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Treatment strategies in different phenotypic forms of bacterial vaginosis

Yulia E. Dobrokhotova, Valeriya D. Kazantseva, Lyudmila A. Ozolinya, Tatyana N. Savchenko

Pirogov Russian National Research Medical University, Moscow, Russia

ABSTRACT

BACKGROUND: Bacterial vaginosis represents the most prevalent non-inflammatory syndrome affecting the lower genital tract in women. It is associated with significant complications in obstetric and gynecological practice. At present, the only recommended treatment regimens for bacterial vaginosis include antibiotics (metronidazole and clindamycin), which have been observed to have only short-term effects. Recurrence of bacterial vaginosis occurs in 50–80% of cases within a year of completing treatment. This may be attributed to the distinctive characteristics of the vaginal microbiome and the fact that following antibiotic treatment, beneficial strains of *Lactobacillus* spp., such as *L. crispatus*, are unable to recolonize the vagina. In the absence of an efficacious and long-term treatment, clinicians and scientists are investigating alternative approaches to the management and prevention of this syndrome. This has led to a rapid evolution in the understanding of the etiology of bacterial vaginosis and of the best patient care. Current research in this field is focused on the use of antiseptics, probiotics, prebiotics, transplantation of the vaginal microbiome, pH modulation and biofilm disruption as potential treatments for bacterial vaginosis.

AIM: The objective is to identify the species of vaginal *Lactobacillus* and the genotypes of *Gardnerella vaginalis* in women before treatment of bacterial vaginosis and after administration of a one-step antibacterial regimen in comparison to a two-step therapy with suppositories containing at least 10^7 live Lactobacillus acidophilus or a lactic acid-glycogen complex.

MATERIAL AND METHODS: A prospective, comparative, randomized study was conducted in 90 women aged 18 to 45 years old diagnosed with bacterial vaginosis based on the molecular genetic characteristics of the vaginal microbiota. The patients were randomized to one of three groups, with 30 subjects in each. Group 1 received only antibiotic therapy, Group 2 received antibiotic therapy concomitantly with a suppository containing ⩾107 live *Lactobacillus acidophilus*, and Group 3 received antibiotic therapy concomitantly with lactic acid and glycogen. Clinical and laboratory efficacy of the treatment was assessed at the end of Week 4.

RESULTS: The results showed that four weeks after treatment, all study groups experienced favorable changes in the symptoms and signs, normalization of vaginal pH, and improvements in molecular genetic testing. These effects were more pronounced in Group 2 patients.

CONCLUSION: The combination of antibiotic therapy with lactic acid and glycogen demonstrated high clinical efficacy and good tolerability. However, further studies are needed to assess the long-term results of this treatment approach.

Keywords: bacterial vaginosis; probiotic; prebiotic; clindamycin; metronidazole; lactic acid.

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Терапевтические стратегии при различных фенотипических вариантах бактериального вагиноза

Ю.Э. Доброхотова, В.Д. Казанцева, Л.А. Озолиня, Т.Н. Савченко

Российский национальный исследовательский медицинский университет им. Н.И. Пирогова, Москва, Россия

АННОТАЦИЯ

Обоснование. Бактериальный вагиноз является самым распространённым невоспалительным синдромом нижнего отдела репродуктивного тракта у женщин и связан с серьёзными осложнениями в акушерской и гинекологической практике. В настоящее время единственные схемы лечения бактериального вагиноза включают антибиотики (метронидазол и клиндамицин), которые чаще всего обеспечивают лишь краткосрочный эффект. В 50–80% случаев наблюдается рецидив бактериального вагиноза в течение года после завершения лечения. Это может быть связано с особенностью микробиома влагалища, а также с тем, что после лечения антибиотиками полезные штаммы *Lactobacillus* spp., такие как *L. Crispatus*, не колонизируют влагалище повторно. В отсутствие эффективного и долгосрочного лечения врачи и учёные изучают различные подходы к лечению и профилактике синдрома, что приводит к быстрой эволюции взглядов на патогенез бактериального вагиноза и ведение пациенток. Современные области исследований по лечению бактериального вагиноза включают антисептики, про- и пребиотики, трансплантацию вагинального микробиома, модуляцию pH и разрушение биоплёнок.

