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The Effect of Space Flight Factors on the Correction Disorders of the Vaginal and Cervical Microflora in Ground-Based Models

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Abstract: This work shows results of a comprehensive study of the vaginal and cervical microflora of women participating in a ground-based model experiment simulating some factors of space flight. Experiments with dry immersion allow to simulate such factors of a space flight as physical inactivity and microgravity, as well as the redistribution of liquid media associated with them. 16 volunteers, participated in 5-days dry immersion experiment, used an oral prebiotic drug based on lactoferrin and intravaginal probiotic capsules based on *Lactobacillus acidophilus*. It was found that the oral use of lactoferrin has a delayed positive effect on the state of the microflora of the vagina and cervical canal of volunteers. This effect is especially pronounced on the 35th day after the end of the immersion. While the use of probiotic capsules has a faster effect, noticeable after 5 days of use during immersion. The combination of lactoferrin and probiotic capsules did not give noticeable effect, which can be explained both by a small group of volunteers or lack of a synergistic effect of these drugs. One of the means that can give high efficiency in the prevention of the dysbiosis of the vaginal microflora are intravaginal capsules made of autostrains isolated individually from each volunteer and addition of lactoferrin into the capsules, the effectiveness of which when using locally was also proven in previously conducted studies in gynecological patients.

Keywords: lactoferrin, vaginal microflora, ground experiments, space medicine

1. INTRODUCTION

The modern development of technology makes space flights one of the necessary conditions for the development of mankind. A person's stay in space flight conditions leads to the need to correct health in an unfavorable environment, which includes microgravity and concomitant changes in the blood supply of organs, psycho-emotional chronic hypo-stress and, most importantly, a change in the ecological system of man-environment, including microflora. If for men these issues were mostly solved in almost half a century of the space age, then the mass participation of women in space flights is a relatively new phenomenon and requires specific solutions to problems, including those related to feminine hygiene. First of all, this concerns what men do not have (and, accordingly, has not been studied and corrected) in previous years - a change in the vaginal microflora. Since the direct study of the parameters of the vaginal microflora does not allow to obtain statistically significant sample volumes and, most importantly, to test methods for correcting violations, ground-based model experiments are a necessary condition and tool for solving this problem. This approach also makes it possible to assess the risks of developing adverse

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disorders and the effectiveness of interventions before these violations lead to serious medical, social and economic (which is extremely important in space flight) consequences. [1,2]

The microbiota of any human biotopes has individuality. [3,4] Such factors as changes in diet, frequency and quality of hygiene procedures, as well as psycho-emotional stress can provoke a cascade of negative changes in the human body, and, in particular, decrease in colonization resistance of all biotopes.

The vaginal microbiota plays an important role not only in the prevention of inflammatory diseases of the pelvic organs, but also affects the success of fertilization, regardless of whether fertilization occurred naturally or as a result of the in vitro fertilization procedure [5].

The main component of the normal vaginal microbiota of women of reproductive age is *Lactobacillus spp.*, which create an environment that prevents the reproduction of opportunistic and pathogenic bacteria, providing colonization resistance of the vaginal biotope. The normal amount of *Lactobacillus spp.* is 10^6-10^8 CFU/ml, therefore, maintaining high quantity of lactobacilli in the vaginal microflora is important for maintaining the health of women participating in long-term space missions and is directly related to the ability to realize reproductive function. In one of the studies, it was found that in 192 studied patients the ones who had low content of vaginal lactobacilli had lower the percentage of pregnancy [6]. In another study, it was shown that the low percentage of pregnancy was associated with the presence of such opportunistic pathogenic microorganisms (OPM) as *Gardnerella vaginalis* and *Atopobium vaginae* in the vaginal microflora. [7]

Conducting ground-based model experiments, such as dry immersion, makes it possible to study the microbiota under conditions simulating weightlessness.

During dry immersion, volunteers experience the influence of such space flight factors as hypodynamia, redistribution of liquid media [8]. The essence of dry immersion is that a volunteer, dressed in underwear, lies on a platform on a waterproofing film, covered with a cotton sheet, in an ergonomically designed immersion bath filled with water. The immersion bath is designed in such a way that when the platform is lowered, the volunteer is completely immersed in water, except for the head. Thus, during the experiment, a volunteer is in an unsupported suspended state (simulated weightlessness). The volunteer is allowed to leave the immersion bath only for ten minutes a day to take a shower and perform hygiene procedures.

In previous studies of the microflora of women participating in a 3-day dry immersion, a decrease in the colonization resistance of the vaginal biotope was revealed, which was accompanied by an increase in the proportion of OPM (especially the aerobic component) and a decrease in the number of protective *Lactobacillus spp.* [9]

To maintain the microbiota, prebiotic and probiotic drugs are currently actively used. Prebiotic preparations are aimed, first of all, at creating a favorable environment for the reproduction of protective microorganisms already living in a particular biotope. Probiotic preparations are "live strains of carefully selected microorganisms which, when administered in adequate amounts, confer a beneficial effect on the health of the host." [10]

Both types of drugs have proven relatively effective in maintaining the state of the microbiota and have been studied most of all in the intestinal microbiota. [11] However, it is possible that pro- or prebiotic drugs can cause allergic reactions. Also in previous isolation experiments, it has been shown that probiotic drugs indeed support the colonization resistance of the intestinal biotope and suppress the development of OPM, but only during the time that a volunteer takes the drug [12]. Meanwhile, autoprobiotic drugs made from dominative protective strains of the microflora of a particular volunteer do not have these disadvantages.

