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Effectiveness of combined use of streptokinase and streptodornase in the treatment of exacerbations of chronic salpingo-oophoritis in women of reproductive age

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Abstract

Background: Inflammatory diseases of the pelvic organs today remain an urgent problem because of the persistent chronic course with frequent relapses, blurred clinical picture, presence of pain syndrome and subacute forms against the background of altered immunological reactivity, and resistance to therapy.

The aim of the study was an optimization of approaches to the treatment of chronic salpingo-oophoritis in women of reproductive age on the basis of the study of certain links of pathogenesis by using a complex preparation containing streptokinase and streptodornase and evaluation of its effectiveness.

Methods: 161 women were examined, including 105 healthy women and 56 women with chronic salpingo-oophoritis in the exacerbation stage, who were divided into 2 groups: comparison group – 21 patients who received standard treatment for 14 days, and study group – 35 patients who, in addition to standard therapy, used the combined preparation with streptokinase and streptodornase for 3 weeks. Levels of C-reactive protein and ferritin in blood serum were determined; functioning of the lipid peroxidation–antioxidant protection (LPO–AOD) system, state of endogenous intoxication, concentration of pro- and anti-inflammatory cytokines, vaginal microbiocenosis, and quality of life were assessed.

Results: In patients with exacerbation of chronic salpingo-oophoritis, hemogram disorders, decreased ferritin content, activation of lipid peroxidation, increased level of endotoxemia, predominance of pro-inflammatory cytokines, changes in the vaginal microbiome against the background of suppression of secretory immunoglobulin A, and deterioration of quality of life were revealed. The use of the combined preparation containing streptokinase and streptodornase in the therapy of patients with exacerbation of chronic salpingo-oophoritis made it possible to reduce the frequency of relapses by 3.5 times compared with standard treatment, to normalize hemogram indices, LPO–AOD indices, endotoxemia, cytokine concentration, vaginal microbiocenosis, and to improve the patients' quality of life.

Conclusion: The use in complex therapy of patients with exacerbation of chronic salpingo-oophoritis of the combined preparation containing streptokinase and streptodornase leads to improvement of the clinical picture and recovery in 92% of cases, normalization of the LPO–AOD system, endotoxemia indices, cytokine ratio, microbiocenosis and local vaginal immunity, as a result of which the quality of life improves.

Keywords: chronic salpingo-oophoritis, microbiocenosis, endotoxemia, LPO–AOD system, women, quality of life, combined preparation containing streptokinase and streptodornase

Introduction

Today, one of the most urgent problems in gynecological practice is inflammatory diseases of the pelvic organs (PID) in women of reproductive age [6, 16]. In recent years, according to the Ministry of Health of Ukraine, an increase in the frequency of PID to 60–80% in the structure of gynecological diseases has been observed. Among outpatients their frequency ranges from 60–65% and up to 30–40% among hospitalized patients. Chronic salpingo-oophoritis, along with endometritis, occurs most often, while the frequency of tubo-ovarian formations of inflammatory etiology has increased three times [3, 25, 41].

The relevance of PID is determined not only by the high prevalence among the female population, but also by the negative impact on menstrual, sexual, and reproductive functions [12, 30].

The basis for the development of the acute PID process is the infectious nature of inflammatory changes, which subsequently does not have a significant effect on the exacerbation of the inflammatory process [15, 34].

A significant role in the normal functioning of the reproductive system is played by vaginal microflora, which is individual and depends on many factors [22, 50]. At the same time, it is important to identify the clinical dependence of vaginal microbiome disorders and the frequency of occurrence of inflammatory diseases of the uterine appendages. The state of vaginal microbiota and the degree of its contamination allow, to a certain extent, to assess not only the effectiveness of the therapeutic measures performed, but also to determine the risk of possible relapse of salpingo-oophoritis [23, 44, 49].

Recently, certain features of PID have attracted attention, such as persistent chronic course with frequent relapses, blurred clinical picture, presence of pain syndrome, subacute forms against the background of altered immunological reactivity, localization of the inflammatory

process in the uterine appendages, and resistance to therapy [4, 38, 39].

Prolonged inflammation is accompanied by the development of pronounced sclerotic and dystrophic changes in the uterine appendages, morphological and functional disorders with subsequent formation of an adhesive process [4, 33]. Histopathological changes are manifested by damage to the epithelial layer with vacuolization and destruction of cells in areas of concentration of intraepithelial lymphocytes with massive diffuse infiltration of the subepithelial tissue by monocytes, neutrophils, T-lymphocytes, and plasma cells.

