Медицинская иммунология
2021, Т. 23, № 4,
стр. 941-948

Краткие сообщения
Short communications

Medical Immunology (Russia)/
Meditsinskaya Immunologiya
2021, Vol. 23, № 4, pp. 941-948

ЭФФЕКТИВНОСТЬ ИММУНОМОДУЛЯТОРОВ И АНТИОКСИДАНТОВ В КОРРЕКЦИИ ПАРАМЕТРОВ ИММУННОГО СТАТУСА ПАЦИЕНТОК С АДЕНОМИОЗОМ

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Резюме. Целью исследования явилось изучение эффективности использования иммуномодуляторов и антиоксидантов в коррекции параметров иммунного статуса у пациенток с аденомиозом. Обследовано 70 пациенток, среди которых 57 женщинам (основная группа), у которых по результатам комплексного клинического, ультразвукового и гистероскопического обследования был выставлен диагноз аденомиоз. Контрольную группу составили 23 гинекологически здоровые женщины. После верификации диагноза все пациентки ОГ получали стандартное лечение (СЛ) (клинические рекомендации МЗ РФ от 2016 года). Среди пациенток ОГ 19 женщин получали только СЛ (1-я подгруппа). 38 обследованных ОГ дополнительно к СЛ получали различные комбинации антиоксиданта, иммуномодулятора и мембранопротектора и были разделены на две подгруппы. Во вторую подгруппу вошли 20 больных дополнительно к СЛ получавших Натрия рибонуклеат; Гипоксен и фосфолипиды. В третью подгруппу вошло 18 пациенток дополнительно получавших Инозин + Никотинамид + Рибофлавин + Янтарная кислота; Меглюмина акридонацетат, и Глицирризиновую кислоту + фосфолипиды. Проводился анализ цитокинового статуса и системы комплимента на момент поступления и к 15-му дню наблюдения. Установленные нами у пациенток с аденомиозом увеличение в системной циркуляции содержания хемокинов и провоспалительных цитокинов (TNFα, IL-8, IL-1β, IL-6, IL-18) со снижением концентрации противовоспалительных цитокинов (IL-1ra, IL-4) отражает реакцию резидентных и рекрутированных клеток врожденного иммунитета на молекулярные паттерны, ассоциированные с повреждением. Выявленные изменения цитокинового статуса, активация системы комплемента, повышение кислородзависимой активности нейтрофилов периферической крови (повышенная продукция активных форм кислорода в результате респираторного взрыва) свидетельствует о наличии иммунного воспаления на системном уровне.

Недостаточная клинико-лабораторная эффективность СЛ в коррекции иммунных изменений обосновала использование в фармакологической терапии аденомиоза препаратов с иммуномодулирующими, антиоксидантными и мембранопротекторными свойствами, что было успешно использовано при лечении других заболеваний с аналогичными нарушениями. Не следует исключать и прямого положительного влияния использованных в работе препаратов на ангиогенез в очагах аденомиоза,

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Образец цитирования:

О.Ю. Иванова, О.В. Телегина, А.А. Конопля «Эффективность иммуномодуляторов и антиоксидантов в коррекции параметров иммунного статуса пациенток с аденомиозом» // Медицинская иммунология, 2021. Т. 23, № 4. С. 941-948.
doi: 10.15789/1563-0625-EOI-2045

For citation:

O.Yu. Ivanova, O.V. Telegina, A.A. Konoplya "Efficacy of immunomodulators and antioxidants in the correction of impaired immune status parameters in patients with adenomyosis", Medical Immunology (Russia)/Meditsinskaya Immunologiya, 2021, Vol. 23, no. 4, pp. 941-948.
doi: 10.15789/1563-0625-EOI-2045

DOI: 10.15789/1563-0625-EOI-2045

контролируемый на локальном уровне ангиогенными факторами роста и цитокинами, секретируемыми перитонеальными макрофагами, клетками эндометроидных гетеротопий и эндотелия. Нами выявлены оптимальные сочетания иммуномодуляторов и антиоксидантов в коррекции иммуного статуса пациенток с аденомиозом. Проведенное исследование показывает эффективность коррекции нарушенных параметром иммунного статуса пациенток с аденомиозом при комбинации стандартного лечения с антиоксидантными и иммуномодулирующими средствами.

