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MODERN TREATMENT OF BACTERIAL VAGINOSIS IN THE SECOND TRIMESTER OF PREGNANCY

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Relevance : Bacterial vaginosis (BV) is a qualitative and quantitative disorder of the microflora of the urogenital tract. In BV, there is an absence or decrease in the total number of lactobacilli and an increase in the number of anaerobic microorganisms, such as Gardrenella vaginalis, Prevotella, Atopobium vaginae, Mobiluncus, Bifidobacterium, Sneathia, Leptotrichia, and other BV-associated bacteria [1]. BV is common in patients of reproductive age. The prevalence of BV in pregnant women is 8-51% [2]. BV in pregnant women is caused by complications during pregnancy, in particular chorioamnionitis, spontaneous miscarriage, premature rupture of the membranes, premature birth (PR) and a deficiency in the child's body weight at birth. Globally, the rate of neonatal mortality associated with HIV reaches 2.9 million. Over 80% of neonatal mortality is accounted for by newborns with OD, 2/3 of whom are premature, 1/3 are full–term infants with low body weight [3]. In the study by X. Zhang et al. Of the 186 pregnant women with gestational diabetes mellitus (GDM), 106 had an abnormal composition of the vaginal microflora. Patients with abnormal microflora showed a high incidence of premature rupture of the membranes (32.1%), PR (7.5%) and choriamnionitis (2.5%) [4].

The Amsel criteria are considered the gold standard for the diagnosis of BV. They are widely used in clinical practice [6].

Currently, the standard treatment regimen for BV is the antibiotics clindamycin and metronidazole. Research results have shown that the recovery rate after antibiotic treatment increases to 80-90% [7]. In a retrospective study, E. Solgi et al. 185 pregnant women participated (gestation period – 25 weeks). The patients were divided into three groups. 40 pregnant women in the first group took an oral probiotic containing L. acidophilus, L. plantarum, L. frementum and L. gasseri for up to 37 weeks. 40 pregnant women of the second group received vaginally a probiotic containing L. plantarum, L. acidophilus, L. rhamnosus, L. gasseri, up to 37 weeks. The control group patients did not receive treatment.

According to the results, PR occurred in 28 (26.7%) patients of the control group, 12 (30%) patients of the second and 9 (22.5%) patients of the first group [8]. In the study by N. Stojanovich et al. 60 pregnant women participated. 30 patients received a probiotic containing L. rhamnosus BMX 54 vaginally, one capsule once a week for 12 weeks. 30 pregnant women did not receive treatment. Every month (three follow-up visits), pregnant women underwent smear tests on the vaginal microflora, measured the pH of the vagina, and the length of the cervix.

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The aim- is to evaluate the effectiveness of modern treatment methods for patients with bacterial vaginosis (BV) in the second trimester of pregnancy.

Показатель	Первая группа	Вторая группа
Возраст, полных лет	28 ± 7,1	28,0 ± 1,8
Рост, см	162,5 ± 5,5	166,3 ± 3,9
Масса тела, кг	67,8 ± 3,8	61,4 ± 3,7
Менархе, полных лет	13 ± 1,4	12,5 ± 1,2

Table 1. Characteristics of the studied patients

Фактор	M ± SD	95%-ный доверительный интервал
Токсикоз	29,5 ± 3,6	27,4–31,6
Угроза прерывания беременности	29,6 ± 6,9	25,4–33,9
Гестационный сахарный диабет	27 ± 5,7	24,8 ± 30,2
Анемия	28 ± 0,6	26,7 ± 29,3

Примечание. Различия статистически значимы, p < 0,05.

Table 2. Comparison of age (full years) in pregnant women with complications

Показатель	До лечения		После лечения		p	
	группа 1	группа 2	группа 1	группа 2	группа 1	группа 2
Lactobacillus spp.	103 ± 1,2	104 ± 1,0	106 ± 1,0	107 ± 1,0	0,001	0,001
Gardnerella vaginalis	106 ± 1,1	105 ± 1,0	103 ± 1,8	102 ± 1,0	0,001	0,001
Atopobium vaginae	105 ± 1,0	105 ± 1,0	102 ± 1,0	103 ± 1,0	0,001	0,001

Примечание. Различия статистически значимы, p < 0,05.