Цель. Провести видовую идентификацию влагалищных *Lactobacillus* spp. и генотипов *Gardnerella vaginalis* у женщин до лечения бактериального вагиноза и после терапии с применением одноэтапной антибактериальной схемы лечения в сравнении с двухэтапной терапией с помощью суппозиториев, содержащих не менее 10^7 живых *Lactobacillus acidophilus,* или комплекса молочной кислоты с гликогеном.

Материал и методы. Проведено проспективное сравнительное рандомизированное исследование с участием 90 женщин 18–45 лет с бактериальным вагинозом, установленным на основании молекулярно-генетических характеристик вагинальной микробиоты. Пациенток рандомизировали на три группы по 30 человек в каждой: участницы 1-й группы применяли только антибиотикотерапию, 2-й группы — антибиотик и комплекс суппозиториев, содержащих не менее 10^7 живых *Lactobacillus acidophilus*, 3-й группы — антибиотик и молочную кислоту с гликогеном. Клинико-лабораторную эффективность проведённого лечения оценивали через 4 недели.

Результаты. Во всех трёх группах через 4 недели после лечения отмечена положительная динамика при оценке клинической картины, а также при измерении pH влагалищного содержимого и при молекулярно-генетическом исследовании, однако более выраженный эффект отмечен у пациенток 2-й группы.

Заключение. Выявлена высокая клиническая эффективность и хорошая переносимость антибиотикотерапии в комплексе с молочной кислотой с гликогеном, однако требуются дальнейших исследования с оценкой долгосрочных результатов.

Ключевые слова: бактериальный вагиноз; пробиотик; пребиотик; клиндамицин; метронидазол; молочная кислота.

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细菌性阴道病不同表型变异的治疗策略

Yulia E. Dobrokhotova, Valeriya D. Kazantseva, Lyudmila A. Ozolinya, Tatyana N. Savchenko

Pirogov Russian National Research Medical University, Moscow, Russia

摘要

背景。细菌性阴道病是女性下生殖道最常见的非炎症综合征，与产科和妇科实践中的严重并发症相关。目前，治疗细菌性阴道病的唯一方案是抗生素（甲硝唑和克林霉素），但这些药物通常只能提供短期效果。治疗结束后一年内，50~80%的病例会复发。这可能与阴道微生物群的特性有关，以及在抗生素治疗后有益的乳杆菌菌株（如 *Lactobacillus crispatus*）未能重新定植于阴道。由于缺乏有效的长期治疗方案，医生和科学家正在探索治疗和预防该综合征的多种方法，这也促进了对细菌性阴道病发病机制及患者管理方式的快速发展。目前针对细菌性阴道病治疗的研究领域包括抗菌剂、益生菌和益生元、阴道微生物群移植、pH调节及生物膜破坏。

研究目的。对细菌性阴道病治疗前后女性阴道乳杆菌（*Lactobacillus spp.*）及加德纳菌（*Gardnerella vaginalis*）基因型进行物种鉴定，比较单一抗菌治疗方案与结合含不少于10^7个活乳酸杆菌（*Lactobacillus acidophilus*）的栓剂或乳酸与糖原组合的两阶段治疗方案的疗效。

材料与方法。开展了一项前瞻性、对照、随机研究，共招募90名年龄在18至45岁之间、通过分子遗传学方法诊断为细菌性阴道病的女性。参与者被随机分为三组，每组30人：第一组仅接受抗生素治疗，第二组接受抗生素治疗并使用含不少于10^7个活乳酸杆菌的栓剂，第三组接受抗生素治疗并使用乳酸与糖原组合的治疗方案。在治疗结束后4周对治疗的临床和实验室效果进行了评估。