The formation of the adhesive process and its further development are accompanied by a pain syndrome of varying intensity, significantly affecting the quality of life of patients. In addition to pronounced pain syndrome and infertility, the adhesive process affects the effectiveness of etiotropic treatment, preventing the penetration of antibacterial drugs to the foci of inflammation [36, 38, 40].

It is known that phagocytosis plays a key role in the development of the inflammatory reaction, since it stimulates the induction of antibodies, specific immunoglobulins, cytokines, and other biologically active substances. Anti-infectious protection is provided by interleukin-1 (IL-1), C-reactive protein (CRP), type 1 interferon, etc. [17, 31, 43]. The diagnostic significance of assessing the concentration of cytokines is based on their increase or decrease in patients, and for assessing the severity and predicting the course of the disease it is advisable to determine the concentration of both pro- and anti-inflammatory cytokines in the dynamics of the development of the pathology as a prognostic criterion of the infectious-inflammatory process [2, 37].

One of the main markers of the acute phase of inflammation is C-reactive protein (CRP) – a component of the nonspecific immune response, which manifests itself at the early stages of inflammation or exacerbation and is synthesized in the liver under the influence of pro-inflammatory cytokines. The important function of CRP is to promote the removal of endogenous substances formed as a result of cell destruction. CRP activates the complement cascade, interacts with fragments of immunoglobulins associated with lymphocytes, recognizes potentially toxic substances formed during the breakdown of the body's own cells, binds them, detoxifies and removes them from the blood [32, 46].

The development of endogenous intoxication in PID is an integrative process of generalization of the pathological process, in which many body systems participate: detoxification, excretion, immune protection, resistance, etc. [4]. In the process of proteolysis in damaged tissues, a large number of protein degradation products with molecular weight (medium molecules) accumulate, which are considered the most important inducer of endogenous intoxication. Endogenous intoxication is accompanied by pronounced catabolism, disturbance of the detoxification system, depression of the immune system due to the growing accumulation in the body of intermediate and final metabolism products [16]. Some of their components are involved in the development of secondary immunodeficiency and disturbance of lipid peroxidation and the antioxidant system (LPO–AOD).

Along with a high level of endotoxemia, macrocirculatory disorders and disturbances of anabolic processes in PID, quantitative and qualitative changes in the main links of the immune system are of decisive importance. However, these data have not yet found proper reflection in the development of new approaches to the therapy of PID. The above causes interest and prompts a thorough study of these issues through a comprehensive examination of patients at the modern biochemical level for further correction of the detected disorders.

Considering various aspects of PID, it should be noted that the literature insufficiently covers issues concerning the quality of life of patients of reproductive age. Late seeking of medical care by patients, untimely detection of pathology, duration of therapy, and recurrence confirm the relevance of the PID problem.

Untimely or inadequate treatment of PID leads to chronization of the process, as a result of which a significant number of complications arise against the background of this pathology and can cause infertility, ectopic pregnancy, chronic pelvic pain syndrome [3, 10].

Thus, taking into account the extreme prevalence and social significance of PID, the development of individualized methods of treatment of patients in this cohort, prevention of disease relapses and development of the adhesive process, and improvement of quality of life are extremely relevant and practically significant tasks of gynecology. Further study of the pathogenesis of the disease will contribute to increasing the effectiveness of therapy.

Today, various schemes for the therapy of PID in women exist [5, 7, 8].

Standard therapy of PID with antibiotics is associated with a high rate of cure within a week from the start of therapy; however, the percentage of relapses over time becomes greater and more frequent [1, 21, 24]. Frequent use of antibiotics and metronidazole contributes to the development of drug-resistant microorganisms [35, 48].

This indicates the need to search for alternative pathogenetically substantiated ways to solve this problem that are therapeutically effective in the exacerbation of chronic PID, make it possible to eliminate the clinical manifestations of the disease, prevent relapses and adhesion formation, and improve the quality of life of patients [45].

In this regard, our attention was drawn to the combined preparation containing the fibrinolytic streptokinase (SK) 15,000 IU and the proteolytic streptodornase (SD) – 1,250 IU in optimal proportions for proteolytic and fibrinolytic effect.

Streptokinase is an activator of the proenzyme plasminogen contained in human blood, which under the influence of streptokinase is converted into plasmin, which has the property of dissolving blood clots; streptodornase is an enzyme capable of dissolving accumulations of nucleoproteins, dead cells or pus without affecting living cells and their physiological functions.

