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## Garnerella-Associated Vaginitis: Comparison of Three Treatment Modalities

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**Abstract:** Objective: To compare three different treatment protocols for *Gardnerella vaginalis* with respect to cure rates and secondary vulvovaginal candidiasis.

**Methods:** In this prospective randomised study, initially 2285 patients with symptoms of bacterial vaginosis were evaluated. Three hundred and seven of them in whom *Gardnerella vaginalis* was recovered were eligible for the study. Group I (114 patients) was given oral metronidazole 500mg twice daily for one week; Group II (96 patients) was prescribed oral metronidazole for one week plus a vaginal suppository of lyophilised lactobacilli, estriol and lactose for twelve days. The third group (97 patients) was treated only with the lactobacilli, estriol and lactose suppositories for twelve days. If the patient was relieved of her symptoms and *Gardnerella vaginalis* was not detected microbiologically at the second visit, it was considered as a cure. The treatment outcomes

were compared by Chi-square test and a p value below 0.05 was considered as significant.

**Results:** The cure rate of Group III(55.6%) was significantly lower than the cure rates of Group I(87.7%)and II (92.7%) ( $p=0.0001$ ). Secondary vaginal candidiasis at the completion of the therapy was significantly lower in the second (3.1%) and the third groups (2.1%), while this rate was 12.2% for the first group ( $p=0.03$ ).

**Conclusion:** Metronidazole followed by lactobacilli, estriol and lactate suppositories were found to be the best therapy model with respect to cure and secondary candidiasis rates.

**Key Words:** Gardnerella vaginalis, vaginitis, metronidazole, lactobacilli

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### Introduction

Bacterial vaginosis (BV) is a disturbance of the vaginal flora with overgrowth of anaerobic bacteria, *Gardnerella vaginalis* (GV) and is characterised by lack of lactobacilli (1-3). It is well known that women are dependent on a normal vaginal flora which is dominated by lactobacilli to maintain a healthy genital tract. The primary mechanism of the dominance of the lactobacilli was thought to be related to the production of lactic acid and the acidic environment of the vagina. The more recently described mechanisms are the generation of hydrogen peroxide by lactic acid bacteria, competition with other organisms for adherence to the vaginal wall, production of protein inhibitors with antimicrobial properties and stimulation of the immune system (4,5).

Oral metronidazole has been proven to be the "gold standard" for the treatment of bacterial vaginosis (6). However, because of the side effects and the potentially teratogenic properties of metronidazole, oth-

er therapeutic measures have been studied. We conducted a randomised prospective clinical trial to compare the effects of three different treatment modalities (oral metronidazole, oral metronidazole plus locally administered lyophilised lactobacilli, and only locally administered lyophilised lactobacilli) on the course of bacterial vaginosis.

### Methods

The study comprised the patients, from 18 to 53 years of age, who have visited the gynaecology clinic from January 1994 to September 1995 for vaginal symptoms. The vaginal symptoms at admittance were itching or irritation in or around the vagina and a discharge of abnormal amount, odor or color. None of the patients were pregnant and none of them had signs of pelvic inflammatory disease. BV was diagnosed if any three of the following four criteria were fulfilled (1): homogeneous discharge, pH greater

than 4.5, clue cells in the wet mount and a positive amine test. All specimens were processed within 2 hours. The cultures were plated on human bilayer tween agar and after an incubation of 48 hours, the plates were examined for colonies exhibiting diffuse hemolysis (7). The following four criteria were also evaluated for the diagnosis of GV: "clue cells", gram variable coccobacilli, absent or decreased lactobacilli and a decrease in the leukocyte count of the vaginal discharge. Only the patients who were diagnosed as BV and whose cervicovaginal cultures revealed GV were included in the study. The patients with *Neisseria gonorrhoea*, *Trichomonas vaginalis*, *Candida albicans* and *Chlamydia trachomatis* were excluded from the study.

The patients were seen by three different gynecologists. Each gynecologist was assigned to one of the treatment protocols. The patients were allocated to one of the groups depending on which gynecologist they have admitted at the beginning of the study. The first group (Group I) was treated with oral metronidazole 500mg twice daily for one week. The second group (Group II) was prescribed the same treatment modality as the first group plus one vaginal suppository each night for twelve days containing at least  $10^7$  to  $7 \times 10^8$  viable micro-organisms from a lyophilised pure culture of *Lactobacillus acidophilus*, 600mg lactose and 0.03mg estriol in each suppository (Gynoflor, Medinova AG, Zürich, Switzerland). The third group (Group III) was given only one vaginal suppository of lactobacilli, estriol and lactate each night for twelve days.

