-infected patients

(5) Diabetes mellitus

(6) Current use of intrauterine device

(7) Premature menopause

(8) Vaginal or cervical ulceration or coinfections

3.6.4 Sample size estimation

Since the primary outcome is proportion of patients who achieve cure after treatment, the formula for sample size estimation of two independent proportions was used.

$$n/group = \frac{[\, Z_{\alpha/2} \sqrt{2\,P\,(1-P)} + Z_{\beta} \sqrt{P_1\,(1-P_1) + P_2\,(1-P_2)}\,]^2}{(P_1 - P_2)^2}$$

The cure rate using single-dose metronidazole has previously reported as 72%.

From research hypothesis, H_2O_2 single vaginal douching should result in 90% cure rate.

To use α equal to 0.05 (two-tail) and power of study is 90%

Number of subjects per group is equal to

$$\frac{[\ 1.96\ \sqrt{2 \times 0.81 \times 0.19} + 1.28\ \sqrt{(0.9 \times 0.1) + (0.72 \times 0.28)}\ ]^{2}}{(0.9 - 0.72)^{2}}$$

$= 98$

Sample size in each group will be 100 cases.

3.6.5 Randomization procedure

Simple randomization was conducted in this study. The random number was generated by computer software (SPSS for Windows). The subjects who met the eligibility criteria were randomly allocated into either the H_2O_2 group or the metronidazole group. The investigators and subjects were blinded for the treatment arm. The code was kept blinded until the study was completed.

3.7 Experimental Maneuver

3.7.1 Preparation of the medication

Metronidazole and placebo

The metronidazole used in this study was 500 mg tablet (B.J. Limited, Thailand). The placebo, produced by the drug company, had similar color and shape as the metronidazole. Research assistants prepared four-tablet packages and labeled the numbers. Each package contained either metronidazole or placebo depending on the codes from random numbers.

H_2O_2 and placebo

Douching solution were either 3%H_2O_2 or placebo. Distilled water was used as placebo. Research assistants prepared a package and labeled the numbers on 30-milliliter bottles. Each bottle contained either H_2O_2 or placebo depending on the codes from random numbers.

3.7.2 Procedure

The protocol was approved by the Institutional Review Board. The study was conducted at outpatient gynecologic clinic in King Chulalongkorn Memorial Hospital.

The eligible patients were randomly allocated into H_2O_2 group or the metronidazole group. The H_2O_2 group received oral placebo and were douched with hydrogen peroxide. The metronidazole group received oral metronidazole and were douched with placebo.

Oral medications had 4 tablets (500 mg metronidazole tablet or visually identical placebo) and the patients had to take them at the clinic.

Douching was performed by investigator using vaginal speculum and sterile syringe while the patients were in lithotomy position. Twenty milliliters of fluid (3%H_2O_2 or placebo) were used. After douching, the subjects were asked to wait about three minutes before changing positions.

Because both interventions were used in single time, there was no problem about compliance. To avoid co-intervention and contamination, the subjects were instructed not to take the other antibiotics or other vaginal preparations during study period. If they had problems, they can contact the investigator by telephone or were allowed freely to come to meet the investigators at the hospital. The co-intervention were assessed by asking the patients at follow up visit.

The patients were asked to avoid sexual intercourse for 2 weeks and to observe any symptoms related to the side effects that occur before follow up visit. They were followed up at 2 weeks after treatment.

3.8 Outcome Measurement

3.8.1 Primary outcome

The primary outcome was the cure rate. Cure were assessed by the investigator who did not know the treatment arm and measured by using Amsel's criteria. The criteria composed of four clinical signs that also be used for diagnosis. The absence of at least three of Amsel's criteria defined as cure.

3.8.2 Secondary outcome

The secondary outcome was the side effect rate. Symptoms after treatment were measured for evaluation the side effects. Gastro-intestinal side effects included nausea, vomiting and unpleasant taste. The subjects who had the symptom that reduced eating or had vomiting were defined as having gastro-intestinal side effects. For vaginal irritation symptoms, the subjects who required treatment were defined as having vaginal irritation.