Ключевые слова: аденомиоз, иммунный статус, иммуномодуляторы, антиоксиданты, эффективность лечения

EFFICACY OF IMMUNOMODULATORS AND ANTIOXIDANTS IN THE CORRECTION OF IMPAIRED IMMUNE STATUS PARAMETERS IN PATIENTS WITH ADENOMYOSIS

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Abstract. The aim of the study was to study the effectiveness of the use of immunomodulators and antioxidants in the correction of immune status parameters in patients with adenomyosis. 70 patients were examined, including 57 women (the main group), who were diagnosed with adenomyosis according to the results of a comprehensive clinical, ultrasound and hysteroscopic examination. The control group consisted of 23 gynecologically healthy women. After verification of the diagnosis, all patients with hypertension received standard treatment (SL) (clinical recommendations of the Ministry of Health of the Russian Federation from 2016). Among the female patients, 19 women received only SL (1st subgroup). 38 exhaust gases examined, in addition to SL, received various combinations of antioxidant, immunomodulator, and membrane protector and were divided into two subgroups. The second subgroup included 20 patients in addition to the SL receiving sodium ribonucleate; Hypoxene and phospholipids. The third subgroup included 18 patients who additionally received Inosine + Nicotinamide + Riboflavin + Succinic acid; Meglumine acridone acetate, and glycyrrhizic acid + phospholipids. The analysis of the cytokine status and the compliment system was performed at the time of admission and by the 15th day of observation. Detected changes of the cytokine status, complement system activation, increased oxygen-dependent activity of neutrophils in the peripheral blood (increased production of active oxygen forms as a result of respiratory burst) confirm the presence of immune inflammation on the systemic level. Insufficient clinical-laboratory efficacy of ST in the correction of immune changes has justified the use of drugs with immunomodulating, antioxidant, and membrane protective properties in the pharmacological therapy of adenomyosis, which have been successfully used in the treatment of other diseases with similar disorders.Optimal combinations of immunomodulators and antioxidants in the correction of the immune status of patients with adenomyosis were revealed. The study performed demonstrates the efficacy of correcting immune status parameters in patients with adenomyosis when the standard treatment is combined with antioxidant and immunomodulating agents.

Keywords: adenomyosis, immune status, immunomodulators, antioxidants, treatment effectiveness

Introduction

According to the WHO definition, endometriosis is a dishormonal, immune-dependent, and genetic pathological process, wherein overgrowth of the benign tissue morphologically and functionally resembling endometrium occurs outside the uterine cavity [1]. There is every reason to believe that the endometrial tissue located in atypical places may acquire antigenic properties, which promotes development of body systemic immune reaction. Potential local immune "failures", acting as specific pathogenetic links of endometriosis, include disorders of: 1) cellular pro-

liferation and localization control; 2) regulation of the apoptosis process; 3) neoangiogenesis mechanisms [3, 4, 7]. The aforementioned facts allow to suppose that adenomyosis conditions are accompanied not only by local, but also systemic changes characterized by the development of chronic systemic inflammatory response, impaired lipid peroxidation, antioxidant protection factors, which leads to the formation of endothelial dysfunction, impaired microrheology, hypoxia, and dysmetabolism [6, 12].

The purpose of the study was to assess efficacy of immunomodulators in correction of immune status parameters in patients with adenomyosis.

Materials and methods

70 patients that underwent examination at the SHI Lipetsk Regional Perinatal Center in 2014-2017 were investigated. The main group included 57 females diagnosed with adenomyosis according to the results of complex clinical, ultrasound, and hysteroscopic examination. 23 gynecologically healthy females were included into the control group.

