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MODERN METHODS OF TREATMENT OF BACTERIAL VAGINOSIS IN WOMEN

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With the purpose to compare the effectiveness of different treatment regimens for bacterial vaginosis 67 patients with bacterial vaginosis detected by vaginal microscopy (age 18–45 years) were observed: 32 patients who received therapy by preparation based on neomycin sulfate, ornidazole, prednisolone sodium phosphate and econazole nitrate; 35 patients who received therapy with intravaginal metronidazole in gel form. The highest clinical efficacy (93.7 % according to R. Amsel criteria) was observed in patients of the group who received combination therapy (neomycin sulfate, ornidazole, prednisolone sodium phosphate and econazole nitrate; $p < 0.05$) in contrast to metronidazole for vaginal use, which showed a result of 45.7 % according to R. Amsel criteria and provoked candidal vulvovaginitis in 20.0 % of cases. Thus, the use of the combined preparation, which has antibacterial, antiprotozoal, antifungal and anti-inflammatory action, in patients with bacterial vaginosis made it possible to achieve high clinical treatment efficacy and did not lead to candidal vulvovaginitis.

Key words: bacterial vaginosis, Amsel criteria, combined treatment, intravaginal metronidazole, candidal vulvovaginitis.

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СУЧАСНІ МЕТОДИ ЛІКУВАННЯ БАКТЕРІАЛЬНОГО ВАГІНОЗУ У ЖІНОК

З метою порівняння ефективності різних схем лікування бактеріального вагінозу під наглядом перебувало 67 пацієнток з бактеріальним вагінозом, виявленим при мікроскопії піхви (вік 18–45 років): 32 пацієнтки, які отримували терапію препаратом на основі неоміцину сульфату, орнідазолу, преднізолону і еконазолу нітрату; $p < 0,05$; 35 пацієнток, які отримували терапію інтравагінальним метронідазолом у формі гелю. Найбільша клінічна ефективність (93,7 % за критеріями R. Amsel) відзначена у пацієнток групи, які отримували комбіновану терапію (неоміцину сульфат, орнідазол, преднізолону натрію фосфат та еконазолу нітрат; $p < 0,05$) на відміну від метронідазолу для вагінального застосування, що показав результат 45,7 % за критеріями R. Amsel і спровокував кандидозний вульвовагініт у 20,0 % випадків. Таким чином, застосування комбінованого препарату, що має антибактеріальну, протипротозойну, протигрибкову та протизапальну дію, у хворих на бактеріальний вагіноз дозволило досягти високої клінічної ефективності лікування і не призвело до розвитку кандидозного вульвовагініту.

Ключові слова: бактеріальний вагіноз, критерії Амсея, комбіноване лікування, інтравагінальний метронідазол, кандидозний вульвовагініт.

Bacterial vaginosis is a dysbiosis of the vaginal microbiota [2, 4, 9], in which the non-pathogenic microbiota of the lower female reproductive tract is replaced by pathogenic microbiota. Bacterial vaginosis is the most common disease in women of reproductive age. In different populations, from 20 % to 50 % of women suffer from bacterial vaginosis [1, 8].

Risk factors for the development of this disease are: hormonal disorders (disorders of the ovarian-menstrual cycle, perimenopausal transition period, post-abortion period), atrophic disorders of the vaginal mucosa, disorders of the receptor function of the vaginal epithelium, previous infectious diseases of the vagina of specific and non-specific etiology, trauma to the genitals, including after childbirth, taking certain groups of drugs (glucocorticosteroids, cytostatics), etc. [5, 10]. Also, a risk factor is the use of combined oral contraceptives and a decrease in estradiol levels [9].

The diagnosis of bacterial vaginosis is based mainly on the criteria of R. Amsel, which include homogeneous gray-white discharge, vaginal discharge $pH > 4.5$, a positive whiff test, and the presence of clue cells during microscopy of vaginal discharge. In the presence of 3 of the 4 criteria, bacterial vaginosis is diagnosed. The classic symptom of bacterial vaginosis is an increase in the amount of grayish vaginal discharge with a characteristic odor described as “fishy”. Its occurrence is associated with the production of amines. Women experience pronounced symptoms of irritation in the perineum (burning, itching, pain) and dysuric disorders. These symptoms occur in 70–90 % of women with bacterial vaginosis [1, 6].