3.9 Data Collection

Any data was fully documented in the case record forms (Appendix A) by the investigator. All the variables were recorded according to the operational definition specified. The investigator (the author) had checked whether the data were correct and complete or not. Data entry was done by the investigator.

3.10 Data Analysis

Descriptive statistics were used for demographic and baseline data and summarized as mean or proportion with 95% confidence interval. The outcome variables were described as proportion with 95% confidence interval and compared between group using Z-test for proportion. Intention-to-treat analysis was applied in analyzing the outcome variables. Statistical tests are 2-tailed and be considered significant only if $p < 0.05$. Data analysis was summarized in Table 1.

Table 1 Data summary and statistical analysis

Data	Type	Data summary	Statistics
Demographic and baseline data	Continuous - age Categorical - marital status - parity - contraception - sexual activity - symptoms	Mean, 95%CI Percent, 95%CI	- -
Outcome Cure rate GI Side effects Vaginal irritation	 Categorical Categorical Categorical	 Percent, 95%CI Percent, 95%CI Percent, 95%CI	 Z-test for proportion* Z-test for proportion* Z-test for proportion*

* p value of less than 0.05 was considered as being a statistically significant difference

3.11 Ethical Considerations

(1) Single-dose oral metronidazole is one of standard treatment for bacterial vaginosis, has accepted efficacy and few side effects. Three percent

H_2O_2 is widely used as mouth wash antiseptic with no serious adverse effect. The result from one study also showed the therapeutic efficacy for treatment of bacterial vaginosis without side effects. If the patients did not cure at 2 weeks after treatment with protocol drugs, they would received 7-day course oral metronidazole and further followed up.

(2) The research proposal were approved by the Institutional Review Board.

(3) Each patient was required to give written consent prior to entry into the study. A full explanation of the nature and purposes of the study was provided by the investigator, both verbally and in the form of an information sheet which was incorporated into the consent form. The patient was completely free to refuse participation or withdraw from the study at any time.

(4) All information obtained during the conduct of the study with regard to the patient's state of health was regarded as confidential.

3.12 Limitations

Since H_2O_2 can produce foam, the investigator may know the treatment arm and it might cause bias. To minimize bias, the evaluator who assessed the outcome was blinded to the treatment arm.

The generalizability of this study is limited to patients with only symptomatic bacterial vaginosis. Further study is required to determine the efficacy of drugs in cases with combined vaginal infections.

3.13 Benefits of the Study

Bacterial vaginosis is the most common cause of vaginal discharge in reproductive age women. Standard oral medications may cause systemic side effects, but current topical therapy is much more expensive. If 3% H_2O_2 vaginal douching has effectiveness in treatment of bacterial vaginosis, it might be a good therapy because it is cheap, easily available and able to avoid systemic side effects.

3.14 Obstacles

There were problems of loss to follow up cases, because when the patients were treated and the symptoms disappear, they did not come back to the hospital. To minimize this problem, patients were informed clearly of the importance of the follow up. In cases who did not come to follow up, they were contacted by telephone or mail.

The other obstacle was number of subjects. From calculation, this study need 200 eligible cases. Because of the uncertainty of the effectiveness of H_2O_2 vaginal douching and time limitation, the author plan to do analysis when seventy percent of total subjects were completed follow up.

CHAPTER 4

RESULTS

The analysis was performed when there were a total of 142 patients enrolled in the study. Because the significant difference was found in the primary outcome, this trial was early terminated. The eligible patients were randomly allocated into two groups. The H_2O_2 group (n=72) were douched with 20 milliliters of 3%H_2O_2 and received oral placebo. The metronidazole group (n=70) received oral metronidazole 2 grams and were douched with placebo.

4.1 Demographic Data

The demographic data of the patients is shown in Table 2. The baseline characteristics of two groups were comparable with respect to age, marital status, parity, sexual activity and contraceptive methods.

All cases presented with increasing vaginal discharge but none of them had gastrointestinal symptoms before treatment (Table 3). Details of symptoms and signs before treatment are presented in Table 3.