Patients with exacerbated extragenital pathology, acute bacterial and viral infections, hematological diseases, gastric and duodenal peptic ulcers, necrotic ulcerative colitis, oncological diseases, as well as those receiving anticoagulants, antiaggregants, non-steroid anti-inflammatory drugs, were not included into the study.

Along with the common clinical and laboratory examination (the Order of the Ministry of Health of Russia dated 1 November 2012 No. 572n) on day 3-7 of the menstrual cycle, all patients underwent ultrasound examination of pelvic organs with subsequent hysteroscopic examination in MG patients. After diagnosis verification, all MG patients were administered with standard treatment (ST) [1], presuming oral Dienogest 2 mg/day for three months. Among MG patients, 19 females took only ST (Subgroup 1). 38 examined MG patients, in addition to ST, were administered with different combinations of antioxidant, immunomodulator, and membrane protector; all subjects were divided into two subgroups. The second subgroup included 20 patients, that (in addition to ST) were administered with Sodium ribonucleate (Ridostin) 1.0 i/m every 48 hours No. 5; oral Hypoxenum 1 tab. TID No. 30; and phospholipids (Essentiale Forte H) 2 capsules 3 TID during meals No. 10. The third subgroup included 18 patients that were additionally administered with Inosine + Nicotinamide + Riboflavin + Succinic acid (Cytoflavin) i/v drip 10 ml BID for 7 days; Meglumine acridoneacetate (Cycloferon) 3 tab. orally every 24 hours No. 10; and Glycyrrhizinic acid + Phospholipids (Phosphogliv) i/v 10 ml every 24 hours No. 7. All drugs were administered according to the guidelines provided in the Federal Guidelines on the Use of Drug Products (formulary system) [2].

Laboratory blood tests were performed when patients were admitted into the inpatient department as well as on day 15. Results obtained in the control group were considered as conditional normal values. Cytokines (TNFα, IL-1β, IL-6, IL-8, IFNγ, IL-2, IL-17, IL-18, G-CSF, IL-4, IL-10, IL-1ra) were detected by using the enzyme-linked immunosorbent assay with the use of Vektor-Best JSC kits (Russia); components of the complement system (C3, C3a, C4, C5, C5A) and factor H – with the diagnostic kit manufactured by Cytokine Ltd (Russia). C1-Inhibitor activity was determined using the chromogenic method based on assessing C1-esterase inhibition. Registration was performed by using the "Sunrise" microplate photometer, Tecan (Austria).

Phagocytic activity of polymorphonuclear leukocytes after their isolation from peripheral blood samples on the density gradient Ficoll-Urographin (d = 1.077) was evaluated, determining the phagocytic index (PI), phagocytic number (PN), and phagocytosis activity index (PAI) by using general methods. The activity of oxygen-dependent neutrophil systems was evaluated on the PD 303 SApel spectrophotometer (Japan) according to the nitroblue tetrazolium test (NBT-test), spontaneous and zymosan-induced (NBT-sp., NBT-st.), neutrophil stimulation index and functional reserve (NSI, NFR).

All clinical, clinical-instrumental examinations, and pharmacological correction were performed after receiving the patient informed consent for use of biomaterials from therapeutic and diagnostic measures related to diseases for scientific-research purposes.

Statistical processing of study results was performed by using analysis of variance criteria with the calculation of means (M) and mean arithmetic error (m) by using the Microsoft Excel 2010 software package. Significance of differences was evaluated by using the U-criteria. Differences with $p < 0.05$ were considered significant.

