

## Improvement of postoperative management of patients with endometrioid ovarian cysts

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### Abstract

**Background:** The relevance of endometrioid ovarian cysts is due to their significant prevalence, progressive course with frequent recurrences and pain syndrome, development of adhesive process, infertility, deterioration of patients' quality of life, which encourages the search for new ways of correction in patients of this cohort.

The aim of the study was to investigate the effectiveness of using a combined preparation containing streptokinase and streptodornase as booster therapy for the prevention and reduction of the frequency of complications in the postoperative period in women with endometrioid ovarian cysts.

**Methods:** 39 women with ovarian endometriomas who underwent laparoscopic cystectomy were examined; they were divided into 2 groups: comparison group – 18 patients who received standard therapy in the postoperative period and study group – 21 patients who received standard treatment after surgery and additionally a combined preparation containing streptokinase and streptodornase rectally for 18 days; the control group included 105 conditionally healthy women.

The levels of SDH in blood serum, functioning of the LPO-AOD system, state of endogenous intoxication, phagocytic activity of neutrophils and monocytes, concentration of pro- and anti-inflammatory cytokines were determined; anxiety level was studied using the hospital HADS anxiety scale, depression – using the HADS depression scale, quality of life – using the CQLS questionnaire.

**Results:** It was established that the clinical picture in patients with endometrioid ovarian cysts is characterized by the presence of pain syndrome, sleep disturbance, weakness, fatigue, dyspareunia, deterioration of mental health and quality of life. Decreased activity of SDH, activation of LPO, increase in endotoxemia, decrease in phagocytic activity of neutrophils and monocytes, increase in cytokine levels with predominance of pro-inflammatory ones were revealed. The obtained results indicate that the use of a combined preparation with streptokinase and streptodornase in patients after endometrioma removal has significant advantages not only in the management of the postoperative period, but also in the prevention of mental health disorders, improvement of patients' quality of life, unlike standard treatment.

**Conclusion:** Additional use in comprehensive postoperative therapy of a combined preparation containing streptokinase and streptodornase allows patients already after 1 month to normalize the levels of SDH, TBA-AP, medium molecules, phagocytic activity of neutrophils and monocytes, reduce the level of cytokines, which positively affected the clinical and indicators of mental health and quality of life.

**Keywords:** Women, endometriosis, ovarian cyst, phagocytosis, LPO-AOD system, endotoxemia, cytokines, quality of life, combined preparation containing streptokinase and streptodornase

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### Introduction

In recent years, researchers' attention has been focused on the problem of endometriosis as the most common pathology [19, 20, 36]. Endometriosis is the cause of 50% of infertility and 60% of pelvic pain in women of reproductive age [2, 4, 42, 43].

The ovaries are one of the common localizations of endometriosis, since ovarian endometriomas account for 35% of all benign ovarian cysts and occur in 17–44% of women with endometriosis, of which in one third of cases they are bilateral [29, 30]. Endometrioid cysts contain high concentrations of biologically active substances, free iron, proteolytic enzymes, which can cause the development of fibrotic changes, metaplasia of the ovarian cortex and the development of adhesive process [22, 29].

The relevance of endometriosis is determined by the significant prevalence of this pathology, the progressive course of the disease, its severity, impairment of the function of the genital organs due to the adhesive process, the risk of developing oncopathology, which significantly affects not only the patient's quality of life, but also social contacts and work [33, 47, 49].

Usually, the clinical manifestations of endometrioid ovarian cysts are patients' complaints of chronic pain, dysmenorrhea, menstrual cycle disorders, decreased quality of life [5, 30, 32, 34]. However, despite certain successes and the introduction of new technologies into gynecological practice, the issues regarding treatment tactics and rehabilitation of patients with endometrioid ovarian cysts have not been finally resolved [12, 31, 45, 46].

Currently, surgical treatment is one of the leading methods for this pathology, since drug therapy is usually effective only temporarily, and complete removal of endometriotic tissues increases the chances of avoiding recurrence and obtaining better observation [5, 40].

At the same time, after organ-preserving interventions and removal of ovarian endometriomas, in most cases, the formation of fibrotic adhesions is observed in women of reproductive age. Fibrotic adhesions often form in response to chronic irritation of the peritoneal surface by endometrioid implants and their secretion products [38, 44]. A possible consequence of peri- or intratubal adhesions is infertility, ectopic pregnancy, chronic pelvic pain [24, 40]. The connection between adhesions and pain is well illustrated by relief and reduction of pain after adhesiolysis in 60-90% of cases [35].

The choice of the volume of surgical intervention and management of the postoperative period in patients with endometriomas depends on many factors and, first of all, on the woman's age, clinical manifestations, cyst size, presence of anatomical changes, cyst rupture, etc [37, 39].

The presence of a large volume of blood loss, especially during urgent operations, increases the risk of developing purulent-septic complications, in connection with which questions arise regarding the choice of the method of surgical intervention and tactics of managing the postoperative period in this cohort of women. Undoubtedly, women of reproductive age with ovarian cysts require precise surgical treatment using organ-preserving methods with maximally radical removal of lesions while preserving the functionality of the organ.

Taking into account the above, it is important to use minimally invasive surgical methods such as laparoscopy, prevention of postoperative complications, including the possible development of adhesive process in the small pelvis, since this requires significant efforts of a high percentage of endometriosis recurrences in the future [1, 21, 26].

Reparative processes in tissues after surgical intervention are possible under conditions of optimal blood circulation and absence of inflammatory purulent process. Along with methods of emergency and planned surgical intervention, many authors propose schemes of accompanying therapy in the postoperative period [25, 27]. At the same time, effective ways of correcting possible complications of the postoperative period in women after removal of endometrioid ovarian cysts have not been finally determined to date.