It should be noted that all biotopes of the human body are interconnected with each other and the violation of colonization resistance of one can lead to a deterioration of microbiota in another [13]. It has been found that oral intake of a pre- or probiotic that directly affects the intestinal microflora can also have a positive effect on the vaginal microflora. For example, this was shown in an experiment involving 8 female volunteers who took a fermented drink based on saccharomyces, bifidobacteria, lactobacilli and enterococci as a dietary supplement. [14]

In this regard, it seems optimal to use a combination of an oral prebiotic preparation and a local autoprobiotic preparation, which will simultaneously strengthen the colonization barrier of a particular biotope and create an environment for favorable reproduction of autoflora.

In present study, we used lactoferrin as an oral prebiotic preparation. Lactoferrin is a polyfunctional protein of the transferrin family found in human secretory fluids: milk, saliva, and tears [15]. Lactoferrin in the human body, being its component, is easily recognized and does not cause allergies.

Lactoferrin also has antibacterial activity. It binds iron to prevents a bacterial cell from assimilating this microelement, which is necessary for growth and reproduction. [16] Lactoferrin receptors also have the ability to bind lipopolysaccharides of the bacterial cell wall, in addition, they initiate peroxidation of the proteins that make up the wall, which leads to a violation of the membrane permeability of the bacterial cell and its subsequent death. There are suggestions that the anti-infective activity of lactoferrin may also be based on stimulation of phagocytosis [17].

The purpose of this study is to evaluate the effect of the combined use of lactoferrin and intravaginal capsules based on *Lactobacillus acidophilus* on the state of the microflora of the vagina and cervical canal of volunteers of the 5-day dry immersion experiment.

2. METHODS AND MATERIALS

The research programs in the isolation experiments "SIRIUS-21" was approved by the bioethical commission of the IBMP (Protocol No. 539 of March 17, 2020) and fully complies with the principles of the Helsinki Declaration of 1964.

To study the state of the microflora of the vagina and cervical canal in a 5-day dry immersion, samples of vaginal and cervical canal microflora were taken from 16 volunteers three times:

a) before the start of the experiment on 19-22 days of the menstrual cycle;
b) on 5-7 day after the end of immersion (19 -22 days of the menstrual cycle);
c) on 34-36 day after the end of immersion (19-22 days of the next cycle).

Probiotic capsules containing *Lactobacillus acidophilus* (strains NK1, NK2, NK5, NK12) were chosen as a local drug for the correction and prevention of dysbiosis of the vaginal microflora. According to the results of in vitro studies, these strains have a pronounced positive effect on vaginal microflora and do not enhance the growth of fungi of the *Candida albicans* species. [18,19].

A food supplement based on a biosimilar of human lactoferrin was used as a probiotic component. [20]

All volunteers were divided into 4 groups.

- Group "Placebo + Placebo" (4 volunteers). During 30 days, starting from the first day of immersion, volunteers once per day took orally the placebo drug with 200 mg of maltodextrin and used glucose-based placebo intravaginal capsules (400 mg glucose in each capsule) once during five days of stay in immersion.
- Group "Placebo + Lactobacilli" (3 volunteers). During 30 days, starting from the first day of immersion, volunteers once per day took orally the placebo drug with 200 mg of maltodextrin and used intravaginal capsules based on *Lactobacillus acidophilus* (titer of *Lactobacillus acidophilus* -10^8 CFU, excipients - magnesium stearate - 3 mg, lactose monohydrate - a sufficient amount to obtain the mass of the contents of the capsule 400 mg), once during five days of stay in immersion.
- Group "Lactoferrin + Placebo" (6 volunteers). During 30 days, starting from the first day of immersion, volunteers once per day took orally the drug with 200 mg of lactoferrin and used glucose-based placebo intravaginal capsules (400 mg glucose in each capsule) once during five days of stay in immersion.
- Group "Lactoferrin + Lactobacilli" (3 volunteers). During 30 days starting from the first day of immersion volunteers once per day took orally the drug with 200 mg of lactoferrin and used intravaginal capsules based on *Lactobacillus acidophilus* (titer of *Lactobacillus acidophilus* -10^8

CFU, excipients - magnesium stearate - 3 mg, lactose monohydrate - a sufficient amount to obtain the mass of the contents of the capsule 400 mg), once during five days of stay in immersion.

Microbiological analysis of the composition of the microbiota of the vagina and cervical canal of women in all experiments was carried out on the basis of FSBI “National Medical Research Center for Obstetrics, Gynecology and Perinatology named after Academician V.I. Kulakov” Ministry of Healthcare of the Russian Federation.

All examiners underwent Gram-stained microscopy of the vaginal discharge and cultural examination in accordance with the medical technology “Integral assessment of the state of the vaginal microbiota. Diagnosis of opportunistic vaginitis” [21]. The material was taken with a sterile Dacron swab from the posterior vaginal fornix and, after treating the cervix with a sterile cotton swab, from the cervical canal. Obtained sample was put into test tubes with Amies transport medium (Medical Wire, England). The vaginal and cervical canal biomaterial was seeded on selective and non-selective agar solid nutrient media. Facultative anaerobic microorganisms were isolated using Columbia agar, Brilliance GBS agar (Oxoid, UK), mannitol salt agar (Himedia, India), enterococcal agar, Endo medium, and Sabouraud agar (GITsPM and B, Obolensk, Russia). Microorganisms were incubated in a CO_2 incubator (Jouan, France). Lactobacilli were cultivated on lactobacillus medium (GITsPM and B, Obolensk, Russia), strict anaerobes were cultivated on prereduced Schedler agar (Oxoid, UK) with the necessary additives in an anaerobic box (Whitley DG 250 Anaerobic Workstation, UK) in three-component gas atmosphere mixtures (N_2-80%; CO_2-10%; H_2-10%). Species identification of microorganisms was performed by MALDI-TOF-MS analysis using a Microflex LT time-of-flight mass spectrometer with Maldi BioTyper software (Bruker Daltoniks; Germany) version 4.0.