结果。所有三组在治疗结束4周后均在临床症状、阴道分泌物pH值及分子遗传学检测结果方面表现出积极变化，但第二组患者的效果更显著。

结论。抗生素联合乳酸与糖原的治疗方案具有较高的临床疗效和良好的耐受性，但需要进一步研究以评估长期疗效。

关键词：细菌性阴道病；益生菌；益生元；克林霉素；甲硝唑；乳酸。

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BACKGROUND

Bacterial vaginosis (BV) is the most prevalent disease, affecting 23%–29% of women of reproductive age [1]. The traditional definition is dysbiosis, i.e., a disruption of the normal balance of the vaginal microbiota, with a massive increase of facultative and obligate anaerobic bacteria (mainly *Gardnerella spp.*) and a loss of lactobacilli. This definition accurately describes the change in the microbiota; however, it does not explain the underlying pathophysiology, leaving unanswered the question of how to treat BV, including refractory and recurrent BV.

Unfortunately, in addition to local dysbiosis of the vaginal microflora, BV is associated with various medical conditions. For example, BV patients are at a 1.53-fold higher risk for pelvic inflammatory disease (PID) and a 3.32-fold higher risk for infertility. In pregnancy, BV increases the risk for preterm birth by a factor of 2.16 and for late miscarriage by a factor of 6.32 as a result of ascending infection [2–4]. Furthermore, BV promotes co-infection with sexually transmitted infections (STIs) such as *Chlamydia trachomatis, Mycoplasma genitalium, Neisseria gonorrhoeae, Trichomonas vaginalis*, human papillomavirus, and human immunodeficiency virus [5].

Until recently, *Gardnerella vaginalis* (*G. vaginalis*) was thought to be the only species in the *Gardnerella* genus. However, genetic differences within the genus have now been identified, resulting in 13 species of Gardnerella spp, including *G. vaginalis, G. piotii, G. leopoldii, and G. swidsinskii*, along with nine additional unnamed species [6]. According to recent research, several species of *Gardnerella* spp. co-occur in BV biofilm [7].

In approximately half of the cases, patients do not report symptoms despite changes in the vaginal microbiota that are characteristic of BV. The disease is characterized by symptoms such as increased homogeneous vaginal discharge that produces an unpleasant fishy odor, as well as vulvar irritation, dyspareunia, and dysuria. Signs of inflammation (redness, swelling, and pain) are usually absent [4].

In the past 20 years, polymerase chain reaction (PCR) tests and sequencing techniques, as well as fluorescence in situ hybridization (FISH), have been evaluated for the diagnosis of BV. In contrast to the reference methods, these techniques are able to map changes to the vaginal microbiota both quantitatively and on the taxonomic level [8]. In Russia, the most informative diagnostic modality in the outpatient practice of an obstetrician-gynecologist is PCR with hybridization and fluorescence detection, which allows for estimation of the ratio of the total number of bacteria and lactobacilli, as well as opportunistic microorganisms associated with BV *(Gardnerella vaginalis, Atopobium vaginae)* in the vaginal biotope [9].

Anaerobic microorganisms play a crucial role in the development of BV. Consequently, clinical protocols recommend 5-nitroimidazole or lincosamide agents such as metronidazole or clindamycin as first-line therapy [10, 11]. Treatment-refractory or recurrent BV involving at least three episodes per year causes impaired quality of life in >65% of affected individuals [12]. The high rate of treatment failure is attributable to several factors. First, the therapeutic effect of antibiotics on polymicrobial biofilms dominated by certain *Gardnerella* species is insufficient. Second, these biofilms are resistant to metronidazole. Third, the biofilms are unable to recolonize the vagina with lactobacilli, which results in re-infection from sexual partners [13]. Consequently, alternative therapeutic agents effective against biofilm (antiseptics, natural antimicrobials, plant extracts, lactic acid-glycogen complex, suppositories containing *live Lactobacillus acidophilus*) are being evaluated as monotherapy or as an adjunct to antibiotic therapy for BV [4, 14–16].

Given the incidence of BV, the variety of its complications in gynecological and obstetrical practice, and the high rate of treatment failure, there is an urgent need to develop new laboratory and therapeutic approaches, as well as methods of reliable prevention of the disease.

The aim of the study was to identify species of vaginal *Lactobacillus* spp. and *Gardnerella vaginalis* genotypes in women prior to treatment of BV and following therapy with a one-step antibacterial regimen versus a two-step therapy with suppositories containing at least 10^7 live *Lactobacillus acidophilus* or a lactic acid-glycogen complex.