Despite the availability of a number of oral and intravaginal antibacterial agents for the treatment of bacterial vaginosis, treatment of this condition remains challenging. Recurrent bacterial vaginosis occurs in more than 50 % of patients receiving recommended treatment [11]. In approximately 10–15 % of women, conventional treatment regimens fail to achieve initial efficacy [3].

The purpose of the study was to compare the effectiveness of different treatment regimens for bacterial vaginosis.

Material and methods. The research was conducted at the clinical base of the Department of Obstetrics and Gynecology II at Azerbaijan Medical University from 2022 to 2024.

The study involved 67 patients with bacterial vaginosis detected by vaginal microscopy. All patients met the inclusion criteria: age 18–45 years, complaints of vaginal discharge, no antibiotic use in the last 4 weeks. The exclusion criteria were: pregnancy and lactation; use of systemic antibacterial drugs for 4 weeks before the study; use of intravaginal antibacterial drugs in the last 72 hours; use of combined oral contraceptives, spermicides, intrauterine devices, vaginal rings for contraception; presence of sexually transmitted infections; acute or chronic pelvic inflammatory diseases in the acute stage; severe somatic diseases in the decompensation phase; malignant diseases of any localization.

All patients underwent a clinical examination: gynecological examination with an assessment of the nature of vaginal discharge, pH-metry of vaginal contents, whiff test. Laboratory examination included a microscopic examination of the discharge from the cervix and vagina, a study of cervical discharge for opportunistic flora.

For clinical diagnosis of bacterial vaginosis, R. Amsel criteria were used. The diagnosis of bacterial vaginosis was established in the presence of at least 3 of 4 criteria: specific vaginal discharge with an unpleasant odor; pH of vaginal discharge >4.5 ; positive whiff test; detection of clue cells during microscopic examination.

All patients were divided into two groups depending on the type of therapy. The first group included 32 patients who received therapy with “Elzhina” (Vertex, RF), a preparation based on neomycin sulfate 65,000 units, ornidazole 500 mg, prednisolone sodium phosphate 3 mg and econazole nitrate 100 mg, in regimen as 1 tablet in the vagina once a day for 9 days, then vaginal capsules “Lactogynal” (BIOSE INDUSTRIE, France) – a preparation based on lyophilized culture of lactobacilli *L. casei rhamnosus* Doderleini (not less than 1×10^8 CFU), 1 capsule 2 times a day for 7 days. The second group consisted of 35 patients who received intravaginal therapy with metronidazole in gel form (0.75 %) 5 ml once a day for 5 days, then vaginal capsules “Lactogynal”, 1 capsule 2 times a day for 7 days. The criteria for treatment effectiveness were the absence of subjective complaints, clinical manifestations of bacterial vaginosis, as well as laboratory-confirmed normocenosis.

The obtained digital materials were processed statistically using the Statistica 7.0 software package. The mean, maximum and minimum numerical value, percentage of the indicators was calculated. The differences between groups were determined using dispersion (F–Fisher) and variation (U–Mann-Whitney) methods. The difference was considered significant at $p < 0.05$.

Results of the study and their discussion. The average age of the patients included in the study was 29.8 ± 3.2 years; no statistically significant age difference was found between the groups ($p = 0.27$). All patients complained of abnormal vaginal discharge accompanied by an unpleasant “fishy” odor during the initial examination. The main reason for seeking medical attention was frequent recurrence of disease symptoms. The most frequent provoking factors were the premenstrual period, change of sexual partner, and orogenital contacts. During clinical examination, vaginal discharge in all patients had a grayish or grayish-white tint, and a specific odor was moderate. In all patients, the result of cytological examination of a smear from the cervical canal was normal before treatment, and no growth of pathogenic microflora was found during bacteriological examination of the discharge from the posterior vaginal fornix. No pathogens for *Chlamydia trachomatis*, *Trichomonas vaginalis*, and *Neisseria gonorrhoeae* were found during examination.

When evaluating the obtained data according to R. Amsel criteria, bacterial vaginosis was confirmed in 32 (100.0 %) patients of the first group and in 35 (100.0 %) patients of the second group. There were no significant differences in the presence of complaints of pathological discharge from the genital tract, the results of bacterioscopic examination, a positive whiff test and pH levels in the groups ($p > 0.05$). A control examination was conducted on the 7th day of treatment and 15 days after the end of treatment.