Results and discussion

All patients were randomized by age (34.7±2.6 years), body mass index (not more than 26 kg/m^2). Patients from the main group in 78% observations complained of dysmenorrhea, 72% – dyspareunia; 65% – chronic pelvic pain, 48% – inability to conceive within the year of regular sex life without using contraception methods. The age of menarche in groups did not significantly differ and was 13±1.4 years ($p_{1-2} > 0.05$). The volume of menstrual blood loss in MG was 134±10.2 mm, which was 3 times larger

compared to CG (43.2±2.3 ml) ($p_{1-2} < 0.05$). Ferritin values among CG patients were 84.6±4.9 ng/ml, which was significantly higher compared to MG results (10.6±1.2 ng/ml). The comparative analysis of contraceptive methods showed that 2/3 (64%) of CG patients underwent the hormonal method, which significantly exceeded the value of this parameter in MG patients (15%). Analysis of pregnancy and labor parity demonstrated that the overwhelming majority of CG patients (72%) had a history of one or more pregnancies, and in 78% cases the delivery was vaginal. 84% CG females did not have intrauterine manipulations. Every third MG patient (31.2%), had delivery via the cesarean section; 86% patients underwent instrumental curettage of the uterine cavity due to pregnancy termination.

The ultrasound study results have shown that 94.6% gynecologically healthy females demonstrate the uniformity of myometrium structure, clear visualization of the basal layer, smooth endometrial contours that correspond to the first phase of the menstrual cycle. In 85% of MG patients, the following signs were detected: non-uniform thickness and structure of the basal layer, asymmetry of the anterior and posterior uterine walls, presence of increased and decreased echogenicity zones that cover more than 2/3 of the myometrium. In 15% observations, non-uniform and irregular endometrial contours were found in combination with multiple hypo- and