Table 3. Assessment of changes in indicators in groups, GE/ml

Диагностические критерии	Первая группа	Вторая группа
Неприятный рыбный запах	Нет	Нет
Выделения	Нет	Нет
pH	3,7–4,0	3,9–4,3
Аминный тест	Отрицательный	Отрицательный

Table 4. Efficacy criteria after treatment in groups for a period of 30 weeks

Material and methods. The study was conducted at the women's clinic in Lobnya, Moscow region, from January to November 2022 (scientific supervisor – Doctor of Medicine,

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Professor I.B. Manukhin). The study involved 50 pregnant women of the second trimester with clinical symptoms of BV. All patients signed a voluntary informed consent. The criteria for inclusion in the study were the age of 18-45 years, the established diagnosis of BV, pregnant women of the second trimester, a single pregnancy, and the presence of signed informed consent. Criteria for non-inclusion: pregnant women of the first or third trimester, detection of sexually transmitted infections during pregnancy, drug intolerance, therapy with other vaginal drugs, erroneous inclusion. Exclusion criteria: chronic concomitant diseases in the stage of decompensation, acute psychotic diseases (psychosis, hallucinations), refusal to participate in the study.

The study included three stages:

Stage I – diagnostics;

Stage II – treatment;

Stage III – observation.

The first stage (diagnosis) included the collection of anamnesis, gynecological examination, assessment according to the Amsel criteria (discharge from the genital tract with an unpleasant fishy odor, an increase in pH above 4.5, a positive amine test, detection of key cells). A microscopic examination of the vaginal microflora smear was performed. Criteria for evaluating smear results: detection of key cells and absence or slight increase of white blood cells. The biocenosis of the vagina was studied using the AmpliSens® Florocenosis test performed on the AmpliSens® PCR test system in real time. The study was conducted in the laboratory of the CMD (Center for Molecular Diagnostics) of the Central Research Institute of Epidemiology of Rospotrebnadzor. The levels of Lactobacillus spp., G. vaginalis, A. vaginae, Enterobacteriaceae, Staphylococcus spp., Streptococcus spp., Ureaplasma parvum, U. urealyticum, Mycoplasma hominis, Candida albicans, C. glabrata, C. krusei, and C. parapsilosis/tropicalis were determined by PCR.

The second stage (treatment) took seven days. On the tenth day after the end of therapy, a follow-up examination was performed: the Amsel criteria were evaluated, a microscopic examination of the vaginal smear and the AmpliSens® Florocenosis test were performed. In pregnant women of both groups, clinical and microbiological studies of the vaginal smear were performed at 30 weeks, and S. agalactiae was inoculated at 35-37 weeks of gestation.

At the third stage, the course and outcome of pregnancy (the method of delivery) were monitored.

The patients were divided into equal groups by random sampling. In the first group, therapy was prescribed in the presence of three Amsel criteria and based on the results of the AmpliSens® Florocenosis test (Lactobacillus spp. < 105 GE/ml, an increase in the amount of G. vaginalis, A. vaginae > 105 GE/ml). Patients with BV in this group received at the same time the probiotic Lactoginal – one capsule twice a day (morning and evening) and clindamycin – one candle at night. In the second group, therapy was prescribed based on three Amsel criteria and the results of the AmpliSens® Florocenosis test (Lactobacillus spp. 104 GE/ml, G. vaginalis, A. vaginae > 105 GE/ml). The patients in this group received only

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the probiotic Lactoginal, one capsule twice a day (morning and evening). As already noted, the duration of treatment in both groups was seven days.

All pregnant women presented clinical complaints of discharge from the genital tract with an unpleasant fishy odor in abundance, itching and burning. Among the patients of the studied groups, BV was diagnosed based on three or four signs of Amsel and the results of PCR diagnostics (AmpliSens® Florocenosis). Complaints of discharge with a fishy odor were noted in 50 (100%) patients of both groups. In the first group, itching was observed in 5 (20%) patients, burning in 20 (80%). In the second group, itching was not observed, burning occurred in 10 (40%) pregnant women.

The effectiveness of treatment was assessed on the basis of clinical (complaints, examination, gynecological examination) and laboratory data (Amsel criteria), the results of microscopic examination of the vaginal smear and vaginal microflora using the AmpliSens® Florocenosis test. The criterion of effectiveness was considered to be the absence of clinical symptoms: less than three Amsel criteria, the absence of key cells in the vaginal smear, a decrease in the titer of G. vaginalis and an increase in the content of Lactobacillus spp. according to the AmpliSens® Florocenosis test. Statistical processing of the obtained data was carried out using the IBM SPSS STATISTICS 23 program. Quantitative indicators were checked for the normality of the distribution using the Kolmogorov–Smirnov criterion and compared using the paired Student t-test. A 95% confidence interval (95% CI) was used for the odds. The results obtained are presented as the arithmetic mean (M) and the standard deviation (± SD). The differences at $p < 0.05$ were considered statistically significant.