A significant place, in our opinion, in the series of new methods of treatment and rehabilitation should belong to enzyme therapy, which provides therapeutic effects directly in the focus of inflammation, allows reducing the doses of antibacterial drugs and medications, reducing the frequency of development of systemic side reactions and allergization of the body, positively influencing the prevention of adhesive complications and regeneration [9].

Today, proteolytic enzymes deserve the most attention, since constituting the proteolysis system, they play a significant role in such important biological processes as protein metabolism, blood clotting, fibrinolysis, immune reactions, regulation of arterial pressure, processes of differentiation and metabolism of connective tissue, etc [6, 15].

When using preparations in the postoperative period in women, one should proceed not only from the requirement to ensure the necessary antimicrobial action, but also to ensure rapid delivery and increase their concentration in the focus of inflammation, in addition, without affecting the pharmacokinetic properties, thereby reducing the risk of developing purulent-septic and adhesive complications and accelerating recovery [8].

In this regard, our attention was drawn to a combined preparation containing streptokinase (SK) and streptodornase (SD). The combined preparation containing SK + SD belongs to the few universal enzyme preparations that have a wide spectrum of action and can confidently be prescribed first at the beginning of treatment in the postoperative period in combination with antibacterial preparations [13, 14].

Rectal suppositories of the combined preparation contain 15000 IU of streptokinase and 1250 IU of streptodornase.

The mechanism of action of the combined preparation with SK+SD is based on the combination of active components that possess pronounced thrombolytic and fibrinolytic effects, promote the elimination of sludge syndrome, improve microcirculation and reduce edema in the focus of lesion due to the increase in macrophage concentration, increase the access of antibacterial preparations to the source of inflammation [10, 23].

Streptokinase as a basic medicinal agent is successfully used in surgical and therapeutic practice for the treatment of thromboses of various localizations, since it is an activator of the proenzyme plasminogen, which is converted into plasmin and dissolves blood clots. When using the preparation in the form of rectal suppositories, no systemic thrombolytic action is observed, as a result of which the risk of developing bleeding of any localization is minimal.

Streptodornase is an enzyme – endonuclease that destroys DNA due to its deep depolymerization. It breaks intermolecular bonds of nucleoproteins of dead cells and purulent masses, facilitates resorption of cells and oligoproteins, as a result of which they completely dissolve, but does not affect healthy cells and their physiological properties and thereby prevents the development of adhesions.

Streptodornase improves the access of other therapeutic preparations such as antibiotics or anti-inflammatory agents to the focus of inflammation and thereby reduces infiltration, edema and clinical manifestations of inflammation, and in combination with streptokinase promotes the elimination of purulent formations, normalization of microcirculation, increase in phagocytosis efficiency. At the same time, the influence of proteolytic enzymes on the clinical efficacy of various antibacterial preparations is associated not only with the transport of antibiotics, improvement of blood circulation and microcirculation in the site of inflammation, but also with the increase in antibiotic permeability inside microorganisms.

The components of the combined preparation containing streptokinase and streptodornase primarily do not pass through the hepatic blood flow, but are maximally concentrated in the focus of inflammation, as a result of which their systemic action and the possibility of developing side effects decrease [11].

The main mechanisms of integral clinical potentiation of the action of the combined preparation containing SK+SD,

which possess pronounced thrombolytic and fibrinolytic properties, are booster effects [13, 28]. The combined preparation containing SK+SD improves the conditions of transportation of etiotropic preparations, improves their absorption, increases the access of antibacterial preparations to the source of inflammation, improves blood microcirculation, promotes the elimination of sludge syndrome and reduces edema in the focus of lesion due to chemotaxis of macrophages and other immunocompetent cells, increases necrosis and cleavage of detritus thereby enhancing the effect of sanitation and cleaning of the membrane of both the host cell and the pathogen, increases membrane permeability. In addition, the preparation reduces acidity in the source of inflammation, which improves the conditions of antibiotic action and changes the properties of microbial biofilms in the presence of proteolytic enzymes. The aim of the study was to investigate the effectiveness of using a combined preparation containing SK+SD as booster therapy for the prevention and reduction of the frequency of complications in the postoperative period in women with endometrioid ovarian cysts.

## Methods

To achieve the set goal, 39 women aged 24-39 years with ovarian endometriomas who underwent surgical intervention by standardized laparoscopic access with cystectomy were examined in dynamics, including 79.5% of women – in planned order, 20.5% – for emergency indications due to cyst rupture. All patients underwent organ-preserving volume of surgical intervention.

The patients were divided into 2 groups: the comparison group included 18 patients after endometrioma cystectomy who received standard therapy according to existing protocols in the postoperative period; the study group included 21 women who in the postoperative period along with standard therapy received a combined preparation containing SK+SD rectally 1 suppository 3 times a day for 3 days followed by administration of 1 suppository 2 times a day for 3 days and 1 suppository 1 time a day up to 18 days. The control group included 105 conditionally healthy women of the same age group, of which 24 formed the control group for biochemical studies.

Somatic status and reproductive system in the study groups were evaluated based on anamnestic and clinical data. Almost all patients had complaints of pain in the lower abdomen, dysmenorrhea, dyspareunia, sexual disorders and infertility. All patients were examined according to the standards approved by the orders of the Ministry of Health of Ukraine, which included general clinical, biochemical, instrumental, ultrasound and bacteriological research methods. All patients underwent laparoscopy, and the volume of surgical intervention depended on the general condition and the amount of blood loss.