Streptodornase is an endonuclease (deoxyribonuclease enzyme) that causes the destruction of DNA, nucleotides and nucleosides, which leads to the weakening of bonds of nucleoproteins of dead and coagulated cells, facilitates the resorption of damaged cells and oligoproteins, activates phagocytosis of dead cells, but at the same time does not affect the structure and function of living healthy cells. In the presence of streptokinase and streptodornase, the concentration of phagocytes significantly increases, their motility improves and the relative percentage of completed phagocytosis increases. Therefore, the use of suppositories

with a combination of SK–SD accelerates the lysis of leukocyte masses, improves blood circulation and microcirculation in the focus of inflammation, and also contributes to an increase in the concentration of antibacterial and other medicinal agents in it. Against this background, the elimination of infiltration, edema and other manifestations of inflammation is accelerated, the development of sclerotic processes is prevented, which in turn reduces pain sensations [11, 47].

SK+SD has an anti-inflammatory effect, improves microcirculation in the focus of inflammation, relieves edema, facilitates the access of antibiotics or chemotherapeutic agents to the focus of inflammation, has an antibiofilm effect, significantly increases the concentration of antibacterial, anti-inflammatory drugs and immune cells in the center of inflammation, accelerates the lysis of dead cells (pus) and their reabsorption (excretion, cleansing) from the source of inflammation, without affecting but preserving healthy tissue [Instructions for medical use of the medicinal product SK+SD [20, 26]].

The combined preparation with SK+SD is included in the treatment regimen from the first days of therapy to restore blood circulation, increase the concentration of antibiotics in the center of inflammation, enhance and accelerate the elimination of the inflammatory process and prevent the formation of the adhesive process. At the same time, pain syndrome and dysuric phenomena (frequent, painful urination, urges to urinate) are eliminated 2.5–3 times faster. When the combined preparation containing SK+SD is used in the treatment regimen, signs of inflammation according to ultrasound data are eliminated 9 times faster, the hospital stay is shortened by 5 days and the processes of reparations are accelerated 3 times [11, 18, 27].

It is very important that the use of the combined preparation containing SK+SD reduces the risk of disease relapse, development of infertility and adhesive disease by 70%, which makes it possible to increase the effectiveness of treatment to 96–98% [19, 20]. The combined preparation containing SK+SD is successfully used for the treatment of gynecological pathology, in proctology, in the postoperative period, as monotherapy for the treatment of aseptic inflammation and reduction of pain syndrome in the treatment of chronic pelvic pain and adhesive process [28].

The rectal form of application ensures a special speed and safety of use of the preparation containing SK+SD [27].

Thus, the combined preparation containing SK+SD affects all links of pathogenetic disorders in PID, in particular facilitates access and contributes to increasing the effectiveness of antibacterial drugs in PID, has proven anti-inflammatory and antibiofilm effects, prevents the development of the adhesive process, which determined our choice in favor of its use in the complex therapy of women of this cohort.

The aim of the study was an optimization of approaches to the treatment of chronic salpingo-oophoritis in women of reproductive age on the basis of the study of certain links of pathogenesis by using the complex preparation containing SK+SD and evaluation of its effectiveness.

Methods

161 women aged 18–42 years were examined, including 105 healthy women who applied for a preventive examination (control group) and 56 women with chronic salpingo-oophoritis in the exacerbation stage. The patients were divided into 2 groups: comparison group – 21 patients who received standard treatment for 14 days (ceftriaxone 1,000 mg once daily parenterally, doxycycline 100 mg twice daily orally and metronidazole twice daily orally for 14 days) and study group – 35 patients who, in addition to standard therapy, used the combined preparation with SK+SD rectally, 1 suppository 3 times daily for the first 3 days, 1 suppository 2 times daily for the next 3 days, and thereafter 1 suppository once daily for 3 weeks. Treatment was carried out under the control of biochemical and general clinical indices.

The study was approved by the local ethics commissions.

At the time of inclusion in the study, the study group and the comparison group did not differ, which allowed them to be combined during statistical processing and analysis.

All patients were examined using traditional methods, which included anamnestic, clinical-biochemical, ultrasound, microscopic, microbiological and psychological examination methods according to unified methodologies.

Dynamic control of the hemogram was carried out, levels of C-reactive protein and ferritin were determined. The functioning of the lipid peroxidation–antioxidant protection (LPO–AOD) system was judged by the amount of thiobarbituric acid (TBA)-reactive products, which were determined in the reaction with 2-thiobarbituric acid [42], and the total antioxidant activity (AOA) of blood plasma, which was determined by the method of E.B. Spektor *et al*. [29].