Results :

The average age in the studied groups was 28 ± 5 years (18-45 years). When collecting anamnesis, it was found that 21 (42%) patients had their first pregnancy, and 29 (58%) had a repeat pregnancy. Pregnancy occurred naturally in 48 (96%) patients, and after in vitro fertilization (IVF) in 2 (4%) patients. All pregnant women took folic acid at a dose of 400 mg (up to 13 weeks of pregnancy), potassium iodide 200 mg, and colecalciferol 2000 units. After 13 weeks, pregnant women received multivitamins (folic acid + metapholine + docosahexaenoic acid), potassium iodide 200 mg and colecalciferol 2000 units. 15 (30%) patients had mild toxicosis in the first trimester. Pregnant women complained of vomiting up to five times a day, nausea, decreased appetite, weakness, and fatigue.

The patients underwent drug therapy: biologically active additives (magnesium lactate, ginger root extract, pyridoxine hydrochloride), one capsule twice a day, artichoke leaf extract 200 mg, two tablets three times a day for 14 days. 13 (26%) patients were diagnosed with a threat of termination of pregnancy based on complaints (pulling pain in the lower abdomen and spotting from the genital tract). GSD was detected in 28 (56%) pregnant women after a glucose tolerance test. Pregnant women with GDM were prescribed diet therapy. 46 (92%) patients had mild anemia. 4 (8%) patients had no anemia. Pregnant women were prescribed therapy with Fe(III) hydroxide polymaltose.

The average age of pregnant women with toxicosis and the threat of termination of pregnancy was 29.5 ± 3.6 and 29.6 ± 6.9 years, respectively, pregnant women with GDM and mild anemia – 27 ± 5.7 and 28 ± 0.6 years, respectively.

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Before treatment, patients in both groups (100%) had positive Amsel criteria: pH > 4.5 and a positive amine test. According to the results of microscopic examination of vaginal smears, all patients of the first group had the presence of key cells in the smear before treatment, and the number of leukocytes was 5-8 in the field of vision. In 15 (60%) patients of the second group, the number of leukocytes is up to 10 in the field of vision, in 10 (40%) - 15 in the field of vision. Key cells were found in the smear of all pregnant women in this group.

After treatment with the probiotic Lactoginal and clindamycin, all patients in the first group had no complaints, the pH was within the normal range of 3.8–4.5, and the amine test was negative. Examination of the vaginal smear showed the absence of key cells in the smear in 22 (88%) pregnant women. The differences are statistically significant ($p < 0.05$). The effectiveness of therapy is 88%.

In the second group, after the use of Lactoginal, the pH value decreased to 4.5 in all pregnant women. The amine test is negative. Microscopic examination of a smear of key cells was not detected in 21 patients. The differences are statistically significant ($p < 0.05$). The effectiveness of treatment is 84%.

After treatment, the number of lactobacilli increased in patients of both groups. In 23 patients of the first group, the level of lactobacilli exceeded 105 GE/ml ($p = 0.001$), the effectiveness was 92%, and the number of opportunistic microorganisms decreased. In 20 (80%) patients of the first group, the titer of G. vaginalis decreased to 103 GE/ml. The effectiveness of clindamycin and Lactoginal therapy was 80%. In the second group, after probiotic therapy with Lactoginal, 22 (88%) patients had a lactobacillus count of 107 GY/ml. G. vaginalis was not detected in 6 (24%) pregnant women. In 19 (76%) patients, the titer decreased to 102 GE/ml. The differences are statistically significant ($p < 0.05$). The effectiveness of treatment is 76%. The content of A. vaginae in the first group was 102 GE/ml, in the second – 103 GE/ml (Table 3).

In the first group after treatment, the level of Lactobacillus spp. The content of G. vaginalis increased significantly from 103 ± 1.2 to 106 ± 1.0 GE/ml, and the content of G. vaginalis decreased significantly from 106 ± 1.1 to 103 ± 1.8 GE/ml. The titer of A. vaginae decreased statistically significantly from 105 ± 1.0 to 102 ± 1.0 GE/ml.

