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# Dependence of the dynamics of changes in the quality of life of patients with bacterial vaginosis on local levels of TNF- $\alpha$ and IL-1 $\beta$

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**Abstract.** *Background and aim:* Bacterial vaginosis is among serious health problem for women of reproductive age commonly associated with aberrant changes in the vaginal microbiome that influences on their local changes in inflammatory mediators and quality of life. The aim was to assess the dependence of the dynamics of changes in the quality of life of patients with bacterial vaginosis on local levels of TNF- $\alpha$  and IL-1 $\beta$ . *Methods:* In the prospective study 37 women aged 19-40 years with bacterial vaginosis were treated according to the Centres for Disease Control and Prevention. Patients received vaginal suppositories of clindamycin phosphate (100 mg) once daily for 3 days before bedtime. TNF- $\alpha$ , IL-1 $\beta$  levels in vaginal secretions by means of ELISA test), as well as the quality of life according to the RAND 36-Item Health Survey 1.0 were studied as in control group (once - to determine the reference values) and in the dynamics (the 1st day - before treatment, on the 7th day - after treatment) in the main group. *Results:* After the treatment microscopy of smears-imprints of vaginal secretions showed the complete absence of pathological microflora. The treatment was well tolerated by all patients. In the result there was proved the role of bacterial vaginosis in a violation of the quality of life of patients mainly due to the mental component of health, even after clinical and laboratory recovery. *Conclusions:* There was proved the relation of vaginal TNF- $\alpha$  and IL-1 $\beta$  with physical and mental health in patients with bacterial vaginosis which can have a prognostic significance of the disease. ([www.actabiomedica.it](http://www.actabiomedica.it))

**Key words:** bacterial vaginosis, inflammatory mediators, TNF- $\alpha$ , IL-1 $\beta$ , quality of life.

## Introduction

Bacterial vaginosis or vaginal dysbiosis is one of the most common pathological conditions associated with aberrant changes in the vaginal microbiome (1).

The prevalence of this pathology varies both internationally and within countries and ranges from 20 to 60%.

The incidence among non-pregnant women is 15-35.5%, and among pregnant women, it reaches 38% (2, 3).

Bacterial vaginosis is characterized by a decrease in the level of resident lactic acid produced by *Lactobacillus spp.* and subsequent overgrowth of anaerobic bacteria such as *Gardnerella vaginalis*, *Megasphaera spp.*, *Atopobium vaginae* (4-7).

Risk factors for the development of bacterial vaginosis include previously transmitted inflammatory diseases of the genital organs, long-term and uncontrolled intake of antibacterial drugs, the presence of various menstrual disorders, the presence of background processes of the cervix, long-term use of IUDs for contraception, use of oral contraceptives (8).

This pathology is a serious health problem for women of reproductive age, their children and partners, as bacterial vaginosis is associated with adverse effects on reproductive health, such as pelvic inflammatory disease, miscarriage, premature birth, and can lead to increased risk of human immunodeficiency virus infection (9,10,11,12).

Successful treatment of bacterial vaginosis depends on the correct and timely diagnosis and pathogenically sound therapy. The purpose of the treatment of bacterial vaginosis is to restore the normal microbiota of the vagina and delay the growth of microorganisms that are not characteristic of this microbiocenosis.

Inflammatory mediators are among the first to respond to the local infectious inflammatory process (13). As demonstrated in a study by Hedges S.R. and co-authors (14) change in the qualitative and quantitative composition of the vaginal microbiota leads to more pronounced changes in the levels of inflammatory mediators (TNF- $\alpha$ , IL-1 $\beta$ , IL-6, IL-8) in vaginal washes than in serum. Given this, the dynamics of changes in local levels of inflammatory mediators can serve as diagnostic and prognostic criteria for the development of an infectious process in the vagina, in particular, bacterial vaginosis.