Laboratory and biochemical studies included determination of general clinical examination indicators, coagulogram. The level of lymphocyte succinate dehydrogenase (SDH), the state of the lipid peroxidation system (LPO) was studied by the amount of thiobarbituric acid active products (TBA-AP) in blood serum [41] and total antioxidant activity (AOA) of blood plasma, which was determined by the method of

E.B. Spektor *et al* [16]. The state of endogenous intoxication of the body was determined by the level of medium molecules at wavelength 254 nm (MM1) and 280 nm (MM2) according to the method of N.I. Gabrielian, V.I. Lipatova [7]. Phagocytic activity of peripheral blood neutrophils and monocytes was determined by the cup method [3, 17]. At the 30th and 120th minutes, the percentage of phagocytic cells was counted; the number of absorbed and digested staphylococci per 1 phagocytic cell, which allowed calculations and determination of the absorptive and digestive capacity of neutrophils and monocytes.

In the dynamics of treatment, the concentration of pro- and anti-inflammatory cytokines (IL-1 ( $\beta$ ), IL-4, IL-8, IL-10, TNF- $\alpha$ , TGF $\beta$ ) in blood serum was determined by enzyme-linked immunosorbent assay.

Patients were surveyed regarding the effectiveness of treatment and evaluation by doctors of effectiveness depending on the treatment conducted.

The level of anxiety was determined using the hospital HADS anxiety scale, depression – using the HADS depression scale, quality of life was evaluated using the standard CQLS questionnaire [18, 50]. Psychometric study of the level of asthenia was studied using the “Subjective Assessment of Asthenia” scale (Multidimensional Fatigue Inventory, MFI-20 [48]).

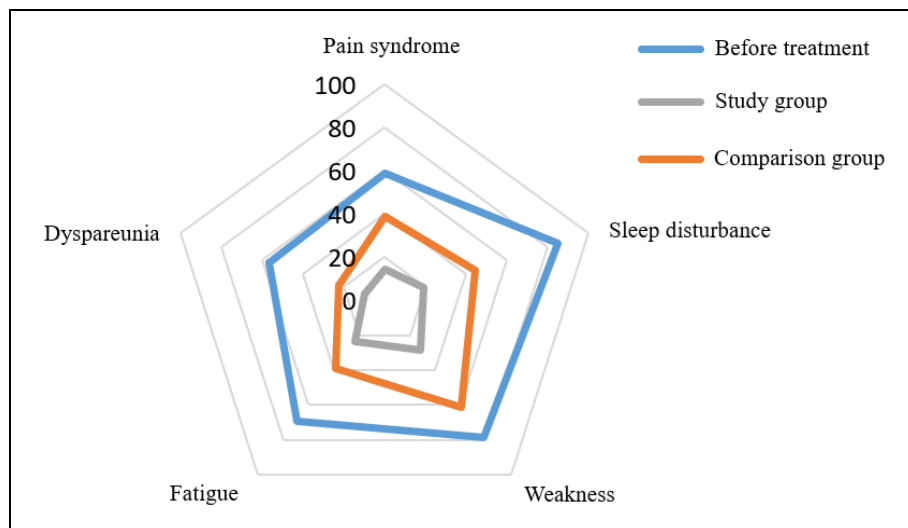
Examination of patients was conducted before, after 1 and after 3 months after surgical treatment. The effectiveness of postoperative treatment of patients and the use of the combined preparation with SK+SD was evaluated by the presence of complaints, self-assessment of well-being, dynamics of clinical manifestations and severity of pain syndrome.

The obtained results were processed statistically using standard computer programs with the use of paired Student's t-test with calculation of the arithmetic mean (M) and standard error of the arithmetic mean (m) or Wilcoxon's sign test depending on the normality of the difference distribution. The normality of data distribution was checked using the Shapiro-Wilk test at a significance level of 0.01. When applying all statistical methods, except the Shapiro-Wilk test, the significance level was taken equal to 0.05 – the difference between the data was considered significant at  $p < 0.05$ . To determine structural connections, correlation analysis was used with determination of pairwise correlation coefficients –  $r$ .

## Results and Discussion

Women in the study and comparison groups did not differ from each other in age parameters, height-weight indicators, gynecological and somatic status, which allowed them to be combined for statistical analysis. The average duration of the disease with endometrioid ovarian cyst was 2.5 years.

Upon hospitalization, the main complaints were constant aching pain in the lower abdomen with irradiation to the rectum, sleep disturbance, weakness, increased fatigue, dyspareunia, with violation of endometrioma integrity – changes in hemodynamics and symptoms of acute abdomen (Fig. 1).



**Fig 1:** Dynamics of clinical manifestations depending on the treatment method in patients after 1 month after removal of endometrioid ovarian cyst

As seen from Fig.1, after 1 month after surgical intervention and the start of treatment, the condition of patients in both groups improved, but a certain number of clinical symptoms remained. In patients who additionally to standard postoperative therapy used a combined preparation with SK+SD, pathological symptoms were observed less frequently compared to the group with standard management: 2.7 times - pain syndrome (14.3% vs 38.9% respectively), 2.3 times – sleep disturbance and dyspareunia (19.0% vs 44.4% and 9.5% vs 22.2% respectively), 2.1 and 1.6 times - weakness and fatigue (28.6% vs 61.1% and 23.8% vs 38.9% respectively). The obtained results indicate

a significant positive influence of the combined preparation containing SK+SD in comprehensive therapy on the course of the postoperative period in patients after endometrioma removal compared to standard treatment.

The results of patient surveys regarding the effectiveness of therapy in the postoperative period and evaluation by doctors of its effectiveness depending on the treatment conducted deserve attention (Table 1). As seen from Table 1, after 1 month after surgical intervention for endometrioma of the ovary in all groups of patients, positive treatment effectiveness was noted.