The obtained data were analyzed using cluster analysis, chi-square test, nonparametric Friedman and Mann-Whitney tests. [22.] Statistical processing was carried out in the program STATISTICA 12.

3. RESULTS AND DISCUSSION

3.1. The results of comparing the state of the vaginal microflora "before", "after", "after + 30 days" in four groups of volunteers with different drugs combination

According to the results of the analysis with non-parametric Friedman criterion, a significant difference was revealed between the points “Before”, “5-7 day” (5-7 days after the end of dry immersion) and “34-36 day” (34-36 days after the end of dry immersion) both for facultative anaerobic OPM and obligate anaerobic OPM in the “Placebo + Placebo” group.

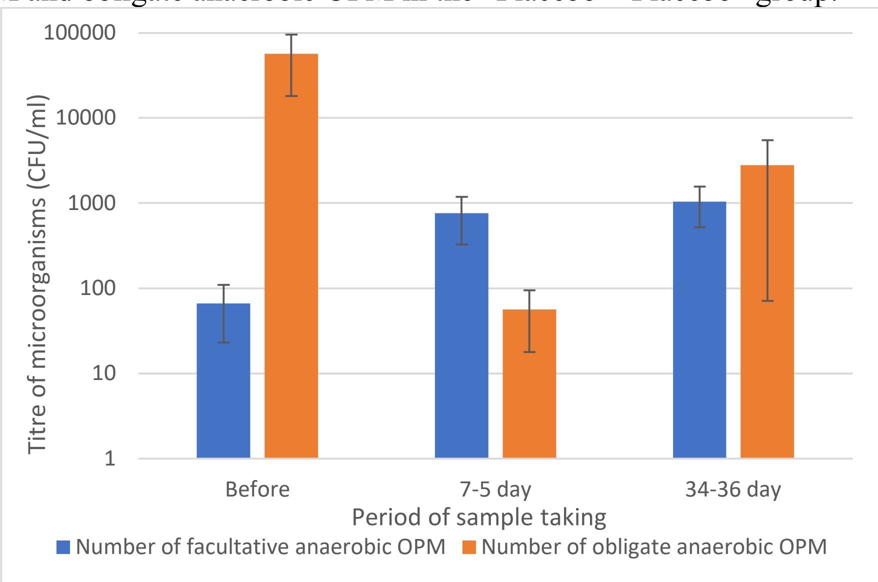


Figure 1. Dynamics of facultative anaerobic and obligate anaerobic OPM in the 5-day dry immersion experiment in the “Placebo + Placebo” group of volunteers

As can be seen from Figure 1, the number of facultative anaerobic OPM increased by the end of the experiment and remained consistently higher than before immersion, including 30 days after the end of exposure. The number of obligate anaerobic OPM decreased after immersion with a subsequent increase on days 34-36 after the end of the experiment.
In the "Lactoferrin + Placebo" group, a significant difference was found in obligate anaerobic OPM (Figure 2).

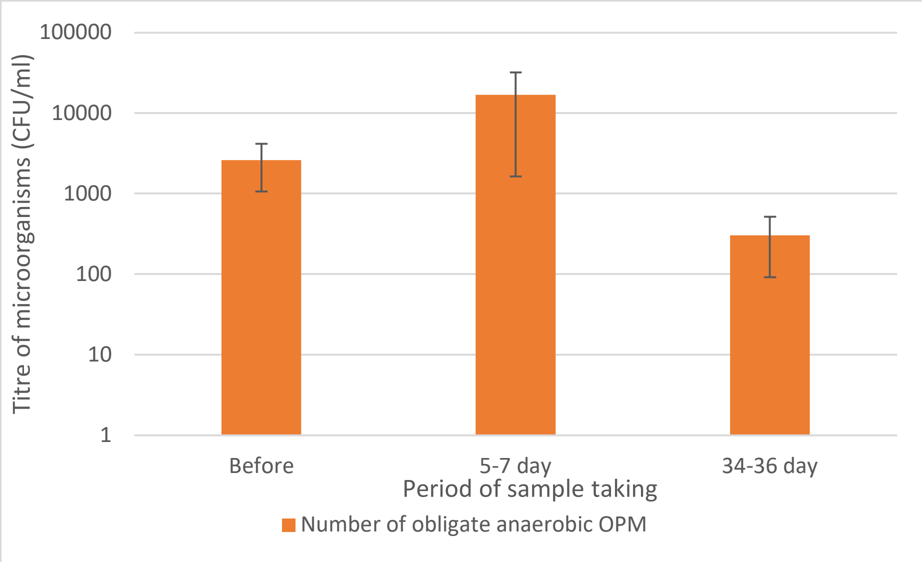


Figure 2. Dynamics of obligate anaerobic OPM in 5-day dry immersion in the "Lactoferrin + Placebo" group of volunteers

As can be seen from Figure 2, the number of obligate anaerobes in this group increased by the end of immersion and then decreased on days 34-36 after the experiment. It should be noted that the use of lactoferrin began on the 1st day of immersion and continued for 30 days, i.e. most of the time after the end of the immersion, the volunteers continued to take lactoferrin, which may have affected the state of the microflora and caused a decrease in the obligate anaerobic OPM.