The state of endogenous intoxication of the body was determined by the level of medium molecules at a wavelength of 254 nm (MM1) and 280 nm (MM2) by the method of N.I. Gabrielyan, V.I. Lipatova [14].

In the dynamics of treatment, the concentration of pro- and anti-inflammatory cytokines (IL-1(β), IL-4, IL-8, IL-10, TNF-α, TGFβ) in blood serum was determined by the enzyme immunoassay method.

Quality of life was assessed using a standard questionnaire [9].

Examination of patients was carried out before treatment, after 1 and 3 months from the start of treatment. The obtained results were processed statistically using standard computer programs with the use of the paired Student's t-test with calculation of the arithmetic mean (M) and the standard error of the arithmetic mean (m) or the Wilcoxon signed-rank test depending on the normality of the distribution of differences. The normality of data distribution was checked using the Shapiro–Wilk test at a significance level of 0.01. When using all statistical methods, except for the Shapiro–Wilk test, the significance level was taken as 0.05 – the difference between the data was considered reliable at $p < 0.05$. For determining structural relationships, correlation analysis was used with determination of pairwise correlation coefficients – r.

Results and Discussion

Both groups of patients with exacerbation of chronic salpingo-oophoritis were representative in terms of age, somatic and gynecological history, as well as the clinical picture of the disease. The duration of the disease at the time of examination ranged from 6 months to several years.

23 (41%) patients were in a state of moderate severity. During vaginal examination, bilateral inflammatory lesions of the uterine appendages were more often observed, which was confirmed by ultrasound examination.

Analysis of clinical data showed that the patients had classic manifestations of exacerbation of chronic salpingo-oophoritis (Table 1). As can be seen from Table 1, before the start of treatment all patients (100%) complained of constant, acute or dull aching pains of unclear localization in the lower abdomen with irradiation to the lumbar region and rectum, increase in body temperature to 38–39°C, increased leukorrhea from the genital tract, pain during sexual intercourse, irritability, increased fatigue, sleep disturbances.

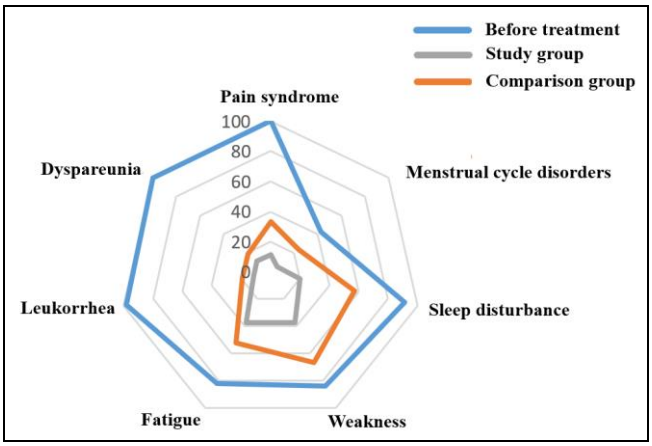

Fig 1: Dynamics of clinical manifestations after 1 month of therapy depending on the treatment method in patients with exacerbation of chronic salpingo-oophoritis

After 1 month from the start of treatment, positive changes in the course of the disease were noted in patients of both groups, but a certain number of clinical symptoms remained. At the same time, pathological symptoms in the study group occurred significantly less frequently than in the comparison group (Fig. 1). Thus, in patients who, in addition to standard therapy for exacerbation of chronic salpingo-oophoritis, received the combined preparation with SK+SD, unlike the group with standard treatment, premenstrual syndrome was noted 4.2 times less often, pain syndrome 2.9 times less often, weakness and dyspareunia 1.8 and 1.7 times less often, respectively.

An important indicator of the effectiveness of treatment of exacerbations of chronic salpingo-oophoritis is the percentage of disease relapses in patients of this cohort. During the observation after 3 months from the start of treatment, we obtained significant differences between the results in the observation groups regarding disease relapses (Fig. 2).