MATERIALS AND METHODS

The following inclusion criteria were used to define the study groups: female patients aged 18 to 45 years, including those diagnosed with BV according to clinical criteria (presence of vaginal discharge, elevated pH of vaginal contents above 4.5) and positive aminotest confirmed by PCR.

After signing a voluntary informed consent to participate in the study, women were divided into three groups based on subsequent treatment. Group 1 patients received antibiotic therapy alone (n = 30), Group 2 patients were recommended antibiotic therapy and suppositories containing at least 10^7 live *Lactobacillus acidophilus* (n = 30), and Group 3 patients received antibiotic therapy in combination with lactic acid and glycogen (n = 30).

Exclusion criteria: inability or unwillingness to participate in the study or fulfill the requirements of the study; age below 18 and above 45 years; premature ovarian failure, early or surgical menopause; acute pelvic inflammatory disease; pregnancy or lactation, taking antibacterial agents in the previous three weeks; concomitant STIs (chlamydia, gonococcal infection, trichomoniasis, or infection caused by *M. genitalium*) and/or other infection requiring additional antibacterial and/or antimycotic therapy; indication of intolerance to the lactic acid-glycogen complex in the history; severe liver function disorders with signs of hepatic insufficiency; diabetes mellitus and severe somatic diseases that may affect the study and interpretation of its results;

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mental disorders that do not allow interpretation of the study results; and malignant neoplasms of any localization.

At the stage of inclusion in the study, the patients underwent a gynecological examination. The pH of vaginal contents was measured using indicator strips (Kolpo-test pH, Russia). A vaginal fluid sample was collected from the upper third of the lateral vaginal vault for a comprehensive test. This test is a multiplex PCR system that is comparable in diagnostic performance to international criteria for the detection of BV.

In the subsequent visit four weeks after treatment, the patients' complaints were re-evaluated. In addition, a gynecological examination was performed together with pH measurement of vaginal contents; vaginal fluid from the upper third of the lateral vaginal vault was collected for PCR testing.

Treatment efficacy was evaluated according to the following criteria: the absence of homogeneous whitish-gray vaginal discharge with malodor, pH of the vaginal fluid less than 4.5, and a decrease in the titer of opportunistic microorganisms and normocenosis according to the results of a PCR test.

The statistical processing of the data was performed using Statistica 8.0 software for mathematical and statistical analysis. The nature of the distribution was assessed using the Kolmogorov–Smirnov and Shapiro–Wilk criteria. Spearman's rank correlation analysis was used to assess the strength and direction of correlation between ordinal and nominative data (significance level was considered reliable at $p < 0.05$).

RESULTS

Initially, all patients presented with complaints of white (77.7%) and gray (22.2%) vaginal discharge in scarce (12%), moderate (58%), and abundant (30%) amounts, accompanied by itching (27%), burning (14%), dysuria (6%), dyspareunia (12%), and malodor (60%).

The mean age of the women studied was 32.1 ± 3.6 years.

There were no statistically significant differences between the groups in the frequency of somatic and gynecological disorders.

The most frequently used method of contraception among the patients was interrupted sexual intercourse (48%), while 37% and 15% of the patients employed barrier and hormonal methods (mainly combined oral contraceptives), respectively.

Upon examination, white discharge was observed in 55% of patients, gray discharge in 45%, and malodor in 40%, with no evidence of hyperemia or swelling of the vaginal mucosa.

The average pH of vaginal discharge was 6, ranging from 5.5 to 6.5.

At the second stage, patients were divided into three groups of 30 individuals based on their treatment regimens. A specialized laboratory test was then conducted to ascertain the species diversity of *G. vaginalis and Lactobacillus* spp. within the vaginal biotope. The nucleic acid amplification method was employed to identify the four most prevalent species of vaginal lactobacilli (*L. crispatus, L. iners, L. jensenii, and L. gasseri*) and five species of *G. vaginalis* (*G. vaginalis* genotype 1, *G. vaginalis* genotype 2, *G. swidsinskii, G. leopoldii, and G. vaginalis* genotype 3), and the totality of indicators was subsequently evaluated after treatment.