**Table 1:** Evaluation of effectiveness depending on the treatment method in patients after 1 month after removal of endometrioid ovarian cyst

Indicators, units of measurement	By patients		By doctors	
	after standard treatment	after treatment with inclusion of SK+SD	after standard treatment	after treatment with inclusion of SK+SD
No changes, %	11.1	0	5.6	0
Satisfactory, %	55.6	33.3	61.1	28.6
Good, %	27.8	57.1	33.3	52.4
Excellent, %	5.6	9.5	0	19.0
Conditional average value	1.28±0.12	1.76±0.11▲	1.28±0.11	1.90±0.10▲

**Note:** ▲ - significant difference (P<0.05) after treatment between corresponding indicators of groups.

Features of evaluation by patients depending on the choice of postoperative management of patients were noted. Thus, after 3 months after surgery and from the start of treatment in the group that received standard treatment, the evaluation satisfactory prevailed, which is confirmed by the conditional average value. In the group that received the combined preparation with SK+SD for 3 weeks, the evaluation good prevailed, and the conditional average value of the evaluation was statistically higher than in the group with standard treatment.

The evaluation of therapy effectiveness by doctors aroused interest. Comparison of the results of evaluation of postoperative treatment effectiveness by patients and doctors on average showed approximately the same results (Table 1). And by doctors, the treatment effectiveness in the group that received the combined preparation with SK+SD was evaluated statistically significantly higher than in the group with standard therapy.

To objectivize the evaluation of the effectiveness of postoperative treatment of women after cystectomy by

doctors and patients, we analyzed the results of paired correlation between evaluation by doctors and patients after 3 months after surgical intervention and from the start of therapy. The strength of paired correlation of conditional average values (+0.67) was statistically significantly high, which indicates the same, in most cases, evaluation of treatment effectiveness by doctors and patients. At the same time, the absence of one hundred percent coincidence speaks of different views of treatment effectiveness by patients and doctors.

To establish pathogenetic changes in patients with endometrioid ovarian cysts, determination of SDH, lipid peroxidation-antioxidant defense system (LPO-AOD), and medium molecules was conducted (Table 2).

As seen from Table 2, in patients with endometriomas before surgical intervention, compared to healthy ones, the activity of the energy metabolism indicator – SDH was statistically significantly lower. Suppression of SDH activity in patients with endometrioid ovarian cysts indicates exhaustion of compensatory possibilities of energy

metabolism of lymphocytes, development of hypoxic states in immunocompetent cells – lymphocytes.

The study of the activity of the lipid peroxidation-antioxidant system in patients with endometriomas before cystectomy, compared to healthy ones (Table 2), showed that they had 1.33 times increased amount of TBA-AP and significantly increased total AOA (51.0±0.59% vs 46.9±0.79% respectively), but at the same time there is a significant 18% decrease in the coefficient of antioxidant defense, which indicates exhaustion of the antioxidant defense system.

Activation of LPO, changes in energy metabolism of cells lead to changes in metabolism of both individual cells and the body as a whole. The consequence of this is increased activity of endogenous intoxication processes, which is determined by the concentration of MM. As seen from Table 2, in patients with endometriomas before surgical intervention, the level of medium molecules is statistically significantly higher than in healthy ones, which indicates an increased level of endotoxiation and disturbance of metabolism of the whole body in this cohort of patients.

**Table 2:** Dynamics of SDH, LPO-AOD system, level of medium molecules in blood serum depending on the treatment method in patients after 1 month after removal of endometrioid ovarian cyst

Indicators, units of measurement	Healthy	Patients with endometrioid ovarian cysts		
		before surgery	in postoperative period	
			with standard treatment	with inclusion of SK+SD
SDH, %	24.56±0.23	22.75±0.27*	23.14±0.33	24.17±0.29●▲
TBA-AP, nmol/l	5.34±0.15	7.08±0.14*	6.35±0.15*●	5.67±0.19●▲
Total AOA, %	46.9±0.79	51.0±0.59*	49.1±1.01	47.9±0.95●
AOD coefficient	8.71±0.39	7.18±0.17*	7.73±0.25*	8.45±0.21●▲
MM level, 254 nm, cu	0.327±0.007	0.396±0.012*	0.365±0.012*	0.338±0.010●
MM level, 280 nm, cu	0.134±0.006	0.198±0.007*	0.173±0.008*●	0.145±0.009●▲

**Notes:** \* – significant difference (P<0.05) compared to corresponding indicators with the group of healthy; ● – significant difference (P<0.05) between indicators before and after treatment; ▲ – significant difference (P<0.05) compared to indicators with the group after standard treatment.

In the postoperative period in patients of both groups, positive changes in biochemical indicators were noted. However, as seen from Table 2, standard management of patients in the postoperative period does not allow complete normalization of the functioning of the LPO-AOD system and the level of endotoxemia relative to data in healthy individuals. In patients who used the combined preparation with SK+SD, there was a significant increase in the content of SDH and AOD coefficient and their approximation to values in healthy ones and simultaneous decrease in TBA-AP and total AOA and MM level (Table 2).

Thus, the results obtained during the study confirm the positive influence of using in therapy of patients after cystectomy the combined preparation with SK+SD on

restoration of normal functioning of the LPO-AOD system and reduction of endotoxemia.