Bacterial vaginosis with its specific clinical manifestations, of course, has a negative impact on the quality of life of women. Therefore, assessing changes in the quality of life in women with bacterial vaginosis, as well as their relationship to local changes in inflammatory mediators such as TNF- $\alpha$  and IL-1 $\beta$ , can help improve the quality of care provided to this group of patients.

*The aim of the study* – to assess the dependence of the dynamics of changes in the quality of life of patients with bacterial vaginosis on local levels of TNF- $\alpha$  and IL-1 $\beta$ .

## Materials and methods

The study included 37 women aged 19 to 40 years ( $29.3 \pm 6.5$  years) with a confirmed diagnosis

of bacterial vaginosis, who formed the experimental group. To determine the reference values of the studied indicators, a control group of 37 relatively healthy women aged 19 to 39 years ( $28.5 \pm 6.8$ ) was formed.

Criteria for inclusion in the study were:

1. Confirmed diagnosis of bacterial vaginosis;
2. Type of vaginal microbiota III in Gram staining with mandatory identification in a smear of *Gardnerella vaginalis*;
3. Age from 18 to 40 years;
4. Absence of pregnancy at the time of inclusion in the study;
5. Absence at the time of inclusion in the study of emergencies and/or exacerbation of chronic diseases.
6. More than 1 month has passed since the last use of systemic or local forms of antibacterial drugs.

The exclusion criteria were:

1. Refusal of treatment;
2. Spontaneous termination of treatment;
3. Development of a severe allergic reaction to clindamycin phosphate;
4. Development of vaginal candidiasis after taking clindamycin phosphate;
5. Emergence of urgent conditions and/or exacerbation of chronic diseases after inclusion in the study.
6. Patients who received systemic or local antibiotic management of the infectious process of any localization before the study.

The diagnosis of bacterial vaginosis was confirmed in the presence of at least 3 of the 4 Amsel criteria:

1. Homogeneous gray-white vaginal discharge;
2. pH of vaginal secretions  $> 4.5$ ;
3. "Fish" smell (direct secretions or with the addition of 10% potassium hydroxide);
4. The presence of "key" cells in the microscopy of the native smear drug.

All patients were treated according to the Centres for Disease Control and Prevention (15) in the form of vaginal suppositories of clindamycin phosphate (100mg)

once daily for 3 days before bedtime. Clindamycin phosphate suppositories were freely purchased by patients at the pharmacy and were presented mainly with the original drug Dalacin® (Pfizer Inc., USA) and generic Milagin (SPERCO, Ukraine).

According to the purpose and objectives of the study, the levels of TNF- $\alpha$  and IL-1 $\beta$  in vaginal secretions, as well as the quality of life according to the RAND 36-Item Health Survey 1.0 were studied. In the control group, the study was performed once to determine the reference values of the studied indicators. In the experimental group, the studied parameters were determined in the dynamics - on the 1<sup>st</sup> day of the study (before treatment) and on the 7<sup>th</sup> day after treatment (10 days of the study).

In the initial examination, smears of vaginal discharge were stained by Gram to determine the type of vaginal microbiota according to the Ison-Hay classification. According to this classification, there are 5 types of vaginal microbiota:

1. Type 0 - epithelial cells, bacteria absent (indicates a recent course of antibiotic therapy);
2. Type I (normal) - normal vaginal microbiota, dominated by the morphotype *Lactobacilli*;
3. Type II (intermediate state) - mixed bacterial microbiota in which *Lactobacilli* are present together with the morphotype *Gardnerella vaginalis* and/or *Mobiluncus*;
4. Type III (bacterial vaginosis) - dominated by the morphotype of *Gardnerella vaginalis* and/or *Mobiluncus*; small amount or complete absence of *Lactobacilli*;
5. Type IV - dominated by gram-positive *Cocci*, and *Lactobacilli* were not detected.

In addition, vaginal secretions were collected in sterile 2 ml phosphate-buffered saline (PBS) tubes with a pH of 7.2 and stored at -70° C until laboratory tests.