The presence of *G. vaginalis* DNA was identified in the vaginal biotope of all subjects via PCR-based diagnostics. No statistically significant differences were observed between groups in the number of detections, suggesting that the study groups were comparable in this regard. A thorough examination of species diversity revealed that in Group 1 patients *G. vaginalis* type 2 *(*24.32%*)* and *G. vaginalis* type 3 (8.1%) were identified less frequently, while a significantly elevated level of *G. leopoldii* was detected in Group 2 patients (66.6%).

The most prevalent species among *Lactobacillus* spp. in patients from all groups was *Lactobacillus iners*, accounting for 60% of cases (see Figure 1). Conversely, *Lactobacillus crispatus and Lactobacillus jensenii* were identified with a lower frequency in Group 3 patients, at 30.76% and 28.3%, respectively.

In the four weeks following treatment, as indicated by the control examination, patients across all groups exhibited predominantly moderate mucous discharge without malodor.

The pH value of vaginal discharge 28 days after treatment ranged from 4.5 in Groups 1 and 3 to 4.0 in Group 2, with an average of 4.25.

No adverse reactions, such as itching and burning in the vagina, were detected in any patient during treatment or by the time of the repeat examination.

A PCR test was conducted to evaluate the species diversity of *G. vaginalis and Lactobacillus* spp. within the vaginal biotope following treatment.

The complete disappearance of Gardnerella was not observed; however, a numerical decrease in *G. vaginalis* type 1 and *G. vaginalis* type 2 with an increase in *G. leopoldii* and *G. vaginalis* type 3 in all groups was observed. A decrease in the prevalence of *Lactobacillus iners* was observed in 59.45% and 53.00% of patients in Groups 1 and 3, respectively. Conversely, Group 2 exhibited an increase in the number of Lactobacillus iners among 62.96% of patients. Many researchers associate an increased number of *Lactobacillus iners* with recurrent BV. A decline in the number of *Lactobacillus jenseni* was observed (48.64%, 11.53%, and 37.14% in Group 1, 2, and 3, respectively). However, this decline was more statistically significant in Group 2 (p <0.05). When evaluating *Lactobacillus gasseri*, a decrease was observed in Group 1 (up to 13.51%) and Group 2 (up to 22.22%), with a slight increase in Group 3 (26.92%). An increase in the number of *Lactobacillus crispatus* was observed in all groups (up to 56.75%, 85.18%, and 46.15%, respectively), but the increase was more statistically significant in Group 2 (p <0.05). According to many researchers, an increased value of Lactobacillus crispatus is associated with a "healthy"