In the first group, all patients complained of profuse discharge from the genital tract with an unpleasant odor; 29 (90.6 %) patients were bothered by genital itching of varying severity, 2 (6.2 %) patients noted dyspareunia. The pH measurement of vaginal discharge before the start of therapy was increased in all women; the pH was 5.8 ± 0.1 . The whiff test was positive in 30 (93.7 %) patients. The average number of leukocytes in the posterior vaginal fornix during microscopy of vaginal smears was 7.231 ± 5.4 in the field of view, the number of superficial epithelial cells was 5.670 ± 3.9 , clue cells were found in all smears.

Bacteriological examination before the start of sanitation revealed the following main pathogens of bacterial vaginosis: *Atopobium vaginae* in 6 (18.7 %) patients, *Gardnerella vaginalis* in 27 patients

(84.3 %). After assessing the state of the vaginal biocenosis, relative normocenosis was determined in 8 (25.0 %) patients, moderate anaerobic dysbiosis in 11 (34.3 %), severe anaerobic dysbiosis in 11 (34.3%), moderate mixed dysbiosis in 2 (6.2 %) women. In 13 (40.6 %) observations, the number of lactobacilli did not exceed 10 %, in 11 (34.3 %) the number of lactobacilli was 11–50 %, the least common was the number of lactobacilli over 50 % – in 8 (25.0 %) observations.

For the purpose of intermediate control of the effectiveness of the therapy, on the 7th day of treatment, an examination of patients receiving the preparation based on neomycin sulfate 65,000 units, ornidazole 500 mg, prednisolone sodium phosphate 3 mg and econazole nitrate 100 mg was conducted. The assessment was carried out using the criteria of R. Amsel. In this group, foamy discharge from the genital tract persisted in 7 (21.8 %) patients, the pH value >4.5 was determined in 10 (31.2 %) examined, the whiff test also remained positive in 10 (31.2 %), clue cells were detected in 6 (18.7 %) samples during bacterioscopic examination.

Fifteen days after the end of treatment, complete regression of disease symptoms was noted in 30 (93.7 %) patients ($p<0.001$), and 2 (6.3 %) women continued to have pathological discharge from the genital tract with an unpleasant odor, and genital itching was noted. When comparing, statistically significant differences were determined in the complaints presented by patients before and after treatment ($p<0.001$).

When comparing the bacterioscopy data before and after treatment, the average number of leukocytes in vaginal discharge was 6.365 ± 2.1 in the field of view, key cells were detected in 2 (6.3 %) cases during microscopy of vaginal smears. Significant differences in bacterioscopic examination of the contents of the posterior vaginal fornix in this group of patients after treatment were in the presence of clue cells ($p<0.001$).

The test for determination of volatile amines after treatment remained positive in 6 (18.7 %) samples. In 28 (87.5 %) cases, the pH in the contents of the posterior vaginal fornix was equal to 4.0. Reliable differences in the whiff test and pH measurement before and after treatment were confirmed by the indicator $p<0.001$.

According to the research results, normocenosis prevailed in patients of this group, which was noted in 30 (93.7 %) patients ($p<0.001$). Expressed mixed dysbiosis was determined in 2 cases (6.3 %). Moderate anaerobic dysbiosis, expressed anaerobic dysbiosis and moderate mixed dysbiosis were not determined after the end of treatment. According to the results of bacteriological examination, the number of lactobacilli in 30 (93.7 %) samples reached normal values (51–100 %), a marked decrease in the number of lactobacilli was observed in 2 (6.3 %) patients. According to the results of the examination of the discharge from the posterior vaginal fornix, *Gardnerella vaginalis* was not found in any observation, *Atopobium vaginae* was detected in 2 (6.3 %) patients after treatment ($p<0.001$).

Thus, the effectiveness of the complex preparation based on neomycin sulfate, ornidazole, prednisolone sodium phosphate and econazole nitrate according to the criteria of R. Amsel was 93.7 %.

In the second group, all patients complained of abnormal discharge from the genital tract with an unpleasant odor, 31 (88.5 %) patients were bothered by itching of the genitals of varying severity, 3 (8.5 %) patients noted dyspareunia, dysuria was noted by 2 (5.7 %) patients. All examined patients had an increase in the pH of vaginal discharge to 6.0 ± 0.2 . The whiff test was positive in 33 (94.3 %) women. During a bacterioscopic examination of a vaginal smear, the average number of leukocytes was 5.741 ± 4.6 in the field of view, the number of surface epithelial cells was 5.426 ± 2.3 , and clue cells were found in all smears.