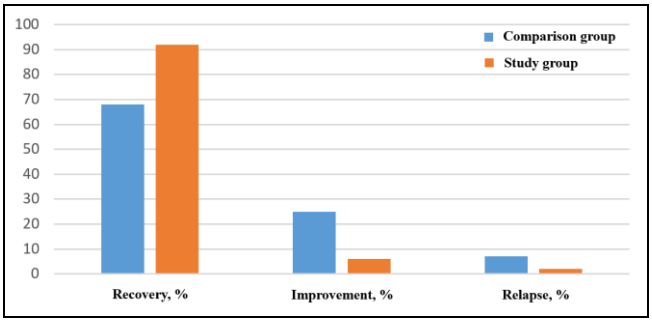

Fig 2: Clinical effectiveness after 3 months of therapy depending on the treatment method in patients with exacerbation of chronic salpingo-oophoritis

As can be seen from Fig. 2, women of the study group who used the combined preparation containing SK+SD in complex therapy recovered in most cases (92%), while in the comparison group with standard treatment this indicator was 1.4 times lower (68%). The frequency of disease relapses in the latter group was 3.5 times higher than in the group of patients who used the combined preparation with SK+SD in addition to standard therapy.

The obtained results confirm the effectiveness of the use in complex therapy of exacerbations of chronic salpingo-oophoritis of the preparation containing SK+SD.

The results of the study of the hemogram in patients with exacerbation of chronic salpingo-oophoritis deserve attention (Table 1).

Table 1: Dynamics of hemogram after 1 month of therapy depending on the treatment method in patients with exacerbation of chronic salpingo-oophoritis

Indicators, units of measurement	Healthy	Patients with exacerbation of chronic salpingo-oophoritis		
		before surgery	with standard treatment	with inclusion of SK+SD
Hemoglobin, g/L	134.2±1.9	120.3±2.3*	122.4±2.5*	130.0±2.4●▲
Erythrocytes, 1×10⁹/L	4.5±0.1	4.0±0.1*	4.3±0.06	4.5±0.11●
Leukocytes, 1×10⁹/L	6.4±0.4	9.9±0.5*	8.2±0.6*	6.8±0.6●
Band neutrophils, 1×10⁹/L	0.22±0.02	0.77±0.04*	0.51±0.05*●	0.25±0.04●▲
Segmented neutrophils, 1×10⁹/L	3.60±0.32	5.98±0.48*	4.85±0.43*	3.93±0.39●
Lymphocytes, % 1×10⁹/L	2.03±0.22	1.79±0.24	1.92±0.27	1.97±0.28
Monocytes, 1×10⁹/L	0.34±0.03	0.77±0.03*	0.50±0.04●	0.37±0.04●▲
Eosinophils, 1×10⁹/L	0.18±0.02	0.53±0.03*	0.40±0.04*●	0.22±0.03●▲
Basophils, 1×10⁹/L	0.026±0.005	0.050±0.004*	0.049±0.005*	0.034±0.006●
Neutrophils/lymphocytes	1.88±0.17	3.77±0.24*	2.79±0.21*●	2.12±0.19●▲
ESR, mm/h	8.4±1.0	19.3±1.6*	14.5±1.3*	9.7±1.0●▲
CRP, mg/L	2.5±0.2	19.4±1.3*	11.1±1.2*●	3.4±0.3●▲
Serum ferritin, μg/L	48.5±3.1	19.4±1.2*	27.3±3.2*●	39.7±2.5●▲

Notes: * – significant difference ($p<0.05$) compared with the control group; ● – significant difference ($p<0.05$) between groups before and after the corresponding treatment; ▲ – significant difference ($p<0.05$) between groups after treatment.

As can be seen from Table 1, in patients with exacerbation of chronic salpingo-oophoritis before treatment a significant decrease in the content of hemoglobin, CRP, ferritin and the number of erythrocytes was observed compared with healthy women, which indicated the presence of latent iron deficiency in women of this cohort. Probably, iron deficiency can negatively affect the course of chronic salpingo-oophoritis and contribute to the development of

exacerbation of the process. At the same time, significant changes in the leukocyte formula in the form of leukocytosis, shift of the leukocyte formula to the left, lymphopenia, and increase in ESR were noted compared with healthy women, which is characteristic of the inflammatory process.

The effect of therapy on hemogram indices was evaluated after 1 month; the analysis showed positive changes in both groups of patients. At the same time, with standard treatment, compared with the data before treatment, reliable normalization concerned not all hemogram and leukogram indices (Table 1). In the group of patients who, in addition to standard treatment, used the preparation containing SK+SD, significant differences were observed for most indices compared with both the data before treatment and the results obtained in the group after standard therapy. In patients of the study group, unlike the comparison group, a significant increase in the content of hemoglobin, CRP and ferritin, a significant decrease in band neutrophils, monocytes, eosinophils, neutrophils and ESR, approximation of these indices to the data of the control group were established, which confirms the effectiveness of including the preparation containing SK+SD in the standard therapy of inflammatory processes of the uterine appendages.