It is known that one of the main links in the pathogenesis of endometriosis in the development of inflammation is changes in the immune system. We studied phagocytosis of neutrophils and monocytes and cytokine levels in patients with endometrioid ovarian cysts in the dynamics of treatment. Table 3 provides the results of analysis at 120 min. of the number of bacteria absorbed by neutrophils (NAN120), monocytes (NAM120); number of destroyed bacteria by neutrophils (NDN120), monocytes (NDM120); neutrophil bactericidal index (NBI120), monocyte bactericidal index (MBI120).

**Table 3:** Dynamics of phagocytosis of neutrophils and monocytes depending on the treatment method in patients after 1 month after removal of endometrioid ovarian cyst

Indicators, units of measurement	Healthy	Patients with endometrioid ovarian cysts		
		before surgery	in postoperative period	
			with standard treatment	with inclusion of SK+SD
NAN120	926±22.3	688±18.8*	824±19.7*●	895±21.0●▲
NDN120	758±17.8	487±15.4*	603±19.7*●	709±20.4●▲
NBI120	81.8±2.18	70.7±2.87*	73.1±3.3*	79.2±0.31●
NAM120	627±17.6	485±15.9*	534±17.6*	598±19.4●
NDM120	450±14.1	307±12.9*	357±13.5*●	421±13.8●▲
MBI120	71.7±2.07	63.2±1.96*	66.8±2.42	70.2±2.23●

**Notes:** \* – significant difference (P<0.05) compared to corresponding indicators with the group of healthy; ● – significant difference (P<0.05) between indicators before and after treatment; ▲ – significant difference (P<0.05) compared to indicators with the group after standard treatment.

As seen from Table 3, in patients with endometrioid ovarian cysts before surgical intervention, a decrease in NAN120, NDN120, NBI120 is noted, which indicates lower phagocytic activity of neutrophils and tension in the neutrophil phagocytic system. In the dynamics of treatment, against the background of improvement in the clinical picture, there is a statistically significant increase in the capabilities of the neutrophil phagocytic system. This

increase occurs especially in the group of patients in the group that received SK-SD. In the latter group, this occurred against the background of improvement in the clinical picture, decrease in MDA activity, increase in AOD coefficient, and significant reduction in endotoxemia. The results of determining the phagocytic activity of monocytes (Table 3) revealed similar changes as in neutrophils, but less pronounced.

The results of the study of cytokine levels synthesized by macro- and microphagocytic cells in patients with endometriomas are presented in Table 4. The data presented in Table 4 indicate that among patients with endometriomas before surgery, the level of cytokines was higher than in healthy ones. The level of IL-1 ( $\beta$ ), pg/ml in patients was 2 times higher, IL-4 - 1.87 times, IL-8 - 2.5 times; IL-10 - 1.5 times; TNF- $\alpha$  - 3.5 times; TGF $\beta$  - 1.7 times. After 1 month after surgical intervention and from the start of treatment,

the level of cytokines decreased both in the study group and in the comparison group. But in the group that received SK+SD, the level of cytokines was lower than in the group with standard therapy, and approached the results obtained in healthy ones. This speaks of the positive influence of using SK+SD in comprehensive therapy of patients after endometrioma removal on normalization of the level of serum cytokines studied.

**Table 4:** Dynamics of serum cytokines depending on the treatment method in patients after 1 month after removal of endometrioid ovarian cyst

Indicators, units of measurement	Healthy	Patients with endometrioid ovarian cysts		
		before surgery	in postoperative period	
			with standard treatment	with inclusion of SK+SD
IL-1 ( $\beta$ ), pg/ml	33.4 ± 1.96	68.4±2.51*	55.7 ± 2.73*●	41.1±2.23●▲
IL-4, pg/ml	19.4 ± 1.47	36.3±1.91*	28.4 ± 1.99*●	22.7 ± 1.84●
IL-8, pg/m	27.1 ± 2.2	67.8± 2.9*	55.2 ± 3.4*●	35.8±3.3*●▲
IL-10, pg/ml	19.4 ± 1.4	29.4 ± 1.8*	27.8 ± 2.4	22.8 ± 1.8●
TNF- $\alpha$ , pg/ml	4.4± 0.3	15.6± 0.8*	10.5± 0.9*	6.2± 0.6●▲
TGF $\beta$ , pg/ml	32.4±1.5	54.1± 2.3*	47.8± 2.6*	37.2± 1.7●▲

**Notes:** \* – significant difference ( $P<0.05$ ) compared to corresponding indicators with the group of healthy; ● – significant difference ( $P<0.05$ ) between indicators before and after treatment; ▲ – significant difference ( $P<0.05$ ) compared to indicators with the group after standard treatment.

Interest was aroused by the ratio between pro-inflammatory: IL-1 ( $\beta$ ), IL-8, TNF- $\alpha$  and anti-inflammatory cytokines: IL-4, IL-10, TGF $\beta$ . As seen from Table 4, the level of pro-inflammatory cytokines increased in patients significantly more than anti-inflammatory ones. To have the opportunity to integrally evaluate the ratio of pro- and anti-inflammatory cytokines, we recalculated the values of cytokine concentrations in percentages relative to the results obtained in healthy women. This allowed determining the integral excess of the level of pro- and anti-inflammatory cytokines, as well as their ratio. It was established that before treatment in patients with endometrioid ovarian cysts, the level of pro-inflammatory cytokines increased to 270% from the values that were in healthy ones. At the same time, the level of anti-inflammatory cytokines was on average only 169%. And therefore their ratio was 1.59. Thus, in patients with endometrioid ovarian cysts, there was a predominance of pro-inflammatory cytokines over anti-inflammatory ones, which led to the development of inflammatory process. After standard treatment of women in the postoperative period, the ratio of pro- and anti-inflammatory cytokines was 1.39, while in the group that received SK+SD 1.13.