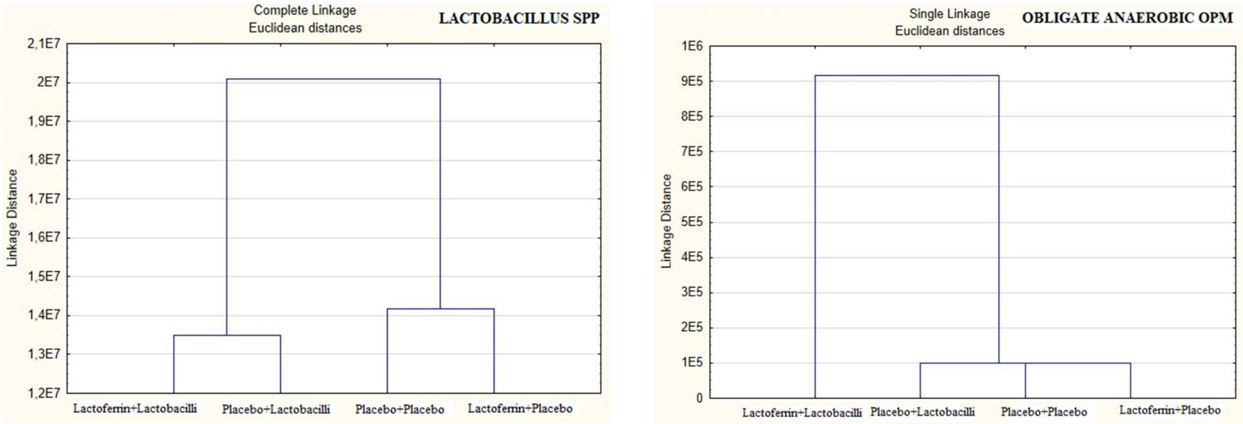
In the "Placebo + Lactobacilli" and "Lactoferrin + Lactobacilli" groups, the nonparametric Friedman test did not reveal any differences.

The obtained data show that immersion has a negative impact on the vaginal microflora: the number of facultative anaerobic OPM increases. Oral intake of lactoferrin has a slight stabilizing effect on the vaginal microflora: the number of facultative anaerobic OPM does not increase, although there is a slight increase in obligate anaerobic OPM immediately after the end of immersion. After long-term use of lactoferrin, this group of microorganisms decreases with a consistently low titer of facultative anaerobic OPM, which indicates a positive effect of this drug after prolonged use.

The lack of differences in the groups "Placebo + Lactobacilli" and "Lactoferrin + Lactobacilli" on three points may be due to the small number of volunteers in these groups.

3.2. The results of comparing the state of the vaginal microflora in the placebo group and groups with different combinations of pre- and probiotic preparations in different periods of the experiment

To compare the groups with each other, cluster analysis and Mann-Whitney test were used.
The results of cluster analysis on days 5-7 after the end of immersion are shown in Figure 3.



A) B)

Figure 3. Results of cluster analysis for *Lactobacillus spp* (A) and obligate anaerobic OPM (B) for all four groups of volunteers with different drugs combination on 5-7 day after finishing of dry immersion.

As can be seen from the figures with anaerobic OPM used for clusterization, the groups “Placebo + Placebo”, “Lactoferrin + Placebo” and “Placebo + Lactobacilli” are the closest to each other. These groups form a single cluster, from which the group “Lactoferrin + Lactobacilli” is equidistant. For lactobacilli, the groups form somewhat different clusters: “Placebo + Placebo” and “Lactoferrin + Placebo” and separately the cluster of “Placebo + Lactobacilli” and “Lactoferrin + Lactobacilli”. These results suggest that, firstly, the “Lactoferrin + Lactobacilli” group differs from the other three groups, and secondly, the greatest effect on lactobacilli, apparently, is not the oral use of lactoferrin, but the local use of capsules.

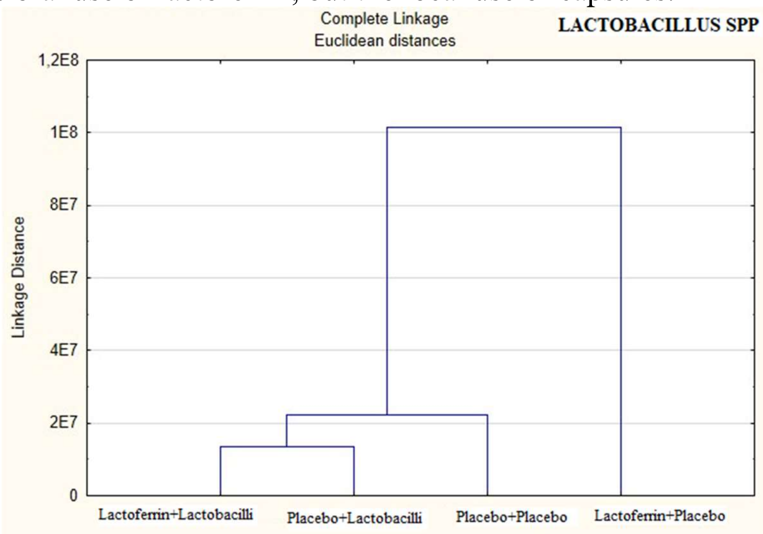


Figure 4. Results of cluster analysis of *Lactobacillus spp* for all four groups of volunteers with different drugs combination at 34-36 day after finishing of dry immersion

Cluster analysis for obligate anaerobic and facultative anaerobic OPM showed that groups “Placebo + Placebo”, “Lactoferrin + Placebo” and “Placebo + Lactobacilli” again turned out to be the closest, which coincides with the situation on days 5-7 after the end of the dry immersion.

