



## Modern Diagnostic Methods and Algorithm for the Treatment of Vaginal Infections

**Yuldasheva Farangiz  
Ismatiloevna**

Assistant of Samarkand State Medical Institute  
[yuldashevafarangiz1930@gmail.com](mailto:yuldashevafarangiz1930@gmail.com)

ABSTRACT

In modern obstetric and gynecological practice, the problem of violation of the vaginal microflora is one of the most urgent because of the possibility of developing a whole complex of complications affecting the reproductive function of a woman. Mixed variants of vaginal infections have been little studied, however, it is necessary to distinguish them, since different forms of pathogen coexistence require an individual therapeutic approach.

**Keywords:**

mixed vaginal infections; pregnancy; gel form of metronidazole; Florocenosis

**Relevance of the study** There are also difficulties in diagnosing vaginal infections. Most often, when examining patients with vaginal discharge, first of all, the doctor focuses on clinical data, as well as the results of microscopic examination. At the same time, there are data in the literature on the variability of secretions in a particular pathology, as well as on the low sensitivity of microscopic examination to detect many infections of the reproductive organs [3]. In cases of violations of vaginal microbiocenosis, the diagnostic search is complicated by the fact that in half of the patients, inflammation and other signs induced by the activity of polymicrobial associations in the genital tract are not accompanied by clinical symptoms, but proceed latently [4, 5]. The problem is also the tendency of many patients to self-diagnosis and self-medication, which further delays the verification of the diagnosis and often ends complications.

Mixed variants of vaginal infections have been little studied, however, it is necessary to distinguish them, since different forms of pathogen coexistence require an individual therapeutic approach [6,9,11]. It is also necessary to understand that without anti-

candidiasis therapy, there is a risk of manifestation of candidiasis vulvovaginitis against the background of the inevitable acidification of the vaginal environment in the treatment of bacterial vaginosis [7]. The main difficulty in managing nonspecific vaginal infections is relapses [8, 9]. Their risk is higher the more pronounced the vaginal dysbiosis, the less committed the patient is to treatment, and the less high-quality the previous antimicrobial therapy was. At the same time, the correction of the vaginal microbiome is of great importance.

Despite the absence of generally accepted therapeutic schemes, the principle of treatment of mixed infections is to detect and eliminate etiologically significant microorganisms with subsequent consolidation of the result by restoring normal vaginal microbiocenosis. The long-term clinical experience of domestic and foreign specialists has shown the effectiveness of two-stage tactics for the treatment of mixed infections and bacterial vaginosis [10, 11, 20]. At the first stage, pathogens are eradicated, and at the second stage, the optimal environment of the vaginal biotope is restored – the physiological pH value and a sufficient number of lactobacilli, which is achieved with the help

of probiotics and drugs that normalize pH. Metronidazole and clindamycin are recognized as the "gold standard" in the treatment of BV. A single oral administration of metronidazole at a dose of 2 g effectively relieves the symptoms of BV, however, the proportion of relapses is higher than when using a week-long course of the same drug. The convenience of a single circuit has relatively low efficiency, and currently the CDC does not recommend this technique even as an alternative option. In addition, the compliance of oral metronidazole treatment significantly reduces its poor tolerability [13,21]. The European guidelines for the management of patients with vaginal discharge also indicate the low effectiveness of a single use of metronidazole at a dose of 2 g in BV. Uncultivated or difficult-to-cultivate microorganisms acquire resistance to this drug, they also provide a persistent recurrent course of the disease. Repeated episodes of vaginitis occur in 30% of women within 3 months after treatment [14,16,17,19].

An attempt of monotherapy on a suspected pathogen (or a group of pathogens typical of an isolated process) with mixed infections can cause even more pronounced violations of the vaginal microbiocenosis – other microorganisms, for example, candida, are activated. The use of metronidazole or clindamycin in the form of monotherapy is fraught with the development of candidiasis vulvovaginitis, which means that appropriate preventive measures are needed. It is possible to avoid this complication of monotherapy with the use of modern combined drugs.

The second stage of treatment of nonspecific vaginal infections involves the local use of probiotics. The expediency and effectiveness of prescribing live lactic acid bacteria in order to restore vaginal microbiocenosis in the treatment of nonspecific vaginitis, bacterial vaginosis and candidiasis vulvovitis (in the form of vaginal suppositories containing at least 10<sup>6</sup> CFU / ml of live lactobacilli) have been proven. Several foreign studies have also appreciated the clinical and microbiological effectiveness of the vaginal use of lactobacilli to restore the normal microbiota of the vagina [16, 12,16,18,21,22].

The aim of the work is to evaluate the effectiveness of the use of a new gel-form combination drug for vaginal infections in pregnant women.