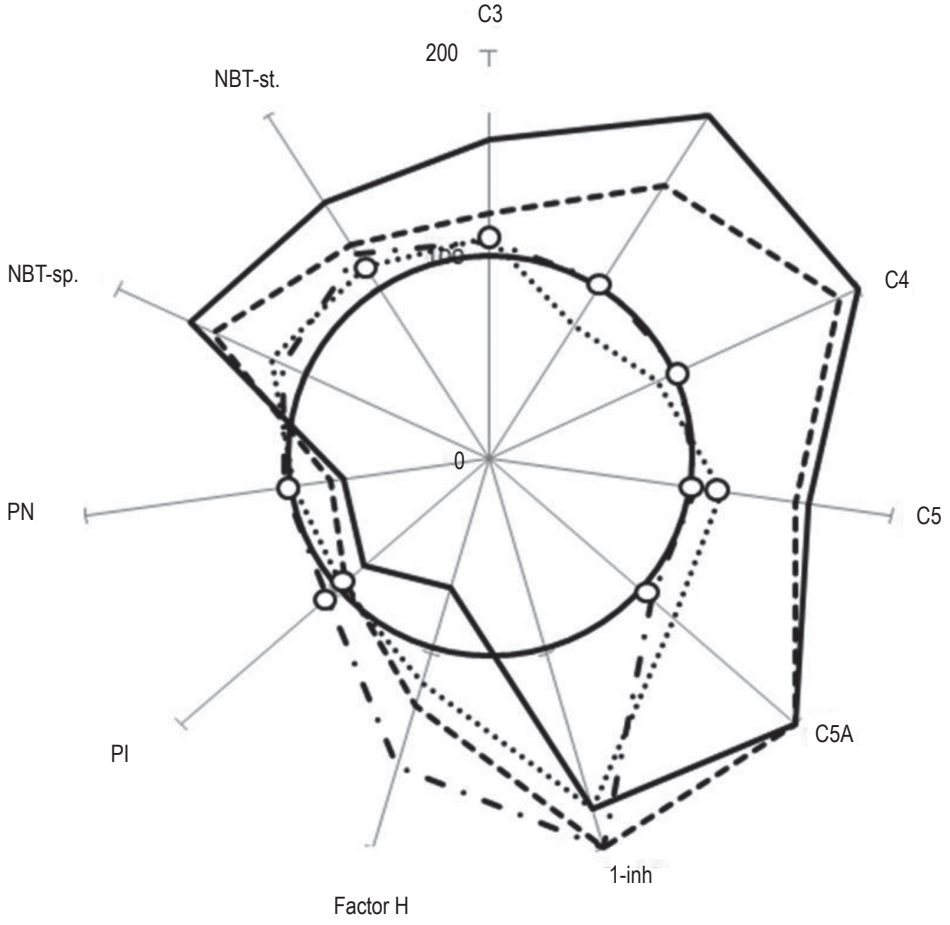

Figure 1. Complement system and functional metabolic activity of blood neutrophils in patients with adenomyosis before and after treatment

Note. 1. Circumference radius, parameters in healthy volunteer donors (CG);
2. — — ·, parameters in patients with adenomyosis (MG);
3. ·····, parameters in patients with adenomyosis after ST (Subgroup 1);
4. ·····, parameters in patients with adenomyosis after ST + Ridostin + Hypoxene + Essentiale H (Subgroup 2);
5. — · —, parameters in patients with adenomyosis after ST + Cycloferon + Cytoflavin + Phosphogliv (Subgroup 3);
6. ○, $p < 0.05$ between parameters relative to MG.

TABLE 1. LEVELS OF BLOOD PLASMA CYTOKINES IN PATIENTS WITH ADENOMYOSIS BEFORE AND AFTER TREATMENT

Parameters	Units of measurement	1	2	3	4	5
		Healthy females	Patients with adenomyosis			
			Before treatment	Standard treatment	ST + Ridostin + Hypoxene + Essentiale H	ST + Cycloferon + Cytoflavin + Phosphogliv
TNFα	pg/ml	3.3±0.2	8.40±0.18* 1	5.20±0.21* 1, 2	3.90±0.22* 2, 3	3.1±0.2* 2, 3
IL-1β	pg/ml	1.90±0.21	8.30±0.24* 1	6.3±0.5* 1, 2	4.90±0.32* 1-3	3.4±0.4* 1-4
IL-6	pg/ml	5.80±0.21	22.90±1.87* 1	14.60±2.17* 1, 2	10.10±1.6* 1-3	4.70±0.23* 1-4
IL-8	pg/ml	5.20±0.12	37.7±2.1* 1	24.8±1.8* 1, 2	14.3±1.3* 1-3	8.10±0.87* 1-4
IL-18	pg/ml	291.4±22.5	409.9±23.6* 1	367.9±21.4* 1, 2	371.5±19.1* 1, 2	309.9±18.5* 2-4
IL-4	pg/ml	10.00±0.45	7.5±0.6* 1	7.5±1.1* 1	7.70±0.45* 1	15.45±0.47* 1-4
IL-10	pg/ml	3.70±0.21	4.1±0.2	6.60±0.34* 1, 2	8.40±0.42* 1-3	9.50±0.75* 1-3
IL-1ra	pg/ml	370.0±17.9	43.9±9.2* 1	277.6±15.0* 1, 2	349.5±33.1* 2, 3	463.67±14.90* 1-4
IFNγ	pg/ml	2.4±0.1	15.3±1.4* 1	13.3±2.2* 1	6.10±0.42* 1-3	5.90±0.44* 1-3
G-CSF	pg/ml	73.6±1.8	112.5±12.1* 1	123.2±5.9* 1	119.5±6.8* 1	90.33±3.11* 1-4
IL-2	pg/ml	0.60±0.56	6.20±0.21* 1	5.9±0.8* 1	4.1±0.8* 1, 2	2.60±0.42* 1-4

Note. *, $p < 0.05$.

hyperechogenic myometrial inclusions spreading to the depth of no more than 1/3 myometrium. Clinical and ultrasound signs in 92% observations were confirmed by the hysteroscopy data.