For lactobacilli, the situation on days 34–36 is somewhat different: the “Lactoferrin + Lactobacilli” group forms a cluster with the “Placebo + Lactobacilli” group, and then combines with the “Placebo + Placebo” group (Figure 4). Perhaps this is due to the prolonged action of lactoferrin, which the volunteers took for 30 days from the first day of immersion, while probiotic or placebo capsules were used just during the immersion, i.e. for 5 days only.

The state of the microflora in different periods of time in different groups was also assessed using the nonparametric Mann-Whitney test.

A significant difference was found between the “Placebo + Placebo” and “Lactoferrin + Placebo” groups on days 34-36 in number of different kinds of lactobacilli. The amount of

Lactobacillus jensenii, *Lactobacillus vaginalis* and *Lactobacillus gasseri* in the "Lactoferrin + Placebo" group was higher than in the "Placebo + Placebo" group, and the number of *Lactobacillus iners* was, on the contrary, lower (Figure 5).

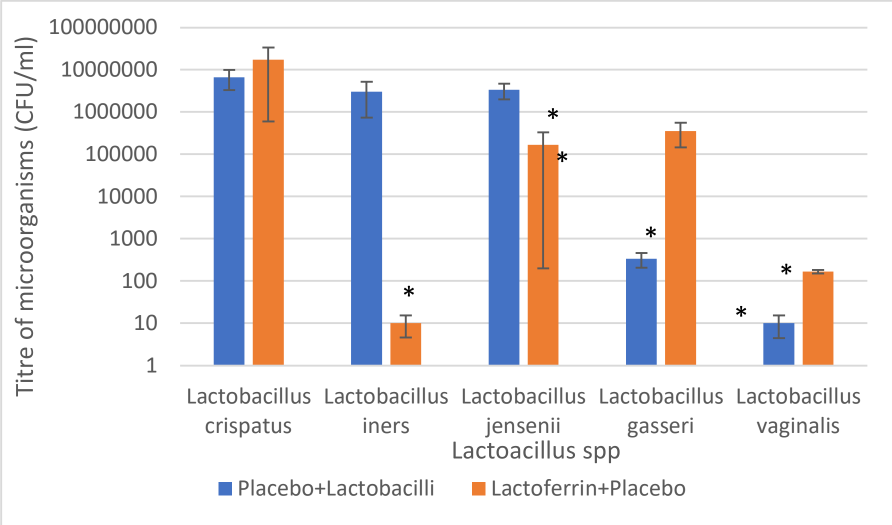


Figure 5. The number of *Lactobacillus spp* in the "Placebo + Placebo" and "Lactoferrin + Placebo" groups of volunteers on days 34-36 after the end of immersion. * - statistically significant differences, $p<0.05$.

These data correlate with data from cluster analysis, where the "Placebo + Placebo" group was quite distant from the "Lactoferrin + Placebo" group (Figure 4B).

It should be noted that the species *Lactobacillus iners* has the lowest probiotic potential and is most often found in patients with infectious and inflammatory pathologies of the vagina. [23,24]. Therefore, the decrease in the number of this kind of lactobacilli in the "Lactoferrin + Placebo" group indicates rather positive change in this group.

Based on the data, it can be concluded that long-term use of lactoferrin has a positive effect on the vaginal microflora: it increases the number of most species of lactobacilli by 30th day after the end of the dry immersion, at the same time inhibiting the growth of *Lactobacillus iners*.

Significant differences were also found between groups "Lactoferrin + Placebo" and "Placebo + Lactobacilli" on obligate anaerobic OPM immediately after the end of immersion. In the "Placebo + Lactobacilli" group, the number of obligate anaerobic OPM was significantly lower than in the "Lactoferrin + Placebo" group. These data partly correlate with cluster analysis (Figure 3B), where the cluster was formed by the "Lactoferrin + Placebo" and "Placebo + Placebo" groups.

Additionally, using the chi-square an eubiotic index (E_i) was calculated and assessed. Eubiotic index shows the ratio of positive changes in the microflora to negative ones. [14] Significant differences between the three groups were found at the "Before/5-7 day" point (Figure 6).

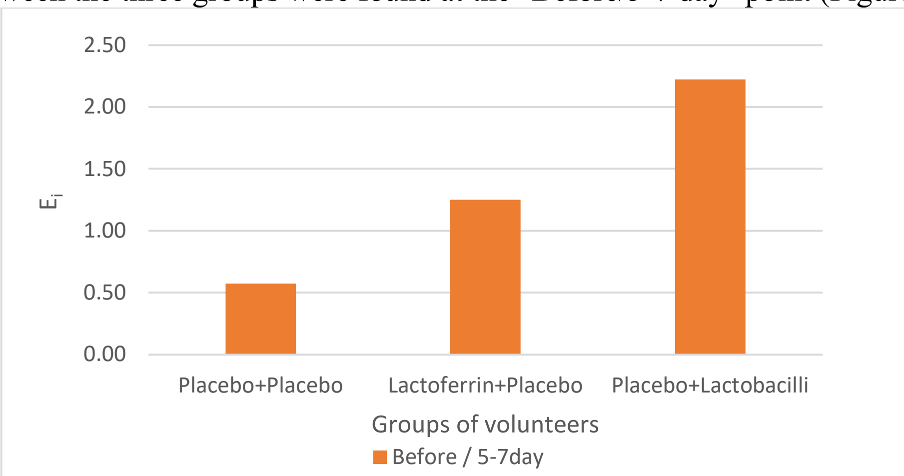


Figure 6. Eubiotic index for volunteers of three groups with different drugs combination for the "Before/5-7 day" point.