**Materials and methods of research.** The study included 200 pregnant women with vaginal infections. The main group consisted of 100 women treated with the new gel drug Metrogil plus for 5 days. The comparison group included 100 patients who were treated with the drug Klion D 100. The drug was prescribed for 1 tab. intravaginally for 10 days (1 tab: Metronidazole 100 mg + Miconazole nitrate 100 mg).

Vaginal infections were detected at the end of the first, beginning of the second trimester of pregnancy (12-15 weeks). The analysis of individual maps of pregnant women, birth histories, and newborn histories was carried out. The anamnesis was studied, the cervix was examined using mirrors, expanded colposcopy, microscopic examination of the vaginal discharge, RARtest, bacteriological examination of the cervical canal, screening tests (pHmetry, aminotest with 10% KOH), determination of antibodies to pale treponema in the blood, HIV. The presence of pathogens of the main sexually transmitted infections (Chlamydia trachomatis, Neisseria gonorrhoeae, Trichomonas vaginalis, Mycoplasma genitalium) was excluded using a multiplex set of reagents "AmpliSens N. gonorrhoeae /C. Trachomatis /M. genitalium /T. Vaginalis MUL TIPRAIMFL". For an extended characterization of the state of the vaginal microflora, the reagents of the Florocenosis series based on the use of real-time multiplex PCR ("AmpliSens Florocenosis /Bacterial Vaginosis FL") were used. The results of this test allowed us to quantify the total content of bacteria, as well as the content of lactobacilli, G. vaginalis, A. vaginae.

The results were interpreted as follows. BV was established based on the results of the assessment in accordance with Nugent's scores; based on the conclusions of PCR data (AmpliSense Florocenosis /Bacterial vaginosis-FL).

Vaginitis of unknown etiology (nonspecific) was established on the basis of laboratory signs

of inflammation (hyperemia during examination, by limorphonuclear leukocytes (PMN) > 10 in the field of view, the ratio of PMN to squamous epithelial cells (PMN: EC) > 1 : 1) in the absence of pathogenic and conditionally pathogenic microorganisms.

Vulvovaginal candidiasis was established upon detection of characteristic clinical signs, laboratory signs of inflammation of PMN: EC > 1: 1, as well as the detection of yeast-like fungi by microscopy and/or upon detection of one of the *Candida* species in concentrations above 10<sup>2</sup> GE/ml during PCR.

Nonspecific vaginitis in combination with bacterial vaginosis was established on the basis of laboratory signs of inflammation (hyperemia during examination, PMJAL > 10 in the field of view, PMJAL : EC ratio > 1: 1) in the absence of pathogenic and conditionally pathogenic microorganisms + evaluation results in accordance with Nugent scores; based on conclusions from PCR (Amplification Florocenosis /Bacterial Vaginosis FL).

Aerobic vaginitis was established in the presence of clinical and laboratory signs of inflammation of PMJAL: EC > 1: 1, with the dominance of coccal flora according to microscopy, as well as with the detection of signs of nonspecific vaginitis according to PCR: a decrease in the number of lactobacilli and their replacement by aerobic microorganisms (enterobacteria, streptococci, staphylococci), if the latter dominated as part of the vaginal microflora.

Bacterial vaginosis + vulvovaginal candidiasis was established by the results of evaluation in accordance with Nugent's scores, based on conclusions from PCR data (AmpliSens Florocenosis / Bacterial vaginosis FL), laboratory signs of inflammation of PMJAL : EC > 1 : 1, as well as when yeast-like fungi were detected by microscopy and/or when one of the species of *Candida* was detected in concentrations above 10<sup>2</sup> GE/ml during PCR.

The "norm" was established in the absence of signs of inflammation during examination, normal microscopy results (less than 10 leukocytes in the field of view, rod flora), the absence of pathogenic and low concentrations

of conditionally pathogenic microorganisms during PCR.

Metrogil plus gel was administered intravaginally to pregnant women. The recommended dose was 5 g (one full applicator) 2 times a day (morning and evening). The course of treatment is 5 days. One gram of gel contains: Metronidazole 10 mg and Clotrimazole 20 mg. The drug is combined, has antibacterial, antiprotozoal and antifungal effects. The second stage was assigned lactobacilli, providing colonization resistance of the vaginal biotope. The drug based on *L. Caseiham nosus* (Lcr35) lactojinal was prescribed 1 capsule in the morning and evening for 7 days or 1 capsule daily for 14 days intravaginally.

After the end of treatment, repeated gynecological (examination in mirrors) and laboratory examination were performed to establish the effectiveness of therapy. The effectiveness of treatment was evaluated in dynamics: 1 month (at 16-19 weeks) and 3 months (at 29-31 weeks) after the end of treatment.

To determine the statistical reliability of the results obtained, the Chi squared method was used, at  $p < 0.05$ , the results were considered statistically significant.