In the second group, after treatment, the titer of Lactobacillus spp. statistically significantly increased from 104 ± 1.0 to 107 ± 1.0 GE/ml. The content of G. vaginalis decreased statistically significantly from 105 ± 1.0 to 102 ± 1.0 GE/ml. The titer of A. vaginae decreased statistically significantly from 105 ± 1.0 to 103 ± 1.0 GE/ml (Table 3).

After the end of treatment, the patients continued to be monitored in the third trimester. At the age of 30 weeks, clinical and laboratory data were evaluated in both groups, and a microscopic examination of the vaginal smear was performed. Diagnostic criteria for BV in pregnant women at 30 weeks of age are given in Table 4.

According to the results of a microbiological examination of the vaginal smear (leukocytes < 10 in the field of view), the absence of key cells was recorded in patients of both groups, the pH was within the normal range (3.7–4.5), the amine test was negative.

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At the age of 35-37 weeks, S. agalactiae was seeded. No growth of opportunistic flora and S. agalactiae was detected in all patients. Complications during childbirth and pregnancy outcomes in patients with BV of both groups were also monitored. In 42 (84%) patients, pregnancy ended with timely delivery. Cesarean section was performed in 8 (16%) patients. Spontaneous labor occurred at 40 ± 1.5 weeks ($p = 0.001$). Four of the eight pregnant women in the probiotic group underwent cesarean section at 38 ± 1.5 weeks ($p = 0.001$). The indicators are statistically significant ($p < 0.05$). Indications for performing a cesarean section were acute fetal hypoxia, IVF, and a scar on the uterus after cesarean section. PR was not registered in the patients of the studied groups. Complications of childbirth through natural routes were not observed. The postpartum period was uneventful.

Discussion :

The results of our study demonstrated the high efficacy of the Lactoginal probiotic in pregnant women of the second trimester. The use of the probiotic Lactoginal is associated with an increase in the number of lactobacilli, a decrease in the growth of opportunistic microorganisms in the vagina, and normalization of the pH of the vagina. That is, there is an anti-inflammatory effect.

Several randomized clinical trials have investigated the potential benefits of probiotics in gynecological and obstetric diseases. In particular, in five studies, the risk of PR was assessed up to 34 weeks, in 11 – up to 37 weeks. It was shown that the use of a probiotic did not increase the frequency of PR up to 34 weeks (relative risk (HR) 1.03; 95% CI 0.29–3.64) and up to 37 weeks (HR 1.08; 95% CI 0.61–2.56). 57 patients in the main group took a probiotic and an antibiotic vaginally for ten days, 59 patients in the control group The groups are just an antibiotic. The use of a probiotic in combination with an antibiotic in patients with premature rupture of the membranes was associated with an increased gestation period (35.4 versus 32.5 weeks) at birth compared with the group whose patients took only an antibiotic [11].

In the study by L. Petricevic et al. 119 pregnant women participated. The patients were divided into two groups:

intermediate vaginal microflora and 4 points on the Nuget scale with lactobacilli;

intermediate microflora and 4 points on the Nuget scale without lactobacilli.

The scientists found that the frequency of PR in the group whose patients received lactobacilli was reduced (odds ratio 0.34; 95% CI 0.21–0.55; $p < 0.001$). In pregnant women who received treatment, the gestation period at birth was 40.1 ± 0.4 weeks, and the newborn's weight was 3941 ± 329 g. In pregnant women who did not receive treatment, the gestation period at birth was 37.1 ± 2.8 weeks, and the newborn's weight was 2838 ± 816 g ($p = 0.047$ and $p = 0.016$). The study showed the advantage of vaginal lactobacilli therapy [13]. As the results of a number of foreign studies show, the use of lactobacilli in pregnant women with BV reduces the frequency of pregnancy. Thus, the use of the probiotic Lactoginal in pregnant women with BV as monotherapy improves the course and outcome of pregnancy.

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Conclusion .

According to the data presented, the probiotic Lactoginal in patients with BV in the second trimester is the drug of choice. The use of probiotics reduces the burden of antibacterial agents on the body, increases the colonization of lactobacilli, which serve as a protective barrier, reducing the content of opportunistic microorganisms.

The simultaneous use of an antibacterial drug and a probiotic helps to reduce the duration of treatment, the frequency of relapses and complications during pregnancy. The method is quite effective and can be recommended for the treatment of patients with BV in the second trimester of pregnancy.

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