As can be seen in Figure 6, the lowest eubiotic index was noted in the “Placebo + Placebo” group, while the highest was in the “Placebo + Lactobacilli” group, i.e. in this group, the number of positive changes in the microflora was greater than the negative ones. Also, it should be noted that the eubiotic index in “Lactoferrin + Placebo” group is higher than one, that is, despite the fact ut is not the highest, nevertheless, positive changes in the microbiota prevail over negative ones, i.e. oral intake of lactoferrin has a slight stabilizing effect on the vaginal microflora.

3.3. The results of the analysis of the cervical canal microbiota "before", "after", "after + 30 days" in four groups of volunteers

The analysis using Friedman's criterion revealed significant differences in obligate anaerobic OPM in the microflora of the cervical canal in the “Placebo + Placebo” group (Figure 7).

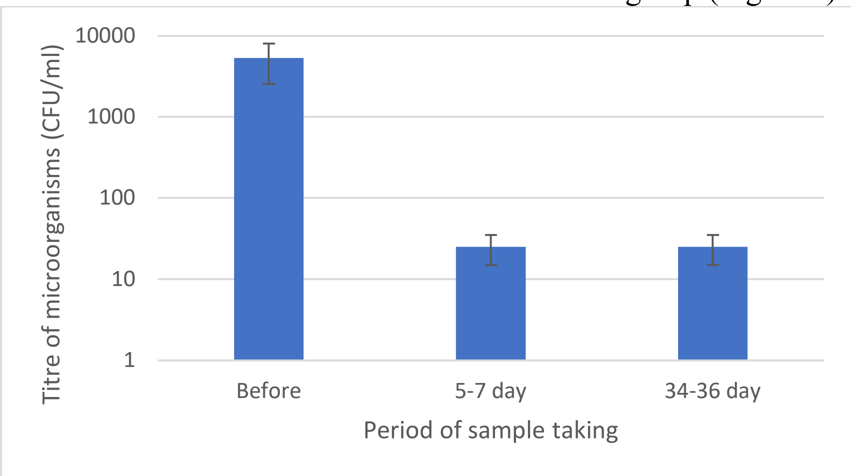


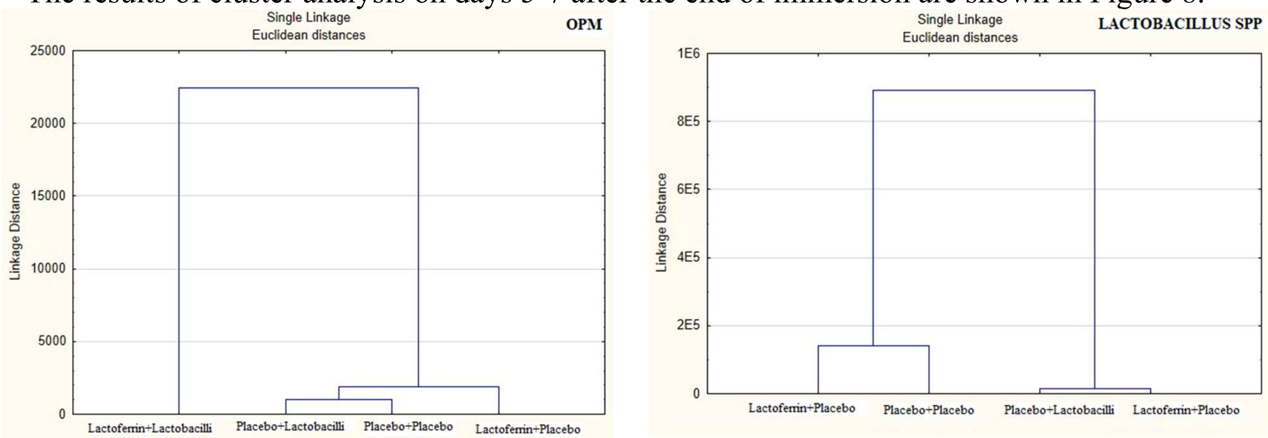
Figure 7. The number of obligate anaerobic OPM in the "Placebo + Placebo" group of volunteers

As can be seen from the figure, the number of obligate anaerobes decreased after the end of immersion and remained consistently low even on days 34–36 after the end of the experiment. These data fit with those obtained in a 3-day dry immersion, where a decrease in the anaerobic conditionally pathogenic component of the microbiota of the vagina and cervical canal was also observed.

In other groups, no significant differences in facultative anaerobic and obligate anaerobic OPM, as well as in lactobacilli, were found.

3.4. The results of comparison of the cervical canal microbiota of the volunteers in the placebo group and groups with different combinations of pre- and probiotic preparations in different periods of the experiment

The results of cluster analysis on days 5-7 after the end of immersion are shown in Figure 8.