The patients were requested to come back after the first menstruation following the completion of the therapy (22-35 days after the admittance). The patients were re-evaluated with the same four criteria and the same microbiologic methods. If the patient was relieved of her symptoms and GV was not detected microbiologically at the second visit, it was considered as a cure. The ratio of secondary vulvovaginal candidiasis was evaluated at the second visit and was confirmed by the culture.

The treatment outcomes were compared by Chi-square test and a p value below 0.05 was considered significant.

## Results

From January 1994 to September 1995, 2285 women were evaluated for vaginal discharge and dis-

comfort. Among them 307 patients were eligible for the study. Group I comprised 114 patients, Group II 96 patients and Group III 97 patients. The three groups were comparable in age, marital status, contraceptive use.

The cure rates were 87.7% (100 of 114) for Group I, 92.7% (89 of 96) for Group II and 55.6% (54 of 97) for Group III. The cure rate for Group I and II are similar, but were significantly higher than the third group ( $p=0.0001$ ).

Serious or unexpected side effects were not noted. None of the patients discontinued the treatment because of the side effects. A total number of 210 patients have received metronidazole and 2.4% have complained from some degree of gastrointestinal discomfort. There was only one patient from the third group who have complained about a burning sensation of the vagina on the third day of the treatment, this discomfort have ceased spontaneously while the patient still continued the treatment.

Vulvovaginal candidiasis were found in 6.2% of the patients at the second visit. The candidiasis rates for Group II (3.1%) and Group III (2.1%) were significantly lower than the first group (12.2%) ( $p=0.003$ ).

## Discussion

In this prospective study, three different treatment protocols for bacterial vaginosis were investigated with respect to the cure rates and secondary vulvovaginal candidiasis. Our cure rates with metronidazole are 87.7% for Group I and 92.7% for Group II, which are consistent with the literature (2,6,8,9). Hallen et al. have reported a success rate of 57% with lactobacilli (10). Our figure (55.6%) is comparable with theirs.

We have chosen Gynoflor, because it contains  $H_2O_2$  producing viable lactobacilli, lactose and estriol. The aim of adding lactose and estriol to the suppositories is to provide the substrates to enhance the production of  $H_2O_2$ . The uterine peroxidase activity is induced by estrogens (11,12). Another advantage of estriol is the positive effect on epithelial growth with intensified desquamation of epithelial cells and increased glycogen supply for the preferential formation of the lactobacilli. With a dose of 0.03mg, estriol promotes the metabolic processes in the epithelium and provides a suitable environment for lactobacilli. Evidently a very small amount of estriol is sufficient to saturate the highly

specific estriol hormone receptors in the vagina that a higher dosage does not produce any additional therapeutic effect and the amount absorbed is negligible.

The rate of secondary vulvovaginal candidiasis is found to be low in the second and third groups when lactobacilli suppositories were prescribed. Since BV is found in the lack of lactobacilli, the suppositories might have helped the vagina to gain its normal lactobacilli content and this might have prevented the colonisation of other pathogen micro-organisms. It is known from previous studies that the prevalence of *C. albicans* is increased after metronidazole treatment (13), Redondo-Lopez et al. have evaluated vulvovaginal candidiasis complicating BV (14). In their study, multiple repetitive vaginal cultures identified *Candida* in 76% of the women with recurrent BV. Although the exact mechanism for the high prevalence of candida infections in BV is obscure, it can be related to the failure to establish a lactobacilli-dominant flora in this group of women.

In a study of Boecke et al. the effect of lactic acid suppositories on BV was compared with metronidazole and placebo. They found that lactic acid suppositories were ineffective in BV, but in the lactic acid category no vaginal *Candida albicans* infection was detected versus five in the metronidazole group and three in the placebo group (15). These studies support our results. In our study we have found with the addition of the suppositories containing lactobacilli, estriol and lactate, the cure rate of metronidazole has not changed, but as a beneficial effect, the rate of the candida superinfection has decreased significantly.

Unfortunately because all of our patients were re-evaluated only once, we do not know whether there is a difference in the relapse rates after subsequent menstruations.

As a conclusion, we have found that metronidazole followed by lactobacilli, estriol and lactate suppositories is the best treatment modality with respect to the cure rate and secondary vulvovaginal candidiasis rate.

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