That is, after a month after surgery in patients after removal of endometrioid ovarian cyst, there was a decrease in cytokines, moreover more significant in pro-inflammatory cytokines, which contributed to the reduction of inflammation. It should be noted that the ratio of cytokines remains significantly greater than in healthy women.

At the same time, the ratio of pro- and anti-inflammatory cytokines in the group of women who received SK+SD (1.13) the level of pro-inflammatory cytokines was lower, which led to a more significant decrease in the level of pro-inflammatory cytokines and approximation of their level to the results obtained in healthy women. This allows asserting that the use of SK+SD in comprehensive therapy of women after surgery allows normalizing cytokine exchange within 1 month, which leads to the elimination of inflammation. During the study, we paid attention to determining the features of the mental state of patients with endometrioid ovarian cysts, their results are given in Table 5. As seen from Table 5, in patients of this cohort before surgical intervention, the levels of anxiety, depression and asthenia were higher than in the control group.

**Table 5:** Dynamics of mental health indicators and quality of life depending on the treatment method in patients after 3 months after removal of endometrioid ovarian cyst, points ( $M\pm m$ )

Indicators, units of measurement	Healthy	Patients with endometrioid ovarian cysts		
		before surgery	in postoperative period	
			with standard treatment	with inclusion of SK+SD
HADS anxiety	3.9±0.4	9.8±0.8*	8.7±0.9*	5.0±0.6▲
HADS, depression	3.5±0.4	8.7±0.7*	6.5±0.8*	3.9±0.4▲
Integral assessment of asthenia by MFI-20	24.5±1.6	47.6±2.8*	37.9±3.1	26.3±2.4▲
Integrative indicator of quality of life by O.S. Chaban	71.4±2.3	57.6±2.4*	63.0±2.5*	69.6±2.4●

**Notes:** \* - significant difference ( $P<0.05$ ) compared to corresponding indicators with the group of healthy; ● – significant difference ( $P<0.05$ ) between indicators before and after treatment; ▲ – significant difference ( $P<0.05$ ) compared to indicators with the group after standard treatment.

Anxiety, depression in patients with endometrioid ovarian cysts before surgery on average had subclinical manifestations, there was an increase in emotional

excitability, as a result of which negative experiences arose, such as anxiety, tension, irritability, confusion. This probably led to deterioration of patients' quality of life. The

integral assessment of asthenia by MFI-20 before treatment was of medium degree.

In the group of patients with endometrioid ovarian cysts after surgical intervention and standard treatment after 3 months, the level of anxiety, depression and asthenia decreased compared to data before treatment, which is probably explained by the general improvement in health status. The level of anxiety remained subclinical, the level of depression on average was within normal limits, and the integral assessment of asthenia corresponded to a moderate level. This speaks of improvement in the psychological assessment of patients after standard treatment due to the general improvement in their health status, however, there was no complete normalization of their psychological status indicators.

After 3 months after surgery and from the start of the study in patients who received additionally to standard treatment SK+SD, a statistically significantly lower level of anxiety, depression and asthenia was noted compared both to data before treatment and the group that used standard therapy. The results obtained in the study group corresponded to normal values and actually approached the values in the control group. This indicates that significant improvement in the clinical picture in patients after removal of endometrioid cyst and homeostasis against the background of additional use of SK+SD plays an important role in various physiological functions and has a positive impact on their mental state.

One of the important criteria for evaluating the effectiveness of long-term therapy results is the quality of life of patients. We determined the indicators of quality of life in patients with endometrioid ovarian cysts depending on the treatment method using the integrative quality of life indicator CQLS. In patients before surgical intervention, the CQLS indicator was significantly lower than in the control group and indicated a low level of quality of life.

After 3 months after cystectomy and postoperative treatment, the assessment of quality of life in both groups of patients increased, but in women who received additionally SK+SD, the point assessment was higher than in the comparison group and corresponded to the average quality indicator, in the group after standard treatment, despite the increase, remained at a low level. In the study group, the integral indicator had no difference from the results obtained in healthy women.

Thus, the obtained results regarding the quality of life of patients indicate that the use of the combined preparation with SK+SD has significant advantages not only in the management of the postoperative period, but also in the prevention of mental health disorders, improvement of patients' quality of life, unlike standard treatment.

Efforts should be intensified regarding timely diagnosis of endometrioid ovarian cysts and adequate treatment in women of reproductive age. Key directions in this should be increasing women's awareness regarding endometrioid ovarian cysts, conducting medical-preventive measures for early detection of pathology, timely treatment and prevention of their development in women of reproductive age.

## Conclusions

1. In women with endometrioid ovarian cysts, pain syndrome, sleep disturbance, weakness, fatigue,

dyspareunia, deterioration of mental health and quality of life are significantly more often noted.

2. It was established that in patients with endometrioid ovarian cyst, there is a decrease in SDH activity and an increase in the amount of TBA-AP, medium molecules, decrease in phagocytic activity of neutrophils and monocytes, increase in cytokine levels with predominance of pro-inflammatory ones.
3. After removal of endometrioid ovarian cysts in patients, there is an increase in SDH, decrease in TBA-AP and medium molecules, increase in phagocytic activity of neutrophils and monocytes, decrease in cytokine level.
4. Additional use in comprehensive postoperative therapy of the combined preparation SK+SD allows patients already after 1 month after cystectomy to normalize the levels of SDH, TBA-AP, medium molecules, phagocytic activity of neutrophils and monocytes, reduce the level of cytokines to indicators obtained in healthy individuals.
5. In the group of women who additionally received the combined preparation with SK+SD after three months, normalization of the clinical picture, indicators of mental health and quality of life occurred.
6. The conducted study allows recommending the use of the combined preparation with SK+SD in the complex of postoperative management of women.