Table 2 Demographic characteristics

Characteristics	H_2O_2 group (n=72)	Metronidazole group (n=70)
Age (yr)		
Mean (Range)	31.2 (18-45)	30.9 (17-43)
[95% CI]	[29.6, 32.9]	[29.4, 32.4]
Marital status *		
Single	5 (6.9) [1.0, 12.8]	5 (7.1) [1.1, 13.1]
Married	62 (86.1) [78.1, 94.1]	61 (87.1) [79.2, 94.9]
Divorced/Separated	5 (6.9) [1.0, 12.8]	4 (5.7) [0.3, 11.1]
Parity (time) *		
0	23 (31.9) [21.1, 42.7]	21 (30.0) [19.3, 40.7]
1	20 (27.8) [17.5, 38.1]	19 (27.1) [16.7, 37.5]
2	17 (23.6) [13.8, 33.4]	24 (34.3) [23.2, 45.4]
3	12 (16.7) [8.1, 25.3]	4 (5.7) [0.3, 11.1]
4	0	2 (2.9) [0, 6.8]
Sexual activity (time/wk) *		
None	22 (30.6) [19.9, 41.2]	16 (22.9) [13.1, 32.7]
1-3	45 (62.5) [51.3, 73.7]	48 (68.6) [57.7, 79.5]
4-6	1 (1.4) [0, 4.1]	6 (8.6) [2.0, 15.2]
> 6	4 (5.6) [0.3, 10.9]	0
Contraception *		
None	25 (34.7) [23.7, 45.7]	23 (32.9) [21.9, 43.9]
Pills	7 (9.7) [2.9, 16.5]	15 (21.4) [11.8, 31.0]
Injectable	0	1 (1.4) [0, 4.2]
Norplant	2 (2.8) [0, 6.6]	1 (1.4) [0, 4.2]
Tubal resection	22 (30.6) [19.9, 41.2]	14 (20.0) [10.6, 29.4]
Condom	12 (16.7) [8.1, 25.3]	12 (17.1) [8.3, 25.9]
Vasectomy	4 (5.6) [0.3, 10.9]	4 (5.7) [0.3, 11.1]

* Value are expressed in number (percent) and [95% confidence interval]

Table 3 Symptoms and signs before treatment

Symptoms and Signs	H_2O_2 group (n=72)	Metronidazole group (n=70)
Symptoms *		
Increase discharge	72 (100)	70 (100)
Vaginal malodor	63 (87.5) [79.5, 95.1]	60 (85.7) [77.5, 93.9]
Vaginal irritation	41 (56.9) [45.5, 68.3]	30 (42.9) [31.3, 54.5]
Nausea & vomiting	0	0
Signs *		
Homogeneous discharge	69 (95.8) [91.2, 100]	70 (100)
pH > 4.5	70 (97.2) [93.4, 100]	66 (94.3) [88.9, 99.7]
Whiff test positive	57 (79.2) [69.8, 88.6]	50 (71.4) [60.8, 81.9]
Clue cell	70 (97.2) [93.4, 100]	68 (97.1) [93.2, 100]

* Value are expressed in number (percent) and [95% confidence interval]

4.2 Primary Outcome Analysis

The cure rate for treatment of bacterial vaginosis were 62.5% (45 in 72 patients) and 78.6% (55 in 70 patients) in H_2O_2 group and metronidazole group respectively. The result was considered statistically significant (p value = 0.036) with difference of cure rate equal to 16.1% (95% CI, 1.3, 30.8).

4.3 Secondary Outcome Analysis

4.3.1 Gastro-intestinal side effects

These side effects included nausea, vomiting and metallic taste. Most of the patients who got these side effects had only nausea for a few days after drug taken. The patients in metronidazole group had gastro-intestinal side effects more than the patients in H_2O_2 group statistically significant (48.6% and 13.9%, p value < 0.001). The difference is equal to 34.7% (95% CI, 20.5, 48.9).

4.3.2 Vaginal irritation

Mild vaginal irritation was found during douching process and no need for treatment. It occurred in H_2O_2 group significantly more frequent than in metronidazole group (33.3% versus 14.3%, p value = 0.008). The difference is equal to 19.0% (95% CI, 5.4, 32.7).