TNF- $\alpha$  and IL-1 $\beta$  levels in vaginal discharge were examined by enzyme-linked immunosorbent assay using the Human TNF- $\alpha$  ELISA kit and the Human IL-1 $\beta$  ELISA Kit (CUSABIO, China).

Quality of life was studied using the RAND 36-Item Health Survey 1.0 with the definition of key integrative indicators, such as: physical functioning

(PF); role functioning, which is due to a physical condition (RP); pain intensity (BP); general health (GH); vital activity (VT); social functioning (SF); role functioning, which is due to emotional state (RE); mental health (MH). In addition, these indicators were grouped into two large groups and the Combined Physical Health Indicator (PCS) and the Combined Mental Health Indicator (MCS) were calculated.

The obtained data were processed using the statistical software package SPSS 20.0 for Windows. The significance of differences in TNF- $\alpha$  and IL-1 $\beta$  was determined by the Student test. The relationship between the scores was assessed using the Spearman correlation coefficient. When comparing the quality of life between the control and experimental groups, the Wilcoxon T-test was used. The Mann-Whitney U-test was used to assess the dynamics of changes in quality of life in the experimental group.

## Results

The treatment was well tolerated by all patients. One patient had itching at the site of suppository administration, which did not significantly affect her general, well-being, did not cause significant discomfort, and passed 1 day after the end of treatment. In 3 patients, as a side effect of topical clindamycin phosphate, vaginal candidiasis developed, due to which these women were excluded from the study, and the results of their survey and laboratory diagnosis were not taken into account.

After the treatment, repeated microscopy of smears-imprints of vaginal secretions showed the complete absence of pathological microbiota.

Local levels of TNF- $\alpha$  and IL-1 $\beta$  in patients of our study were presented in table 1.

On the 1<sup>st</sup> day of the study a high and statistically significant ( $p < 0.001$ ) increase of TNF- $\alpha$  and IL-1 $\beta$  levels in vaginal secretions, were observed relative to similar indicators of the control group. Thus, TNF- $\alpha$  was 5.1, and IL-1 $\beta$  - 5.9 times higher than in relatively healthy women.

On the 10<sup>th</sup> day of the study, all women in the experimental group showed a significant decrease in the levels of the studied indicators, and both indicators slightly exceeded the corresponding values of the

control group and did not differ statistically significantly from them ( $p > 0.05$ ). At the same time, statistical differences from the indicators of the experimental group on day 1 of the study were significant ( $p < 0.001$ ).

Regarding the correlations between the levels of TNF- $\alpha$  and IL-1 $\beta$ , a strong positive relationship ( $r_s = 0.95$ ;  $p < 0.001$ ) was proved between them.

Indicators of quality of life in patients of our study were presented in table 2.

In the statistical analysis of the main integrative indicators of quality of life, all indicators of physical health had similar dynamics.

Thus, the initial values of these indicators in the experimental group were statistically significantly lower than similar indicators in the control group. On the 10<sup>th</sup>

day of the study, all women in the study group showed a significant increase in the studied physical health indicators with the achievement of normal values. The indicators did not differ statistically significantly from the control group ( $p > 0.05$ ). At the same time, statistical differences from the indicators of the experimental group on the 1<sup>st</sup> day of the study were significant.

Similar to the previous set of indicators, all mental health indicators had similar dynamics.

Thus, the values of these indicators for the 1<sup>st</sup> day of the study in the experimental group were statistically significantly lower than similar indicators in the control group. On day 10 of the study, all women in the study group showed a significant increase in the studied mental health indicators relative to the initial

**Table 1.** Local levels of TNF- $\alpha$  and IL-1 $\beta$  in the studied contingent

Indicator	Control group	Experimental group	
		1 day	10 day
TNF- $\alpha$ , pg/ml	21,0 $\pm$ 6,3 <sup>*E1</sup>	107,2 $\pm$ 17,4 <sup>*C,E10</sup>	23,8 $\pm$ 6,3 <sup>*E1</sup>
IL-1 $\beta$ , pg/ml	147,4 $\pm$ 15,0 <sup>*E1</sup>	865,4 $\pm$ 126,8 <sup>*C,E10</sup>	154,4 $\pm$ 15,3 <sup>*E1</sup>

**Note.** \* – differences between groups are significant ( $p < 0.001$ ).

C – control group; E1 – experimental group, 1 day; E10 – experimental group, 10 day.