## Conflict of interests

The authors declare no conflict of interests regarding the content of the presented manuscript.

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## References

1. Gladchuk IZ, Volianska AH, Neporada SM. Operatyvna laparoskopia v likuvanni bezplidnykh khvorykh z endometriozom. *Visnyk morskoi medytsyny*,2010;(4):33-6.
2. Dubchak AE. Endometrioz i besplodie. *Diskusionnye aspekty lechenia endometriozu. Reproduktyvnoe zdorove zhenshchiny*,2007;2(31):177-80.
3. Drannik GN. *Klinicheskaia immunologii i allergologii*. Kiev: Poligraf Plus, 2010, 552.
4. Zakharenko OS, Yuzko OM, Zakharenko LV. Henitalnyi endometrioz yak prychna zhinochoho bezpliddia. *Neonatolohiia, khirurgiia ta perynatalna medytsyna*,2013;3(1):76-89.
5. Kaminskyi VV, Borys EN, Sukhanova AA, Konoplianko VV. Endometrioidnaia bolezni: kak izbezhat giperdiagnostiki i iatrogenii? *Doktor*,2006;5(35):2-7.
6. Karimova DF, Karimova FD, Khodzhaeva MA. Opyt primeneniia preparata Distreptaza v profilaktike oslozhnenii i reabilitatsii zhenshchin posle kesareva secheniia. *Zdorove zhenshchiny*,2010;2:81-2.
7. Kireev SS, Bakhmut TA, Kurochkin Miu. Opreделение tiazhesti endotoksikoza pri kriticheskikh sostoianiiakh u detei. *Pediatriia*,1997;2:88-8.
8. Pashchenko SM, Reznichenko HI, Samsonova VV, *et al.* Efektyvnist zastosuvannia preparatu Distreptaza dlia profilaktyky pisliaoperatsiinykh hniino-septychnykh uskladnen u khvorykh na rak товstoho kyshechnyka. *Suchasni medychni tekhnolohii*,2010;4:19-22.