4.4 Summary of Results

The primary outcome, the secondary outcome and clinical signs at follow up visit were summarized in Table 4.

Table 4 Summary of outcome

	H_2O_2 group (n=72)	**Metronidazole group (n=70)**
Cure *	45 (62.5)	55 (78.6)
Side effects *		
Gastro-intestinal	10 (13.9)	34 (48.6)
Vaginal irritation	24 (33.3)	10 (14.3)
Signs after treatment *		
Homogeneous discharge	22 (30.6)	15 (21.4)
pH > 4.5	35 (48.6)	19 (27.1)
Whiff test positive	19 (26.4)	11 (15.7)
Clue cell	26 (36.1)	18 (25.7)

* Value are expressed in number and (percent)

CHAPTER 5

DISCUSSION

Standard treatment for bacterial vaginosis are (1) oral metronidazole 500 mg twice daily for 7 days, (2) single-dose oral metronidazole 2 g, (3) oral clindamycin 300 mg twice daily for 7 days, (4) 2% clindamycin vaginal cream once daily for 7 days, and (5) 0.75% metronidazole vaginal gel twice daily for 5 days.[1,13] Topical antimicrobial therapy has similar efficacy as oral medications but has less systemic side effects. However, it cost more expensive than oral metronidazole[1] and not available in Thailand.

Winceslaus and colleague[16] had conducted one study using a single vaginal washout with 3% H_2O_2 for treatment of recurrent bacterial vaginosis. Twenty three symptomatic women with clinically confirmed bacterial vaginosis were recruited. After treatment, symptoms cleared completely in 78% (18/23) and laboratory findings confirmed the efficacy. No side-effects were observed in the treated women.

For testing the effectiveness of single vaginal douching with 3% H_2O_2 in the treatment of bacterial vaginosis, the most appropriated research design is randomized controlled clinical trial. Randomized controlled study can minimize the selection bias, measurement bias and other confounders. Single dose oral metronidazole was selected to be a control because it is one of standard treatment, low cost and taken only one time.[37] This study can avoid

the compliance problem because both experimental and control groups are able to complete treatment at initial visit. To blind the subjects and the investigators, double dummies (placebo for metronidazole and placebo for H_2O_2) were used.

The numbers of H_2O_2 group (n=72) and metronidazole group (n =70) were not equal because simple randomization could not guarantee the equal number in each group. However, the baseline data revealed no significant differences between two groups with regard to demographic characteristics (Table 2) and patients' symptoms and signs before treatment (Table 3). The comparable baseline data of treatment groups should allow valid between-group comparisons.

In this study, it was demonstrated that the cure rate of treatment of bacterial vaginosis with single vaginal douching with 3% H_2O_2 was significantly lower than with single dose oral metronidazole ; 62.5% versus 78.6% (p value = 0.036). The difference of cure rate equaled to 16.1% with 95% confidence interval 1.3 to 30.8. Cure rate with single vaginal douching with 3% H_2O_2 in this study is only 62.5% which is not appropriate for clinical application. The reason may be either vaginal douching with 3% H_2O_2 is not effective for treatment of bacterial vaginosis or a single time is not adequate. The result was much differ from previous study[16] which was not a controlled study. It may cause from different population and using different criteria.

The effectiveness of a single dose oral metronidazole for treatment of bacterial vaginosis in this study was 78.6% cure rate. The result is similar with previous studies that shown cure rate between 67% - 87% (Table 5).

Table 5 Cure rate from using single dose oral metronidazole

Authors	n	Cure rate (%)
This study	70	78.6
Blackwell et al[39]	20	80
Ison et al[40]	29	86
Mengel et al[41]	37	75
Swedberg et al[42]	46	87
Purdon et al[43]	21	67

This study did not found severe adverse effects. The patients in metronidazole group had more gastro-intestinal side effects, which included nausea, vomiting and metallic taste, than in H_2O_2 group statistically significant (48.6% and 13.9%, p value < 0.001). This is a disadvantage of oral metronidazole, however, most of the patients had only nausea and symptoms clear within two days. It is important to instruct the patients to take drug immediately after meal and not taking alcohol within 48 hours. To record these side effects in the future study, the author suggest to divide into each symptom.