Clarification of the nature of pathogenetic changes and relationships between various systems of the woman's body in PID is important, since they are assigned a significant role both in providing protective-adaptive reactions under the action of extreme stimuli and in the implementation of adaptive-trophic processes in the tissues of organs that have undergone aggression. In this regard, during the study, to establish pathogenetic changes in patients with exacerbation of chronic salpingo-oophoritis, we determined the state of the LPO–AOD system, the results of which are presented in Table 2.

Table 2: Dynamics of the LPO–AOD system, endotoxemia indices after 1 month of therapy depending on the treatment method in patients with exacerbation of chronic salpingo-oophoritis

Indicators, units of measurement	Healthy	Patients with exacerbation of chronic salpingo-oophoritis		
		before surgery	with standard treatment	with inclusion of SK+SD
TBA-AP, nmol/l	5.34±0.15	6.57±0.12*	6.05±0.15*●	5.44±0.18●▲
Total AOA,%	46.9±0.79	51.3±0.54*	48.6±1.03	47.8±0.88●
AOD coefficient	8.71±0.39	7.8±0.16*	8.07±0.29	8.76±0.19●
MM level, 254 nm, cu	0.327±0.007	0.382±0.011*	0.357±0.010*	0.331±0.009●
MM level, 280 nm, cu	0.134±0.006	0.184±0.005*	0.163±0.006*●	0.141±0.007●▲

Notes: * – significant difference ($p<0.05$) compared with the control group; ● – significant difference ($p<0.05$) between groups before and after the corresponding treatment; ▲ – significant difference ($p<0.05$) between groups after treatment.

As can be seen from Table 2, in patients with exacerbation of chronic salpingo-oophoritis before the start of treatment a statistically significant increase in the amount of TBA-AP and total AOA was revealed compared with the values obtained in healthy women. As a consequence of this, a significant 10% decrease in the AOD coefficient compared with the control group was noted.

In patients who received standard therapy for exacerbation of chronic salpingo-oophoritis, after 1 month from the start of therapy the level of TBA-AP significantly decreased, total AOA slightly increased and, accordingly, the AOD coefficient increased by 3%. The most pronounced changes regarding the LPO–AOD system were observed in the group of patients who used the complex preparation containing SK+SD in addition to standard treatment. In this group, compared with the data before treatment, the content of TBA-AP, total AOD and, accordingly, the AOD coefficient increased by 12% significantly. Also in the study group, a significant decrease in the content of TBA-AP compared with the data of the group with standard treatment was obtained (Table 2).

Obviously, metabolic disorders in patients with exacerbation of chronic salpingo-oophoritis lead to an increase in the activity of endogenous intoxication processes, which is determined by the concentration of MM. As can be seen from Table 2, the concentration of MM in patients before treatment was significantly higher than in healthy women.

After standard therapy in patients there was a decrease in the level of endogenous intoxication compared with before treatment, but it remained significantly higher than in healthy women. A similar trend was observed in patients who additionally received the complex preparation with SK+SD. Also in this group, a statistically significant, compared with standard treatment, decrease in the level of MM 280 nm, and therefore a decrease in the level of endotoxemia, was established.

Thus, in patients with exacerbation of chronic salpingo-oophoritis activation of the LPO system, an increase in the amount of TBA-AP and some increase in total AOA are observed, but at the same time a decrease in the AOD coefficient is noted. The dynamics of changes in the LPO–AOD system in patients with exacerbation of chronic salpingo-oophoritis and the presence of a significant difference in indices compared with the control group indicate exhaustion of compensatory capabilities. This indicates that activation of LPO in women of this cohort can lead to changes in the metabolism of both individual cells and the body as a whole.

We obtained biochemical confirmations of the effectiveness of additional use, in addition to standard therapy, of the preparation containing SK+SD. In women after treatment with the use of the preparation with SK+SD, the LPO–AOD and MM indices approached the corresponding data in healthy women. A statistically significant difference was established between the level of TBA-AP and MM 280 nm in the comparison group and the study group. The better results obtained in the study group can probably be explained by the presence in the composition of the complex preparation of precisely SK+SD, which neutralize free radicals.

It is known that immunodeficiency in gynecological patients with PID has a complex pathogenesis, in the development of which, along with a high level of endotoxemia, macrocirculatory disorders and disturbances of anabolic processes, quantitative and qualitative changes in the main links of the immune system are of decisive importance. This

prompted us to study pro- and anti-inflammatory cytokines in the dynamics of treatment of patients with exacerbation of chronic salpingo-oophoritis, which take an active part in the immune response of the body and the inflammatory process, which is the pathogenetic mechanism of the development and course of inflammation (Fig. 3).