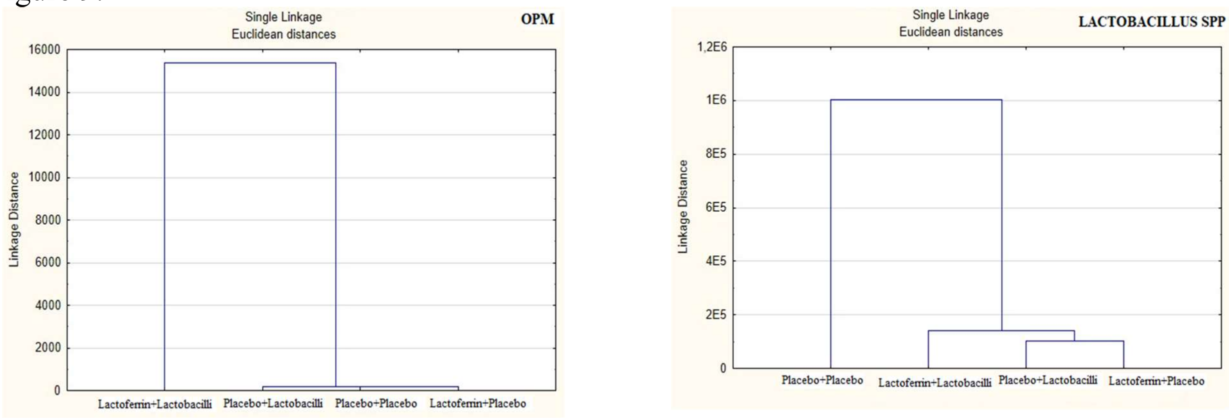


A) B)

Figure 8. Results of cluster analysis for OPM (A) and *Lactobacillus spp.* (B) for all four groups of volunteers with different drugs combination on 5-7 day after the end of the experiment

As can be seen in the figure, for opportunistic microorganisms, the cluster “Placebo + Placebo” and “Lactoferrin + Placebo” is formed and “Placebo + Lactobacilli” group is close to this cluster. The group “Lactoferrin + Lactobacilli” is the furthest.

The results of cluster analysis on days 34-36 after the end of the experiment are shown in Figure 9.



A) B)

Figure 9. Results of cluster analysis for OPM (A) and *Lactobacillus spp*. (B) for all four groups of volunteers drugs combination on days 34-36 after the end of the experiment

It can be seen that using opportunistic component of microflora for grouping “Lactoferrin + Lactobacilli” group is the most distant from the other three groups. For lactobacilli, clusters are formed, first of all, by “Placebo + Lactobacilli” and “Lactoferrin + Placebo” groups, then, quite close to them, is a “Lactoferrin + Lactobacilli” group, and the most distant group is “Placebo + Placebo”.

According to the results of comparison of all groups immediately after the end of immersion, no significant differences were found, however, on days 34-36 after the end of the experiment, according to the Kruskal-Wallis criterion, significant differences were noted both in OPM and in lactobacilli (Figure 10).

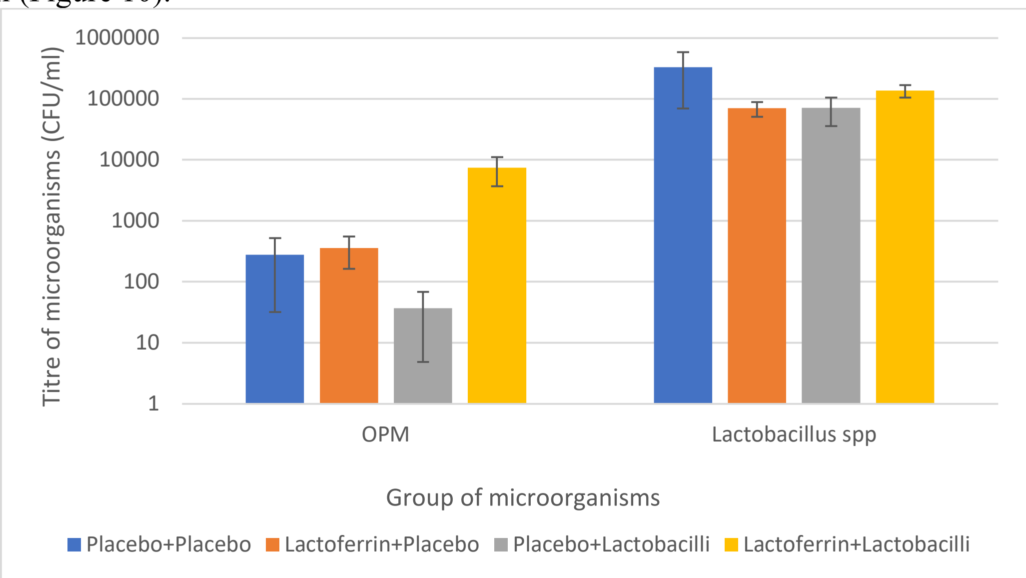


Figure 10. Number of OPM and Lactobacillus spp. in the placebo group and groups of volunteers with different combinations of probiotic preparations in participants of the 5-day "dry" immersion on days 34-36 after the end of immersion

Amounts of lactobacilli in all four groups look quite close to each other, while significant differences were noted between groups “Placebo + Placebo” and “Lactoferrin + Placebo”. In “Placebo + Placebo” group, the number of lactobacilli is slightly higher than in “Lactoferrin + Placebo” group. These data fit with the data of cluster analysis, in which these two groups are the most distant from each other. The highest number of amount of OPM was noted in the “Lactoferrin + Lactobacilli” group, and the lowest - in the “Placebo + Lactobacilli” group, thus, the local probiotic preparation created the most optimal conditions for maintaining the normobiota: a low amount of OPM with a consistently high number of lactobacilli. This is also reflected in the results of the cluster analysis presented above, where the group “Lactoferrin + Lactobacilli” was the most distant from all other groups.