No patient who participated in this study had severe vaginal irritation. Mild irritation, found during douching process, occurred in H_2O_2 group significantly more frequent than in metronidazole group (33.3% versus 14.3%, p value = 0.008). This finding support the previous study[16] that no serious adverse effect after douching with 3% H_2O_2.

CHAPTER 6

CONCLUSION

By conducting a randomized double blind controlled trial comparing the effectiveness in term of cure rate in 142 patients diagnosed as symptomatic bacterial vaginosis who were treated with a single vaginal douching with 3% H_2O_2 (n = 72) versus those who received a single dose oral metronidazole (n = 70), the results shown that, base on the basis of the intention-to-treat analysis, the cure rate in patients who were treated with a single vaginal douching with 3% H_2O_2 was significantly less than with a single dose oral metronidazole ; 62.5% versus 78.6% (p value = 0.036). The difference of cure rate equaled to 16.1% with 95% confidence interval 1.3 to 30.8. However, the patients who received metronidazole had more gastro-intestinal side effects than those who were H_2O_2 vaginal douched (48.6% and 13.9%, p value < 0.001). Mild vaginal irritation, found during douching process, occurred in those who were H_2O_2 vaginal douched significantly more frequent than in metronidazole group (33.3% versus 14.3%, p value = 0.008).

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APPENDICES

APPENDIX A

Case Record Form	**Check List for Eligibility Criteria**			
	I.D. Number			

Eligibility Criteria	**Yes**	**No**
Inclusion criteria (1) Age between 15 and 45 years (2) Diagnosed as having bacterial vaginosis by Amsel's criteria (3) Informed about the study and having signed the informed consent form		
Exclusion criteria (1) History of H_2O_2 or metronidazole allergy (2) Having taken antibiotic treatment within the two weeks prior to trial entry or need to receive antibiotics from other diseases (3) Pregnancy (4) Immuno-compromised host included HIV-infected patients (5) Diabetes mellitus (6) Current use of intrauterine device (7) Premature menopause (8) Vaginal or cervical ulceration or coinfections		

Case Record Form	First Visit page 1 of 2			
	I.D. Number			

Date ……./……./…….

1. Name…….……..

2. H.N. ……/……

3. Date of birth ……./……./……

4. Marital status Single ……

Married ……

Divorced/Widow ……

5. PARA ……./……/……/…….

6. Last child age ……year (s)

7. Last abortion ……year (s)

8. Current contraception None ……

Oral pills ……

Injectable ……

Implant ……

IUD ……

Others …… (specify)……

9. Average number of sexual acts per week

none ……

1-3 ……

4-6 ……

> 6 ……

10. Last menstrual period ……./……./……

11. History of medical diseases or drug allergy none ……

Yes (specify)……

Case Record Form	First Visit page 2 of 2			
	I.D. Number			

12. Symptoms

12.1 Increase discharge	Present	.....
	Absent	.....
12.2 Vaginal malodor	Present	.....
	Absent	.....
12.3 Vaginal irritation	Present	.....
	Absent	.....
12.4 Nausea and vomiting	Present	.....
	Absent	.....

13. Signs

13.1 Discharge	Homogeneous	.....
	Others	.....
13.2 pH	> 4.5	.....
	< 4.5	.....
13.3 Whiff test	Positive	.....
	Negative	.....
13.4 Clue cell	Positive	.....
	Negative	.....

14. Diagnosis of Bacterial vaginosis	Yes	.....
	No	.....

<u>Intervention</u>

Take oral medication	Done	.....
Vaginal douching	Done	.....

Note.....

Case Record Form	**Follow-up Visit**			
	I.D. Number			

Date ……./……./…….