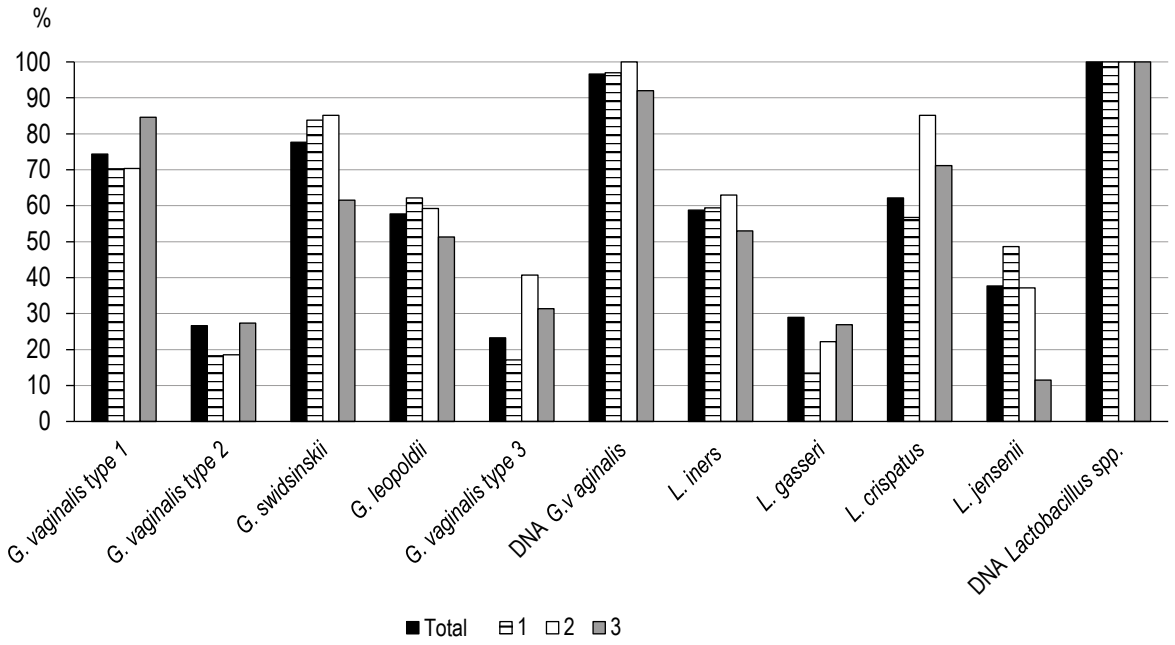

Fig. 1. PCR data of patients with bacterial vaginosis before treatment.

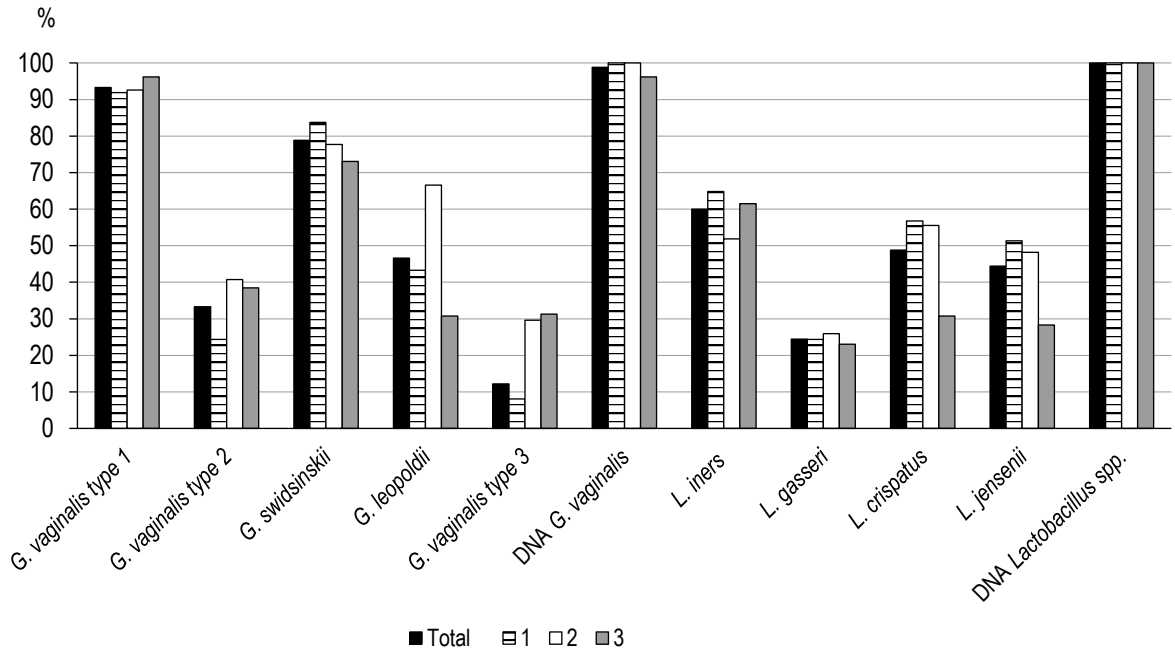

Fig. 2. PCR data of patients with bacterial vaginosis after treatment.

vaginal microbiome. The results obtained one month after treatment are presented in Figure 2.