Blood plasma tests in patients with adenomyosis have confirmed the increased concentration of proinflammatory cytokines (TNFα, IL-1β, IL-6, IL-8, IL-18) and decreased levels of anti-inflammatory (IL-4 and IL-1ra) cytokines. The levels of IFNγ, IL-2, and the G-CSF growth factor were higher than those in healthy donors; the concentration of anti-inflammatory cytokine IL-10 remained unchanged. After ST, the levels of all examined anti-inflammatory cytokines and IL-1ra were slightly closer to healthy donor parameters; the IL-10 concentration was increased as a compensatory measure, whereas levels of other cytokines remained unchanged. Introduction of Ridostin, Hypoxene, and Essentiale Forte H (Subgroup 2) additionally normalized TNFα and IL-1ra concentrations, corrected IL-1β, IL-6, IL-8, IFNγ, IL-2 levels to a larger extent, and even more increased the IL-10 level; the level of other cytokines remained unchanged. The inclusion of Cycloferon, Cytoflavin, and Phosphogliv into ST (Subgroup 3) compared to the prior drug combination additionally normalized the IL-18 concentrations, increasing in a compensatory manner the level of analyzed anti-inflammatory cytokines higher than control group values, and to a larger extent corrected IL-1β, IL-6, IL-8, G-CSF, IL-2 levels (Table 1).

On hospital admission, the complement system activation (increased levels of all analyzed components) was observed in the blood plasma of the main group patients, with the opposite changes of its inhibitors

(C1-inhibitor increase, H factor decrease). ST adjusted the concentration of complement components closer to control parameters (except for C5), increasing the level of inhibitors higher than those in donors. The administration of Ridostin, Hypoxene, and Essential Forte H (Subgroup 2) normalized the levels of C3a, C4, and C5A complement components, strongly adjusting concentrations of C3 and C5 components to those in control group. The use of Cycloferon, Cytoflavin, and Phosphogliv (Subgroup 3) together with ST additionally normalized the C5 component concentration and significantly increased the level of complement system inhibitors compared to control values (Figure 1).

The analysis of functional-metabolic activity (FMA) of neutrophils in patients with adenomyosis has revealed decreased phagocytosis activity and intensity parameters (PI, PN, and PAI) as well as increased parameters of oxygen-dependent systems (NBT-sp., NBT-st., NFR). ST normalized two FMA parameters (PI and NFR) and corrected PAI; other parameters of neutrophil FMA remained unchanged. In the second subgroup, parameters of phagocytic (PN and PAI) and oxygen-dependent (NBT-st.) activity were additionally normalized. In the third subgroup, NST-sp. also normalized, and PAI increased (Figure 1).

While performing a quantifiable comparison for the number of impaired immune status parameters, it has been demonstrated that before treatment onset, 97.9% of all parameters were changed compared to controls. After the standard treatment, 18.4% parameters became normalized, 34.7% were corrected to healthy donor magnitude, but not to their values, whereas 46.9% remained at the level found at treatment onset. After using Ridostin, Hypoxenum, and Essentiale Forte H as a part of ST, 44.9%, 40.8%, and 14.3% of parameters analyzed were normalized, corrected, and remained unchanged, respectively. After including Cycloferon, Cytoflavin, and Phosphogliv addition into ST, 69.4% immune status parameters were normalized, and 30.6% parameters were corrected.

The majority of studies devoted to the role of immune mechanisms in the pathogenesis of adenomyosis reveal the decreased activity of natural killer cells, increased activity of serum and peritoneal fluid proinflammatory cytokines , decreased ability of white blood cells for interferon production, increased amount of peritoneal macrophages as well as subsequent proinflammatory cytokine and chemokine secretion both in the peritoneal fluid and in endometroid implants [4, 7, 10, 11].