1. Symptoms

1.1 Increase discharge	Present	……
	Absent	……
1.2 Vaginal malodor	Present	……
	Absent	……
1.3 Vaginal irritation	Present	……
	Absent	……
1.4 Nausea and vomiting	Present	……
	Absent	……

2. Signs

2.1 Discharge	Homogeneous	……
	Others	……
2.2 pH	> 4.5	……
	< 4.5	……
2.3 Whiff test	Positive	……
	Negative	……
2.4 Clue cell	Positive	……
	Negative	……

3. Diagnosis Cured ……

Not cured ……

APPENDIX B

ใบยินยอมเข้าร่วมการวิจัย

ชื่อโครงการ การสวนล้างช่องคลอดด้วยไฮโดรเจนเพอร์ออกไซด์ครั้งเดียว เปรียบเทียบกับการรับประทานยาเมโทรนิดาโซลครั้งเดียว ในการรักษาภาวะแบคทีเรียลวาไจโนสิส

สถานที่ทำการวิจัย คลินิกนรีเวชวิทยา ตึก ภปร. ชั้น 7 โรงพยาบาลจุฬาลงกรณ์

ผู้ทำการวิจัย นายแพทย์สุรสิทธิ์ ชัยทองวงค์วัฒนา

อาจารย์ที่ปรึกษา ศาสตราจารย์นายแพทย์จิตร สิทธิอมร

รองศาสตราจารย์นายแพทย์สมภพ ลิ้มพงศานุรักษ์

ข้อมูลทั่วไป

ภาวะแบคทีเรียลวาไจโนสิส เป็นการเปลี่ยนแปลงของแบคทีเรียในช่องคลอด ทำให้เกิดระดูขาวที่มีกลิ่นเหม็น นอกจากนี้ยังเกี่ยวข้องกับภาวะแทรกซ้อนทางสูติศาสตร์และนรีเวชวิทยา เช่น การอักเสบในอุ้งเชิงกราน เป็นต้น

การรักษาภาวะนี้ ในปัจจุบันนิยมการรับประทานยาเมโทรนิดาโซล ซึ่งอาจรับประทานเพียงครั้งเดียว หรือรับประทานนาน 7 วัน, การรับประทานยาคลินดามัยซิน 7 วัน หรือการใช้ยาสอดทางช่องคลอดเป็นเวลา 7 วัน การรักษาด้วยวิธีต่างๆ เหล่านี้ ได้ผลการรักษาไม่แตกต่างกันนัก แต่พบว่า การรับประทานยาอาจทำให้เกิดผลข้างเคียงต่อร่างกายได้ อย่างไรก็ตาม ยาที่ใช้สำหรับสอดช่องคลอดมีราคาแพง และยังไม่มีจำหน่ายในประเทศไทย

ในช่องคลอดของสตรีปกติ จะพบแบคทีเรียที่สร้างไฮโดรเจนเพอร์ออกไซด์ ซึ่งเป็นสารที่มีฤทธิ์ในการทำลายแบคทีเรีย และเชื่อว่าเป็นกลไกที่ป้องกันการเกิดภาวะแบคทีเรียลวาไจโนสิส นอกจากนั้น ได้มีผู้ทำการศึกษาเบื้องต้นของการใช้ไฮโดรเจนเพอร์ออกไซด์สวนล้างช่องคลอดเพียงครั้งเดียว พบว่าวิธีนี้มีประสิทธิภาพดีในการรักษาภาวะแบคทีเรียลวาไจโนสิส และไม่พบผลข้างเคียงที่เป็นอันตราย

ข้อมูลของโครงการวิจัย

การศึกษาในโครงการวิจัยนี้ เป็นการเปรียบเทียบประสิทธิผลของการสวนล้างช่องคลอดด้วยไฮโดรเจนเพอร์ออกไซด์ครั้งเดียว กับการรับประทานยาเมโทรนิดาโซลครั้งเดียว ในการรักษาภาวะแบคทีเรียลวาไจโนสิส โดยมีขั้นตอนดังนี้

1. ผู้ป่วยที่ตรวจพบภาวะนี้ จะได้รับการซักประวัติเพิ่มเติม จากนั้นผู้ป่วยจะได้รับประทานยาจำนวน 4 เม็ด และได้รับการสวนล้างช่องคลอดโดยแพทย์ผู้ทำวิจัยนาน 3 นาที
2. หลังการรักษา 2 สัปดาห์ จะนัดผู้ป่วยมาเพื่อตรวจการหายของโรค