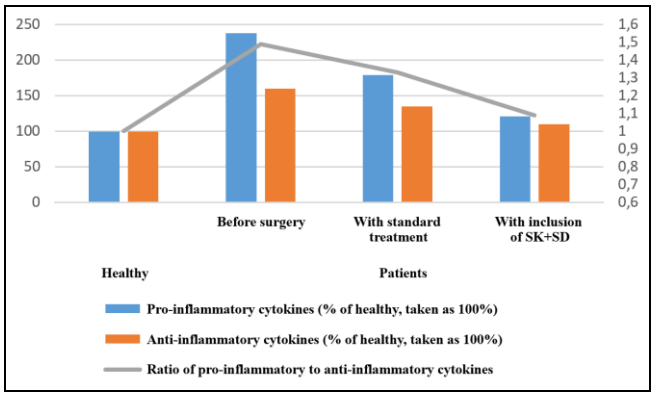

Fig 3: Dynamics of serum cytokines after 1 month of therapy depending on the treatment method in patients with exacerbation of chronic salpingo-oophoritis

As can be seen from Fig. 3, in patients with exacerbation of chronic salpingo-oophoritis before treatment a significant increase, compared with the group of healthy women, in the content of both pro-inflammatory (IL-1(β), IL-8, TNF-α) and anti-inflammatory cytokines (IL-4, IL-10, TGFβ) was established, and pro-inflammatory ones were 1.5 times more than anti-inflammatory ones, as indicated by their ratio. In patients after standard therapy, after 3 months from the start of treatment, the concentration of cytokines decreased, but remained elevated compared with the results obtained in healthy women (the ratio of pro- to anti-inflammatory cytokines decreased to 1.33). In women who used the complex preparation with SK+SD in addition to standard treatment, the concentration of cytokines was substantially normalized, since the levels of IL-1(β), IL-8, TNF-α and TGFβ had significant differences regarding the results in the comparison group, and the ratio of pro- to anti-inflammatory was 1.09. This indicates the positive effect of the preparation containing SK+SD on the level of cytokines, which reflect the immune response in women with exacerbation of chronic salpingo-oophoritis.

In this regard, interest was aroused by the state of the microbiocenosis of the vaginal biotope in patients with exacerbation of chronic salpingo-oophoritis. During the study, we determined the vaginal microbiome in healthy women and in patients depending on the therapy performed (Table 3).

Table 3: Vaginal microbiocenosis after 1 month of therapy depending on the treatment method in patients with exacerbation of chronic salpingo-oophoritis (lg CFU/mL)

Indicators, units of measurement	Healthy	Patients with exacerbation of chronic salpingo-oophoritis		
		before surgery	with standard treatment	with inclusion of SK+SD
Lactobacillus spp.	6.7±0.26	4.5±0.19*	5.5±0.28*●	6.4±0.17*●▲
Escherichia coli	2.9±0.18	4.4±0.22*	4.0±0.29*	3.1±0.21●▲
Proteus	2.4±0.24	3.3±0.26*	2.9±0.29	2.6±0.23●
Clostridium spp.	2.2±0.21	3.0±0.29*	2.8±0.28	2.5±0.26
Staphylococcus spp.	2.8±0.25	4.8±0.37*	4.2±0.32*	3.4±0.23●▲
Streptococcus spp.	2.2±0.19	3.5±0.34*	3.1±0.31*	2.5±0.23●
Corynebacterium spp.	2.3±0.21	3.0±0.21*	2.7±0.27	2.5±0.19
Yeast-like fungi of the genus Candida	2.5±0.26	3.7±0.33*	3.1±0.28	2.7±0.18●
Gardnerella vaginalis	2.4±0.23	4.2±0.31*	3.3±0.22*●	2.8±0.16●
Mobiluncus spp.	2.3±0.19	4.0±0.25*	3.1±0.23*●	2.6±0.19●
SIgA in mucous secretion, mg/L	57.9±2.6	43.5±2.8*	49.4±3.2	54.5±2.7●

Notes: * – significant difference ($p<0.05$) compared with the control group; ● – significant difference ($p<0.05$) between groups before and after the corresponding treatment; ▲ – significant difference ($p<0.05$) between groups after treatment.