**Table 2.** Indicators of quality of life in the studied contingent

Indicator	Control group	Experimental group	
		1 day	10 day
Physical functioning (PF)	89,86 $\pm$ 4,93 <sup>#E1</sup>	85,14 $\pm$ 7,12 <sup>*C, #E10</sup>	88,51 $\pm$ 5,64 <sup>#E1</sup>
Role functioning, which is due to a physical condition (RP)	83,78 $\pm$ 15,83 <sup>*E1</sup>	63,51 $\pm$ 22,51 <sup>*C, #E10</sup>	81,08 $\pm$ 18,07 <sup>#E1</sup>
Pain intensity (BP)	87,43 $\pm$ 8,73 <sup>*E1</sup>	76,96 $\pm$ 8,64 <sup>*C, #E10</sup>	87,03 $\pm$ 8,86 <sup>#E1</sup>
General health (GH)	70,27 $\pm$ 7,63 <sup>*E1</sup>	52,43 $\pm$ 6,52 <sup>*C, #E10</sup>	68,65 $\pm$ 7,61 <sup>#E1</sup>
Vital activity (VT)	63,24 $\pm$ 6,99 <sup>*E1, <math>\Delta</math>E10</sup>	55,14 $\pm$ 4,33 <sup>*C, #E10</sup>	59,46 $\pm$ 5,50 <sup>#E1, <math>\Delta</math>C</sup>
Social functioning (SF)	81,42 $\pm$ 12,37 <sup>*E1, <math>\Delta</math>E10</sup>	67,23 $\pm$ 14,24 <sup>*C, #E10</sup>	72,97 $\pm$ 15,17 <sup>#E1, <math>\Delta</math>C</sup>
Role functioning, which is due to the emotional state (RE)	68,47 $\pm$ 28,27 <sup>#E1, <math>\Delta</math>E10</sup>	48,65 $\pm$ 30,02 <sup>#C, #E10</sup>	53,15 $\pm$ 28,82 <sup>#E1, <math>\Delta</math>C</sup>
Mental health (MH)	68,76 $\pm$ 6,92 <sup>*E1, #E10</sup>	57,62 $\pm$ 5,45 <sup>*C, #E10</sup>	63,35 $\pm$ 6,36 <sup>#E1, #C</sup>
Combined physical health indicator (PCS)	83,81 $\pm$ 4,89 <sup>*E1</sup>	72,45 $\pm$ 6,24 <sup>*C, #E10</sup>	82,23 $\pm$ 5,42 <sup>#E1</sup>
Combined mental health indicator (MCS)	68,93 $\pm$ 6,86 <sup>*E1</sup>	56,36 $\pm$ 6,65 <sup>*C, #E10</sup>	61,43 $\pm$ 7,07 <sup>#E1</sup>

**Note.**  $\Delta$  – Differences between groups are significant ( $p < 0,05$ ).

# – differences between groups are significant ( $p < 0,01$ ).

\* – differences between groups are significant ( $p < 0,001$ ).

C – Control group; E1 – experimental group, 1 day; E10 – experimental group, 10 day.

values. Although there was an increase in the values of the studied indicators, but on the 10th day of the study, they were statistically significantly different from the indicators of the control group.

Correlation analysis showed a weak positive relationship ( $r_s = 0.28$ ;  $p < 0.01$ ) between both combined physical and mental health indicators.

Correlations between the levels of inflammatory mediators studied and both combined physical and mental health indicators were presented in Table 3.

As can be seen from Table 3, in all cases, the correlation analysis showed a moderate negative relationship between the studied indicators. However, it should be noted that the levels of the two inflammatory mediators studied were somewhat stronger with physical health than with mental health.