ประโยชน์ของโครงการวิจัย

1. ทำให้ทราบอัตราการหายของโรค ด้วยการรักษาโดยการสวนล้างช่องคลอดด้วยไฮโดรเจนเพอร์ออกไซด์ครั้งเดียว กับการรับประทานยาเมโทรนิดาโซลครั้งเดียว
2. สามารถหลีกเลี่ยงการรับประทานยานาน 7 วัน เพื่อลดผลข้างเคียง
3. ผู้ป่วยได้รับการตรวจติดตามจนโรคหาย

ความเสี่ยงหรือความไม่สะดวกที่อาจเกิดจากการศึกษาวิจัย

1. การศึกษานี้ ใช้ไฮโดรเจนเพอร์ออกไซด์ที่มีความเข้มข้นเดียวกันกับน้ำยาสำหรับใช้บ้วนปาก นอกจากนั้นมีผู้ทำการศึกษาเบื้องต้นของการสวนล้างช่องคลอดด้วยไฮโดรเจนเพอร์ออกไซด์ไม่พบผลข้างเคียงเป็นอันตราย ดังนั้นจึงไม่น่าเพิ่มความเสี่ยงแก่ผู้ป่วย
2. เพื่อป้องกันการกลับมาเป็นซ้ำ จึงแนะนำให้ผู้ป่วยหลีกเลี่ยงการมีเพศสัมพันธ์ในระยะ 2 สัปดาห์หลังการรักษา อาจทำให้ผู้ป่วยไม่สะดวกบ้าง
3. การนัดตรวจติดตามเพื่อดูการหายของโรค จะนัดในช่วงบ่าย และเพื่อความสะดวกของผู้ป่วยจะมีการเตรียมบัตร และอุปกรณ์ต่างๆ พร้อม ทำให้ใช้เวลาไม่นาน
4. เพื่อประโยชน์ในการดูแลผู้ป่วยภาวะนี้ต่อไป จะมีคำถามเกี่ยวกับเรื่องเพศบ้าง อย่างไรก็ตาม ข้อมูลทุกอย่างจะถูกเก็บเป็นความลับ

จากข้อมูลข้างต้น ท่านเป็นผู้ตัดสินใจเองว่า ยินยอมเข้าร่วมในโครงการศึกษาวิจัยนี้ ทั้งนี้ ท่านสามารถยกเลิกการเข้าร่วมการศึกษาได้ตามต้องการ

หากท่านสงสัยในปัญหาใดๆ หรือมีคำถามอื่นๆ ในภายหลัง รวมทั้งต้องการทราบผลตรวจต่างๆ กรุณาสอบถามรายละเอียดเพิ่มเติมได้จาก นายแพทย์สุรสิทธิ์ ชัยทองวงศ์วัฒนา เบอร์วิทยุติดตามตัว 1500 เรียก 211431

ข้าพเจ้ายินดีเข้าร่วมในการศึกษานี้

ชื่อ..... นามสกุล.....

ลายเซ็น.....

ชื่อผู้วิจัย..... นามสกุล.....

ลายเซ็น.....

วันที่.....เดือน.....พ.ศ.....

VITAE

Dr. Surasith Chaithongwongwattana was born on March, 21, 1966 in Bangkok, Thailand. He graduated from Faculty of Medicine, Chulalongkorn University in 1989. He worked as staff at Prasrimahapoh Psychiatric Hospial, Ubonrachathani for 3 years. After completed three-year residency training in Department of Obstetrics and Gynecology, King Chulalongkorn Memorial Hospital, Faculty of Medicine, Chulalongkorn University, he has been working there as the instructor since 1995.

Currently, Dr. Surasith Chaithongwongwattana is acting as an Assistant Professor in the Division of Infectious Diseases, Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University.

Since June 1998, he has been admitted in the Master Degree Program of Health Development in Faculty of Medicine, Chulalongkorn University. He had principle research interest in bacterial vaginosis and therapeutic options. During this course, he has conducted a clinical trial comparing the effectiveness and side effects of a hydrogen peroxide single vaginal douching versus a single-dose oral metronidazole for the treatment of bacterial vaginosis.