9. Podolskyi VV. Efektyvnist zastosuvannia preparatu Distreptaza v akushersko-hinekolohichnii praktytsi. *Zdorove zhenshchiny*,2007:2(30):201-4.
10. Potapov VA, Mutana E, Stepanova DIu, Polishchikov PI. Strategiiia rannei posleoperatsionnoi reabilitatsii reproduktyvnoi funktsii u zhenshchin s leiomiomoi matki. *Zdorove zhenshchiny*,2012:10:101-5.
11. Potapov VA. Distreptaza: novoe reshenie problemy patogeneticheskoi korrektsii vospalitel'nogo otveta i narushenii krovobrashcheniia v organakh malogo taza u zhenshchin s obostreniem khronicheskogo salpingooforita. *Reproduktyvnoe zdorove zhenshchiny*,2008:4(38):48-52.
12. Pro zatverdzhennia klinichnykh protokoliv z akusherskoi ta hinekolohichnoi dopomohy. *Nakaz MOZ Ukrainy vid*,2005:15(12):582.
13. Reznichenko HI, Reznichenko NIu, Makiienko TS, *et al.* Efektyvnist Distreptazy u profilaktytsi pisliaoperatsiinykh uskladnen u zhinok pry ekstyrypatsii matky. *Zdorove zhenshchiny*,2012:1:153-6. Available from: [http://nbuv.gov.ua/UJRN/Zdzh\\_2012\\_1\\_31](http://nbuv.gov.ua/UJRN/Zdzh_2012_1_31)
14. Reznichenko HI, Samsonova VV, Reznichenko NIu, *et al.* Zastosuvannia Distreptazy u zhinok iz pozamatkovoiou vahitnistiu ta apopleksiieiu yaiechnyka. *Medychni aspekty zdorovia zhinky*,2010:7:60-4.
15. Senchuk AIA, Ropiak AM, Doskoch IO, *et al.* Stan systemy hemostazu v khvorykh iz khronichnym salpinhooforytom u stadii zahostrennia do ta pislia protyzapalnoi terapii. *Aktualni pytannia pediatrii, akusherstva ta hinekolohii*,2009:1:76-8.
16. Spektor EB, Ananenko AA, Polytova LN. Opreddenie obshchei antioksidantnoi aktivnosti plazmy krovi i likvora. *Laboratornoe delo*,1984:1:26-8.
17. Frolov VM, Peresadin NA, Pshenichnyi IA. Opreddenie fagotsitarnoi aktivnosti monotsitov perifericheskoi krovi u bol'nykh. *Laboratornoe delo*,1990:9:27-9.
18. Chaban OS. Yakist zhyttia patsiienta z pozytsii medychnoi psykholohii. *Mystetstvo likuvannia*,2008:5(51):40-3.
19. Chervak NM. Endometrioz: stan problemy. *Medychni aspekty zdorovia zhinky*,2014:8(83):2-7.
20. Abbas S, Ihle P, Köster I, Schubert I. Prevalence and incidence of diagnosed endometriosis and risk of endometriosis in patients with endometriosis-related symptoms: findings from a statutory health insurance-based cohort in Germany. *Eur J Obstet Gynecol Reprod Biol*,2012:160(1):79-83. doi:10.1016/j.ejogrb.2011.09.041.
21. Abbott J, Hawe J, Hunter D, *et al.* Laparoscopic excision of endometriosis: a randomized, placebo-controlled trial. *Fertil Steril*,2004:82(4):878-84. doi:10.1016/j.fertnstert.2004.03.046.
22. Agarwal N, Arulselvi S. Endometriosis: morphology, clinical presentations and molecular pathology. *J Lab Physicians*,2010:2(1):1-9.
23. Al-Khateeb TH, Nusair Y. Effect of proteolytic enzyme serrapeptase on swelling, pain and trismus after surgical extraction of mandibular third molars. *Int J Oral Maxillofac Surg*,2008:37:264-8.
24. Albert L, Sinaii N, Segars J, *et al.* Pelvic pain location to surgical findings of endometriosis. *Obstet Gynecol*,2011:118(2):223-30.
25. Alkatout I, Mettler L, Beteta C, *et al.* Combined surgical and hormone therapy for endometriosis is the most effective treatment: prospective, randomized, controlled trial. *J Minim Invasive Gynecol*,2013:20(4):473-81. doi:10.1016/j.jmig.2013.01.019.
26. Alpay Z, Saed GM, Diamond MP. Postoperative adhesions: from formation to prevention. *Semin Reprod Med*,2008:26(4):313-21. doi:10.1055/s-0028-1082389.
27. Arung W, Meurisse M, Detry O. Pathophysiology and prevention of postoperative peritoneal adhesions. *World J Gastroenterol*,2011:17(41):4545-53.
28. Bhagat S, Agarwal M, Roy V. Serratiopeptidase: a systematic review of the existing evidence. *Int J Surg*,2013:11:209-17.
29. Bulun SE. Endometriosis. *N Engl J Med*,2009:360(3):268-79.
30. Chapron C, Santulli P, de Ziegler D, *et al.* Ovarian endometrioma: severe pelvic pain is associated with deeply infiltrating endometriosis. *Hum Reprod*,2012:27(3):702-11. doi:10.1093/humrep/der462.
31. Chapron C, Wang Y, Liu X, Olive DL. Management of ovarian endometriomas. *Hum Reprod Update*,2002:8(6):591-7.
32. Cheong Y, Stones W. Chronic pelvic pain: etiology and therapy. *Best Pract Res Clin Obstet Gynaecol*,2006:20(5):695-711. doi:10.1016/j.bpobgyn.2006.04.004.
33. Culley L, Law C, Hudson N, *et al.* The social and psychological impact of endometriosis on women's lives: a critical narrative review. *Hum Reprod Update*,2013:19(6):625-39. doi:10.1093/humupd/dmt027.
34. Fauconnier A, Chapron C. Endometriosis and pelvic pain: epidemiological evidence of the relationship and implications. *Hum Reprod Update*,2005:11(6):595-606.
35. Ferrero S, Venturini PL, Ragni N, *et al.* Pharmacological treatment of endometriosis: experience with aromatase inhibitors. *Drugs*,2009:69(8):943-52.
36. Buck Louis GM, Hediger ML, Peterson CM, *et al.* Incidence of endometriosis by study population and diagnostic method: the ENDO study. *Fertil Steril*,2011:96(2):360-5.
37. Hart RJ, Hickey M, Maouris P, Buckett W. Excisional surgery versus ablative surgery for ovarian endometriomata. *Cochrane Database Syst Rev*,2008:(2):4992. doi:10.1002/14651858.CD004992.pub3.
38. Imudia AN. Pathogenesis of intra-abdominal and pelvic adhesion development. *Semin Reprod Med*,2008:26(4):289-97. doi:10.1055/s-0028-1082387.
39. Kaminski P, Mazanowska N. Operative treatment of endometriosis. In: Wielgoś M, editor. *Endometriosis*. Gdansk: Via Medica, 2010, 39-54.
40. Kennedy S, Bergqvist A, Chapron C, *et al.* ESHRE guideline for the diagnosis and treatment of endometriosis. *Hum Reprod*,2005:20:2698-704.
41. Korobeynikova EN. Modification of the determination of lipid peroxidation products in reaction with thiobarbituric acid. *Lab Delo*,1989:7:8-9.
42. Macer ML, Taylor HS. Endometriosis and infertility: a review of the pathogenesis and treatment of

- endometriosis-associated infertility. *Obstet Gynecol Clin North Am*,2012;39(4):535-49.
43. Meuleman C, Vandenabeele B, Fieuws S, *et al.* High prevalence of endometriosis in infertile women with normal ovulation and normospermic partners. *Fertil Steril*,2009;92(1):68-74. doi:10.1016/j.fertnstert.2008.04.056.
  44. Murphy AA. Clinical aspects of endometriosis. *Ann N Y Acad Sci*,2002;955:1-10.
  45. Olive DL, Pritts EA. Treatment of endometriosis. *N Engl J Med*,2001;345(4):266-75.
  46. Seracchioli R, Mabrouk M, Frasca C, *et al.* Long-term cyclic and continuous oral contraceptive therapy and endometrioma recurrence: a randomized controlled trial. *Fertil Steril*,2010;93(1):52-6. doi:10.1016/j.fertnstert.2008.09.052.
  47. Simoens S, Dunselman G, Dirksen C, *et al.* The burden of endometriosis: costs and quality of life of women with endometriosis treated in referral centres. *Hum Reprod*,2012;27(5):1292-9.
  48. Smets EM, Garssen B, Bonke B, De Haes JC. The Multidimensional Fatigue Inventory (MFI): psychometric qualities of an instrument to assess fatigue. *J Psychosom Res*,1995;39(3):315-25. doi:10.1016/0022-3999(94)00125-O.
  49. Szpak R, Bugała-Szpak J, Drosdzol A, Skrzypulec V. Health-related quality of life in women with endometriosis. *Wiad Lek*,2009;62(2):129-34.
  50. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*,1983;67(6):361-70. doi:10.1111/j.1600-0447.1983.tb09716.x.