## Discussion

The absence of pathological microbiota during repeated microscopy of vaginal smears showed the adequacy of the selected antibacterial therapy, complete elimination of the cause of the disease, and recovery of patients.

As mediators of inflammation, TNF- $\alpha$  and IL-1 $\beta$  are among the first to respond to the presence of a local infectious inflammatory process (13).

In our study, there was demonstrated that local levels of TNF- $\alpha$  and IL-1 $\beta$  increased significantly in the presence of an infectious process, and normalized within 7 days after treatment.

Similar dynamics of changes in the levels of inflammatory mediators in vaginal secretions in various gynaecological pathologies, in particular, in bacterial

vaginosis, have been repeatedly demonstrated in the scientific literature (1, 14, 16, 17).

It should be noted that the synchronicity of the rise and fall of the levels of the studied indicators were demonstrated. A strong positive association between TNF- $\alpha$  and IL-1 $\beta$  levels was statistically demonstrated.

As shown by our results, the physical health of patients, although reduced in the presence of bacterial vaginosis, but after treatment quickly returned to normal. There was a strong positive association between the data and the levels of inflammatory mediators in vaginal discharge. This is because the disappearance of the infectious agent and the inflammatory process associated with its influence eliminated all the physical manifestations of the disease and improved the quality of life of patients.

Mental and physical health decreased synchronously in the presence of bacterial vaginosis, but did not return to normal at the same time after treatment. Thus, against the background of complete recovery of physical health and laboratory data, there was a delay in the normalization of mental health. Correlation analysis also showed a weak relationship between physical and mental health. In addition, the relationship between the levels of the two inflammatory mediators studied and the combined physical health score was slightly higher than the combined mental health score.

The lack of synchronicity between the normalization of mental and physical health and laboratory data indicates that bacterial vaginosis causes some psychological discomfort in women who have suffered from this pathology.

In conversations with women after their recovery, it was found that 31 (91.18%) of 34 women in the study contingent were worried about the possible reaction of others to the manifestations of bacterial vaginosis (their own vaginal discharge, as well as their unpleasant "fish" odour). Although objectively there was a complete regression of symptoms. The fact that people around them could smell or see spots from vaginal discharge, as reported by patients, worsened mood and caused insecurity and actions, which was not the case before the disease. Such thoughts arose in women with varying frequency throughout the day, especially during active social interaction.

**Table 3.** Correlations between the levels of inflammatory mediators studied and the combined indicators of physical and mental health

Mediators of inflammation	Combined physical health indicator (PCS)	Combined mental health indicator (MCS)
TNF- $\alpha$	$r_s = -0,44$ ; $p < 0,001$	$r_s = -0,55$ ; $p < 0,001$
IL-1 $\beta$	$r_s = -0,43$ ; $p < 0,001$	$r_s = -0,55$ ; $p < 0,001$

Taking into account the results of our study, in which there was found a tendency of the psychological discomfort development in women who had undergone bacterial vaginosis. In our opinion, to obtain much more reliable conclusions, it is necessary to continue to study this problem in more depth in much larger trials with numerous respondents with the additional use of specific psychological tests for complex analysis of their status. In addition, a serial comprehensive study of the psychological status of this contingent of women with the same problem should be carried out to assess the long-term results of the disease and the dynamics of changes in the studied indicators over time.

## Conclusions

1. Bacterial vaginosis, with its ease of diagnosis and treatment, is a serious social problem that causes a violation of the quality of life of patients mainly due to the mental component of health, even after complete recovery, confirmed by clinical and laboratory.
2. Levels of TNF- $\alpha$  and IL-1 $\beta$  in vaginal secretions are moderately negatively related to both physical and mental health of patients with bacterial vaginosis and can serve as diagnostic and prognostic markers of the disease.

**Conflict of Interest:** Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

**Informed consent:** Written informed consent was obtained from the patient for publication of this article.

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