### Research results and their discussion:

The average age of the patients was  $29.5 \pm 4.7$  years in the main group and  $28.9 \pm 4.2$  years in the comparison group. After the study of the vaginal biotope, it was found that bacterial vaginosis was most often observed: 27% in the main group and 28% in the comparison group. Signs of inflammation during microscopy were found in another 21% of women in the main group and in 22% of the comparison group. At the same time, the cause of inflammation was not detected by any of the methods used, which corresponded to vaginitis of unknown etiology. Vulvovaginal candidiasis was diagnosed in 18% of pregnant women of the main group and in 17% of the comparison group, nonspecific vaginitis in combination with data on the presence of bacterial vaginosis – in 16% and 15%, respectively. Aerobic vaginitis was found in 10% of women in the main group and in 9%

of patients in the comparison group Bacterial vaginosis in combination with signs of vaginal candidiasis – in 8% and 9% of women, respectively. Consequently, the groups were identical in terms of existing vaginal infections in the patients. After the treatment, dynamic monitoring of pregnant women showed an improvement in the condition and clinical picture due to the elimination of symptoms that occurred at the time of the first treatment, the discharge stopped after 5-6 days, itching, burning disappeared after 3-5 days. Analysis of the results of the study of control smears showed the effectiveness of treatment in the main group of 100% of cases, as evidenced by the fact of the conclusions "norm", which was established in the absence of signs of inflammation during examination, normal microscopy results (less than 10 leukocytes in the field of view, rod flora), the absence of pathogenic and low concentrations of conditionally pathogenic microorganisms during PCR, which It allowed us to conclude about the clinical and laboratory effectiveness of the use of Metrogil plus in pregnant women with vaginal infections. During the control bacterioscopic and cultural examination of the material, positive dynamics was observed in the main group (a decrease in the leukocyte reaction and the absence of growth of facultative anaerobic conditionally pathogenic microorganisms).

1 month after the end efficacy in the main group was 99%, in the comparison group – 94% ( $p = 0.12$ ), 3 months after treatment, relapses were detected in 2% and 10% of cases, respectively ( $p = 0.02$ ).

During the study, the peculiarities of the course of pregnancy, complications of childbirth and after the labor period were evaluated. Placental disorders manifested in the form of fetal development delay, fetal hypoxia, the threat of spontaneous abortion, polyhydramnios, gestational pyelonephritis, pregnancy-induced edema and preeclampsia were observed in the main group less frequently than in the comparison group ( $p = 0.025$ ).

Complications of childbirth and the postpartum period (premature discharge of amniotic fluid, purulent-inflammatory diseases after

childbirth, pyelonephritis of maternity women) were also noted less frequently in the main group than in the comparison group (Table. 3), which is associated with a significantly lower number of relapses after treatment ( $p=0.004$ ).

**Conclusions:** In modern conditions, the concept of the norm for vaginal microecology is rather vague – the quantitative ranges of the presence of bacteria in the vaginal environment differ significantly, and the presence of yeast-like fungi and other facultative microorganisms is quite acceptable when they reach a certain quantitative threshold. Description of the microbiology of pathological shifts of the vaginal biotope becomes a difficult task. It is a difficult task to understand the diagnosis and, moreover, the correction of the equilibrium existence of various types of microorganisms that make up the vaginal biotope. For an extended characterization of the state of the vaginal microflora, the use of reagent kits of the Florocenosis series based on the use of real-time multiplex PCR ("Ampliens Florocenosis /Bacterial Vaginosis FL") is appropriate. The results of this test allowed us to characterize quantitatively the total content of bacteria, as well as the content of lactobacilli, *G. vaginalis*, *A. Vaginae*. The results obtained made it possible to interpret several vaginal biotopes: bacterial vaginosis, nonspecific vaginitis, vulvovaginal candidiasis, nonspecific vaginitis + bacterial vaginosis, aerobic vaginitis, bacterial vaginosis + vulvovaginal candidiasis.

Today, almost the only available and adequate way to correct the pathological biocenosis of the vagina is to influence pathogenic microorganisms with antimicrobial combined agents and achieve the restoration of vaginal physiological microbiocenosis of the vagina. Currently, the most optimal method of treating vaginal infections is a two-stage method of correction of the vaginal biotope. Treatment of vaginal infections with a new gel-form drug (Metrogil plus) in pregnant women is highly effective and is 99%. The number of relapses after treatment with a combined drug in the form of a gel after 3 months is only 2%. Analysis of individual charts of pregnant

women and birth histories showed high therapeutic efficacy of Metrogil plus during pregnancy, as indicated by the low incidence of complications of pregnancy and childbirth, the physiological course of the early postpartum period in women. Therefore, the use of an effective combination drug in the treatment of vaginal infections can reduce the frequency of complications of pregnancy, childbirth and the postpartum period.

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