The laboratory results indicated that all treatment groups exhibited clinical efficacy following antibiotic monotherapy (particularly clindamycin) and two-component therapy (an antibiotic complex with lactic acid and glycogen, or suppositories containing at least 10^7 live *Lactobacillus acidophilus*). However, Group 2 demonstrated a more substantial reduction in the species of *G. vaginalis* and *L. iners*, accompanied by an increase in *L. crispatus*. The validity of the second stage of BV therapy, as well as the selection of pharmaceutical agents, remains a subject of debate. The controversy surrounding the efficacy of live *Lactobacillus acidophilus* in recovering healthy vaginal microbiota, as opposed to the complex of lactic acid and glycogen to create an acidic environment conducive to the proliferation of lactobacilli, remains unresolved.

The findings suggest genetic diversity of microorganisms in the vaginal biotope; however, it is unknown whether these results are associated with the use of pre- and probiotics.

Further follow-up is necessary to assess long-term outcomes and develop recommendations for the treatment of BV.

CONCLUSION

A comparative analysis was conducted to assess the efficacy and safety of suppositories containing *Lactobacillus* spp. and a lactic acid-glycogen complex following antibiotic therapy, with the aim of preventing the recurrence of BV. The analysis took into account the species identification of *Lactobacillus* spp. and *Gardnerella vaginalis* genotypes isolated from the vaginal samples of the study participants. Further research is necessary to evaluate the long-term outcomes of BV treatment.

ADDITIONAL INFO

Authors' contributions. Yu.E. Dobrokhotova edited the manuscript; V.D. Kazantseva collected and reviewed study data, processed statistical data, wrote the text; L.A. Ozolinya developed study concept and design, wrote the text; T.N. Savchenko collected and reviewed study data, wrote the text. All authors confirm that their authorship meets the international ICMJE criteria (all authors have made a significant contribution to the development of the concept, research and preparation of the article, read and approved the final version before publication).

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Consent for publication. Written consent was obtained from all the study participants before the study screening in according to the study protocol approved by the local ethic committee.

Ethical statement. The study was performed within the framework of the dissertation of Valeria Dmitrievna Kazantseva and was approved by the local ethical committee of N.I. Pirogov Russian National Research Medical University (extract from protocol No. 213 dated 13 December 2021).

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AUTHORS' INFO

***Valeriya D. Kazantseva,** Graduate Student;
address: 1 Ostrovityanova Str., 117997 Moscow, Russia;
ORCID: 0000-0002-4011-3195;
eLibrary SPIN: 6973-6276;
e-mail: shapee08@mail.ru

Yulia E. Dobrokhotova, MD, Dr. Sci. (Medicine), Professor;
ORCID: 0000-0002-7830-2290;
eLibrary SPIN: 2925-9948;
e-mail: pr.dobrohotova@mail.ru

Lyudmila A. Ozolinya, MD, Dr. Sci. (Medicine), Professor;
ORCID: 0000-0002-2353-123X;
eLibrary SPIN: 9407-9014;
e-mail: ozolinya@yandex.ru

Tatyana N. Savchenko, MD, Dr. Sci. (Medicine), Professor;
ORCID: 0000-0001-7244-4944;
eLibrary SPIN: 3157-3682;
e-mail: 12111944t@mail.ru

* Corresponding author / Автор, ответственный за переписку

ОБ АВТОРАХ

***Казанцева Валерия Дмитриевна,** аспирант;
адрес: Россия, 117997, Москва, ул. Островитянова, д. 1;
ORCID: 0000-0002-4011-3195;
eLibrary SPIN: 6973-6276;
e-mail: shapee08@mail.ru

Доброхотова Юлия Эдуардовна, д-р мед. наук, профессор;
ORCID: 0000-0002-7830-2290;
eLibrary SPIN: 2925-9948;
e-mail: pr.dobrohotova@mail.ru

Озолиня Людмила Анатольевна, д-р мед. наук, профессор;
ORCID: 0000-0002-2353-123X;
eLibrary SPIN: 9407-9014;
e-mail: ozolinya@yandex.ru

Савченко Татьяна Николаевна, д-р мед. наук, профессор;
ORCID: 0000-0001-7244-4944;
eLibrary SPIN: 3157-3682;
e-mail: 12111944t@mail.ru