The eubiotic index for cervical canal is showed in Figure 11. Significant differences were found between the “Placebo + Placebo” and “Lactoferrin + Placebo” groups. Significance of the results were proved by a nonparametric chi-square test.

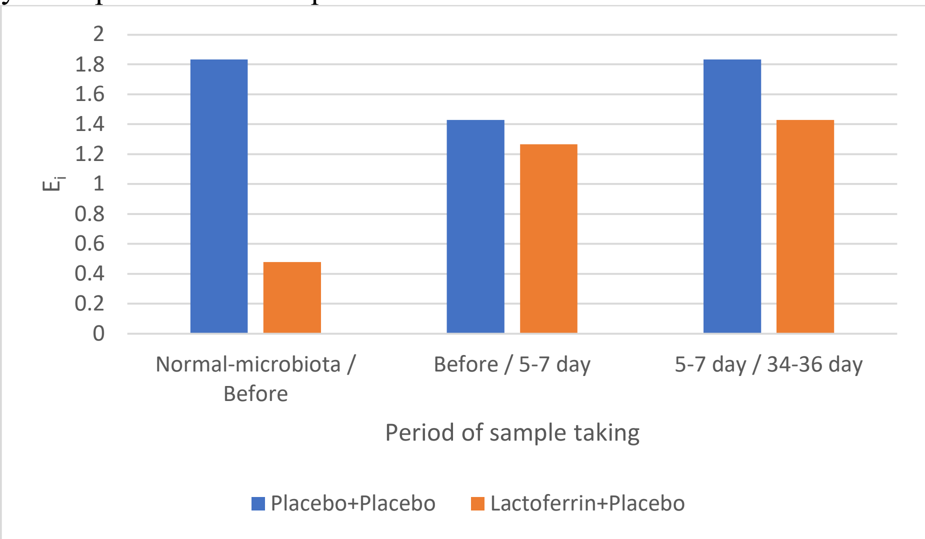


Figure 11. Eubiotic index (E_i) calculated for the "Placebo+Placebo" and "Lactoferrin+Placebo" groups

As can be seen in the figure 11, in the “Placebo + Placebo” group, the state of the microflora was initially close to the normobiota: a large number of lactobacilli was combined with a low amount of OPM. In the “Lactoferrin + Placebo” group, the eubiotic index was initially below 1, while in the “Placebo + Placebo” group E_i was almost three times higher. At the same time, after the end of the immersion, the state of the microflora of the “Placebo + Placebo” group worsened, and the state of the “Lactoferrin + Placebo” group improved - E_i became higher, i.e. the number of positive changes in the microflora was higher than the number of negative ones. By the 30th day after the end of the immersion, the index in the “Lactoferrin + Placebo” group continued to grow, significantly exceeding the initial value, while in the “Placebo + Placebo” group, the index returned to its original value. This indicates a positive effect of long-term use of lactoferrin on the microflora of the cervical canal.

4. CONCLUSION

1. Immersion has negative impact on the vaginal microflora: the number of facultative anaerobic OPM increases, but the number of protective lactobacilli decreases.
2. Oral use of lactoferrin during immersion has slight stabilizing effect on the vaginal microflora: despite the fact that the amount of obligate anaerobic OPM on days 5-7 after the end of immersion slightly increases, the number of facultative anaerobic OPM was stably low.
3. It was found that the amount of obligate anaerobic OPM was decreasing at the time of 30-day taking of lactoferrin. Another positive effect of lactoferrin was that small amount of facultative anaerobic OPM and high amount of most species of lactobacilli was observed.

4. According to the results of the cluster analysis of data on the vaginal microflora, as well as the Kruskal-Wallis analysis for the cervical canal, local use of the probiotic capsules had the greatest effect on lactobacilli in both biotopes.
5. When evaluating the general state of the vaginal microflora using the eubiotic index, its highest value was noted in the “Placebo + Lactobacilli” group, which confirms the effectiveness of intravaginal capsules against dysbiosis that is often observed in dry immersion.
6. The results of comparison of cervical canal microflora showed significant differences between the “Placebo + Placebo” and “Lactoferrin + Placebo” groups. At the same time, despite the fact that in the “Placebo + Placebo” group the microbiota was more balanced at the beginning of the experiment (the eubiotic index was higher than in the “Lactoferrin + Placebo” group), the eubiotic index in “Lactoferrin + Placebo” goup was increasing, starting from the background period, and did not have a sharp decline on the 5-7 days after immersion as in the “Placebo + Placebo” group.
7. Summarizing obtained results, we can conclude that long-term use of lactoferrin has positive effect on the vaginal microflora, while the fastest and most effective countermeasure are probiotic vaginal capsules. The combination of lactoferrin and a local probiotic drug did not significantly increase their effectiveness.
8. The most promising, probably, is the use of probiotic capsules based on autologous strains of vaginal lactobacilli, as well as the addition of lactoferrin to these capsules, because effectiveness of lactoferrin when applied locally has been established in previous studies in gynecological patients [25]. This is currently the subject of further study.

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