Bacteriological examination before the sanitation revealed the following pathogens: *Atopobium vaginae* in 7 (20.0 %) patients, *Gardnerella vaginalis* in 33 (94.2 %). After assessing the state of the vaginal biocenosis, relative normocenosis was determined in 9 (25.7 %) patients, moderate anaerobic dysbiosis in 12 (34.2 %), and severe anaerobic dysbiosis in 14 (40.0 %). There were no cases of moderate mixed dysbiosis or severe mixed dysbiosis in this group of patients. In 14 (40.0 %) observations, the number of lactobacilli was 0–10 %, in 12 (34.2 %) observations, the number of lactobacilli was 11–50 %, in 9 (25.7 %) observations, the number of lactobacilli exceeded 50 %.

For the purpose of intermediate control of the effectiveness of the therapy, on the 7th day of treatment, an examination of patients receiving metronidazole was conducted. The assessment was carried out using the criteria of R. Amsel. In this group, foamy discharge from the genital tract persisted in 10 (28.5%) patients, the pH value >4.5 was determined in 18 (51.4 %) examined patients, the whiff test remained positive in 12 (34.2 %), clue cells were detected in 11 (31.4 %) samples during bacterioscopic examination.

Fifteen days after the treatment, the women were examined to monitor the effectiveness of the therapy. In this group, the symptoms of the disease completely disappeared in 16 (45.7 %) women. Itching

and burning in the area of the external genitalia were noted by 7 (20.0 %) women ($p>0.05$), pathological discharge was reported by 16 (45.7 %) ($p<0.001$), 7 (20.0 %) patients paid attention to the unpleasant odor of discharge from the genital tract ($p<0.001$). When comparing complaints of itching and burning of the genitals, there were no reliable differences before and after treatment ($p>0.05$).

When comparing the bacterioscopy data before and after treatment, the average number of leukocytes in vaginal discharge was 6.450 ± 3.8 in the field of view. After treatment, clue cells were detected in 8 (22.8 %) patients during microscopy of vaginal smears. Significant differences during bacterioscopic examination of the contents of the posterior vaginal fornix after the therapy were in the presence of clue cells ($p<0.001$). Also, fungal mycelium was detected during microscopy of vaginal smears in 9 (25.7 %) patients.

The whiff test after treatment in this group remained positive in 13 (37.1 %) samples. In half of the samples after the therapy, $pH=4.0$ was recorded. Reliable differences were revealed when conducting the whiff test and measuring pH before and after treatment ($p<0.001$).

According to the results of the analysis, normocenosis prevailed in 24 (68.5 %) cases. Among dysbioses, pronounced anaerobic dysbiosis was most often detected – in 7 (20.0 %) examined patients, moderate anaerobic dysbiosis was the least common – in 1 (2.8 %) patient, pronounced mixed dysbiosis was recorded in 3 (8.5 %) women. Reliable differences in this group before and after treatment were determined in the indicators of normocenosis, moderate anaerobic dysbiosis and pronounced anaerobic dysbiosis ($p<0.05$). No statistically significant difference was observed when pronounced mixed dysbiosis was detected ($p>0.05$). After treatment, the number of lactobacilli according to the analysis results in 25 (71.4 %) cases was normal (51–100 %), a significant decrease in the number of lactobacilli was observed in 10 (28.5 %) samples.

According to the results of bacteriological examination of the discharge from the posterior vaginal fornix, *Atopobium vaginae* was detected in 6 (17.1 %), *Gardnerella vaginalis* in 12 (34.2 %), and *Candida albicans* in 7 (20.0 %) patients after treatment ($p<0.001$).

Thus, the effectiveness of metronidazole for vaginal use according to the criteria of R. Amsel was 45.7 %. In 7 (20.0 %) cases, the use of metronidazole provoked vulvovaginal candidiasis.

Comparative characteristics of the treatment results of patients in the study groups showed the following. On the 7th day of treatment, the effectiveness of therapy according to R. Amsel criteria did not differ significantly in the studied parameters in patients of the first and second observation groups. Foamy discharge ($p=0.780$), a positive whiff test ($p=0.590$), a pH value of >4.5 ($p=0.070$) and clue cells ($p=0.250$) were determined in patients of both the first and second groups.