Increased levels of serum chemokines and proinflammatory cytokines (TNFα, IL-8, IL-1β, IL-6, IL-18) along with decreased concentration of proinflammatory cytokines (IL-1ra, IL-4) in patients with adenomyosis reflect the reaction of resident and recruited innate immune cells to damage-associated molecular patterns [13].

High IFNγ level (effector of the cellular immune response of inflammatory type) and prolonged preservation of the increased serum IFNγ/IL-4 ratio not decreasing after performed ST suggest about activation of IFNγ-produced NK-cells as a part of type 1 innate lymphoid cells (ILC1), which promote polarization of T-cell differentiation towards Type 1 T-helpers (Th1) followed by activating macrophages that express enzymes for reactive oxygen species formation, activation of NO-synthetase with NO formation. A significantly increased level of the colony-stimulating factor G-CSF and IL-2 which also does not decrease after the ST performed, may activate mature neutrophils and support growth of both mixed granulocytic-monocytic lineage colonies as well as separate granulocyte and monocyte/macrophage colonies, whereas IL-2 markedly able to stimulate activity of almost all cytotoxic cell clones activates monocytes and macrophages, thus increasing production and secretion of chemokines, proinflammatory cytokines, colony-stimulating factors.

Detected changes in the cytokine profile, complement system activation, increased neutrophilic oxygen-dependent activity in the peripheral blood (increased production of reactive oxygen species as a result of respiratory burst) confirm ongoing systemic immune inflammation.

Insufficient clinical-laboratory efficacy of ST in the correction of immune changes has justified the use of drugs with immunomodulating, antioxidant, and membrane protective properties in the pharmacological therapy of adenomyosis, which have been successfully used in the treatment of other diseases with similar disorders.

Pharmacological drugs Hypoxene and Cytoflavin that were used in the current study exert antioxidant and energy-correcting properties, minimize oxidative stress signs found in endometriosis, prevent development of free radical oxidation and activation of lipid peroxidation, thus stabilizing the phospholipid layer of damaged cell membranes, including immune cells. Substituting and embedding into cellular membranes, phosphatidyl cholines of the Essentiale H and Phosphogliv can restore membrane functional activity and intracellular metabolism. Ridostin and Cycloferon belong to immunomodulators, which function to correct immune system functioning manifested by enhancing of weakened immunity and inhibition of stimulated immunity. It is also possible that they may normalize complement system, cells producing cytokines and chemokines, function

of phagocytes, which are important suppliers of non-oxidated radicals. It is logical to presume that detection and correction of immune disorders can have an impact on severity of adenomyosis symptoms. A more significant efficacy of combining Cycloferon, Cytoflavin, and Phosphogliv might potentially be related to the presence of a trisodium glycyrrhizinic acid salt in Phosphogliv; this substance exhibits immunomodulating properties, primarily able to activate natural killers (NK-cells) and T-lymphocytes. Cytoflavin also contains succinic acid, inosine, vitamins PP and B2; these thoroughly selected and balanced components have self-potentiating metabolic and energy-correcting effects.

it might not be ruled out that the drugs in the study could exert direct positive impact on the angiogenesis in adenomyosis foci that is controlled at the local level by angiogenic growth factors and cytokines secreted by peritoneal macrophages, cells of endometroid heterotopies and endothelium.

Thus, the study performed demonstrates the efficacy of correcting immune status parameters in patients with adenomyosis by combining the standard treatment with antioxidant and immunomodulating agents.

Authors are grateful to the rector of FSBEI HE KSMU, Ministry of Health of Russia, Professor Viktor Anatolievich Lazarenko, Doc.Med.Sci., and the authorities of the State Healthcare Institution "Lipetsk Regional Perinatal Center", peronal acknowledgement to the Chief Physician Larisa Vyacheslavovna Zakhryapina for allowing perform the study.

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Поступила 29.04.2020
Отправлена на доработку 17.05.2020
Принята к печати 31.05.2021

Received 29.04.2020
Revision received 17.05.2020
Accepted 31.05.2021