As can be seen from Table 3, the microscopic picture of the mucous secretion of the vagina in healthy women was characterized by the predominance of *Lactobacillus spp.*, a small amount of *Escherichia coli*, *Proteus*, *Clostridium spp.*, *Staphylococcus spp.*, *Streptococcus spp.*, *Corynebacterium spp.*, yeast-like fungi of the genus *Candida*, *Gardnerella vaginalis*, *Mobiluncus spp.* Before treatment, the microbial landscape of the vaginal biocenosis in patients with exacerbation of chronic salpingo-oophoritis had a significant increase in all the indicated microorganisms against the background of a significant decrease in *Lactobacillus spp.* compared with the control group.

The composition of vaginal secretion in patients of the comparison group after 1 month after the performed standard therapy improved compared with the data before treatment, but did not reach the values obtained in the control group. Statistically significant results concerned only an increase in the concentration of *Lactobacillus spp.* and a decrease in *Gardnerella vaginalis* and *Mobiluncus spp.* (Table 3).

In the group of patients who used the combined preparation containing SK+SD in addition to standard treatment, significantly positive differences were established for the content of most microorganisms compared with the data both before treatment and with the results of the comparison group and approximation of them to the results obtained in the control group. In the study group, compared with the group with standard treatment, a significant increase in the number of *Lactobacillus spp.*, a significant decrease in the content of *Escherichia coli* and *Staphylococcus spp.* were observed.

Analysis of the indices of SIgA concentration in the mucous content in healthy women showed a wide range of individual indices from 5.0 mg/L to 150.7 mg/L, and the average level was 57.9±2.6 mg/L. In patients with exacerbation of chronic salpingo-oophoritis before treatment, the average SIgA index turned out to be significantly (by 24.9%) lower than in the control group and was 43.5±2.8 mg/L ($p<0.05$). After 1 month from the start of therapy, the indices of SIgA concentration in both groups

of patients increased, but a significant difference compared with the data before treatment was noted only in the study group and approached the values in healthy women.

This indicates that against the background of restoration of the immune response with additional use of the combined preparation with SK+SD, normalization of the vaginal microbiocenosis also occurs and testifies to its high effectiveness in the treatment of patients with exacerbation of chronic salpingo-oophoritis.

A special interest was aroused by the study of the quality of life of patients, since it is one of the important criteria for assessing the effectiveness of long-term results of therapy. Thus, before treatment in patients with exacerbation of chronic salpingo-oophoritis the integrative quality of life index CQLS was significantly lower compared with healthy women (58.1±2.3 points versus 71.4±2.3 points, respectively, $p<0.05$) and corresponded to a low assessment of quality of life. Patients who additionally used the combined preparation containing SK+SD for the treatment of exacerbation of chronic salpingo-oophoritis had a higher integrative quality of life index than in the comparison group (69.5±2.4 points versus 65.4±2.5 points, respectively). In the study group after 3 months from the start of treatment the integral quality of life index corresponded to the average level, while in the comparison group, despite the increase, it remained at a low level.

This indicates that the use of the combined preparation containing SK+SD has significant advantages not only in the treatment and prevention of psychological state disorders, unlike standard therapy for exacerbation of chronic salpingo-oophoritis, but also in the preservation and improvement of the quality of life of patients.

Conclusions

It has been established that in patients with exacerbation of chronic salpingo-oophoritis there are hemogram disorders, decreased ferritin content, activation of lipid peroxidation, increased level of endotoxemia, predominance of pro-inflammatory cytokines, changes in the vaginal microbiome against the background of suppression of secretory immunoglobulin A and deterioration of quality of life.

The use in complex therapy of patients with exacerbation of chronic salpingo-oophoritis of the combined preparation containing SK+SD leads to improvement of the clinical picture and recovery in 92% of cases.

The use in complex therapy of patients with exacerbation of chronic salpingo-oophoritis of the combined preparation containing SK+SD has undoubted advantages and clinical effectiveness compared with standard therapy: symptoms of the disease and well-being, such as pain syndrome, sleep and menstrual cycle disorders, are eliminated faster.

One of the main links of the positive effect of the combined preparation containing SK+SD is the lipid peroxidation–antioxidant protection system, endotoxemia indices and the ratio of cytokines and normalization of microbiocenosis and local vaginal immunity.

Improvement of the clinical picture and reduction of pathogenetic changes in patients who, in addition to standard therapy for exacerbation of chronic salpingo-oophoritis, received the combined preparation with SK+SD led to an improvement in their quality of life.

The results of the conducted study of the use of the combined preparation containing SK+SD in patients with exacerbation of chronic salpingo-oophoritis allow us to recommend its widespread use in other inflammatory pathological processes for the prevention of complications.

Further research should be directed at studying the effect of the combined preparation containing SK+SD during surgical interventions on the uterine appendages.

Conflict of interests

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