When examining patients of the study groups after treatment, a reliable difference was obtained in patients of the first group in the value of $pH> 4.5$ ($p=0.008$). After treatment, reliable differences were observed in patients of the first group in the detection of normocenosis, in the indicators of moderate anaerobic dysbiosis and severe anaerobic dysbiosis ($p=0.040$) in relation to the second group. The number of lactobacilli according to the study of the microflora of the urogenital tract in women after treatment showed that in the second group, compared with the first group, lactobacilli were significantly more often determined in an amount of 0–10 % ($p=0.010$). Similarly, in the first group, compared with the second group, lactobacilli were significantly more often determined in a ratio of 51–100 % ($p=0.010$). After treatment in the second group, in relation to the first group, reliable differences were determined in the detection of *Gardnerella vaginalis* ($p=0.040$) and *Candida albicans* ($p=0.010$). Treatment in the second group was complicated by the development of vulvovaginal candidiasis ($p=0.005$).

As a result of the pharmacotherapy, the patients showed an improvement in their condition on the 15th day after treatment for all target indicators. The highest clinical efficacy was observed in patients of the first group who received combination therapy with the preparation based on neomycin sulfate 65,000 units, ornidazole 500 mg, prednisolone sodium phosphate 3 mg and econazole nitrate 100 mg ($p<0.05$).

To conduct the analysis, an integral indicator of the effectiveness of pharmacotherapy was calculated, which included the results of the treatment of patients with bacterial vaginosis. The analysis was performed on the proportion of patients who achieved clinical improvement and the proportion of patients who did not have relapses. The analysis showed that in patients of the first group, the value of the integral indicator of the effectiveness of pharmacotherapy was 80.0 units, which is 1.4 times higher than the same indicator in patients of the second group, equal to 57.5 units.

There are a number of studies devote to treatment of bacterial vaginosis. The previous studies of clindamycin, tinidazole and secnidazole in the treatment of recurrent bacterial vaginosis have focused on patients with evidence of resistance to metronidazole [3, 7].

Faught BM, et al recommended treatment for recurrent bacterial vaginosis which consists of an extended course of metronidazole (500 mg twice daily for 10-14 days); if ineffective, 0.75 % metronidazole vaginal gel for 10 days and then twice weekly for 3–6 months is an alternative regimen [3].

According to Muzny CA, et al, a refractory response is more likely in the non-compliant patient and with the use of single-dose therapy rather than multi-dose therapy using 5–nitroimidazole medications [7]. In our study we successfully used the complex preparation included antibiotic neomycin sulfate, ornidazole, prednisolone sodium phosphate and econazole nitrate, that makes results more effective.

Initial studies of biofilm disruption, probiotic and prebiotic use, and herbal treatment have shown some promise but need further study before clinical use [5, 6]. Despite limitations, antimicrobial therapy will remain the mainstay of treatment for recurrent bacterial vaginosis for the foreseeable future.

Conclusion

Significant differences in bacterioscopic examination of the contents of the posterior vaginal fornix in this group of patients after treatment were in the presence of clue cells ($p < 0.001$). Reliable differences were revealed when conducting the whiff test and measuring pH before and after treatment ($p < 0.001$). As a result of the pharmacotherapy, the patients showed an improvement in their condition on the 15th day after treatment for all target indicators. The highest clinical efficacy was observed in patients of the group who received combination therapy with the preparation based on neomycin sulfate 65,000 units, ornidazole 500 mg, prednisolone sodium phosphate 3 mg and econazole nitrate 100 mg ($p < 0.05$).

Thus, the use of the combined preparation based on neomycin sulfate, ornidazole, prednisolone sodium phosphate and econazole nitrate, which has antibacterial, antiprotozoal, antifungal and anti-inflammatory action, as part of the complex therapy of patients with bacterial vaginosis made it possible to achieve a clinical treatment efficacy of 93.7 % and did not lead to the development of such a complication as candidal vulvovaginitis, in contrast to metronidazole for vaginal use, which showed a result of 45.7 % according to R. Amsel criteria and provoked candidal vulvovaginitis in 7 (20.0 %) cases.

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