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Pathogenetic rationale for the use of immunomodulating and systemic enzyme therapy in treatment of nulliparous women with endometrioid ovary tumors

Патогенетическое обоснование применения иммуномодулирующей и системной энзимотерапии в комплексном лечении нерожавших женщин с опухолеподобными образованиями яичников

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Abstract

The modern approach to the treatment options and assessment of its effectiveness in nulliparous women with endometrial cysts is build on optimal pathogenetically substantiated therapy based on features of the disease not only on the system, organ and tissue levels, and taking to consideration the cellular and molecular features of the functioning of the body. Therefore, the aim of our work was to determine the effectiveness of various treatment regimens for nulliparous women with ovary tumor-like formations based on features of the immune status.

In the study of immune status in nulliparous women with endometrioid tumor-like formations of ovaries (n = 30) was the inconsistency of the phagocytic system, the imbalance of T- and B-cell immunity, dysimmunoglobulinemy. Based on the identification of changes, the patients were assigned with pathogenetically

substantiated combination therapy that included, in addition to conventional treatment regimens, the appointment of immunomodulators and systemic enzyme therapy. Treatment results show the full normalization of phagocytic, T- and B-cells and partially humoral systems.

Key-words: immunomodulating therapy, nulliparous women, tumor-like endometrioid ovarian formation.

Резюме

Современный подход выбора варианта лечения и оценки его эффективности у нерожавших женщин с эндометриоидными кистами состоит в формировании оптимальной патогенетически обоснованной терапии с учетом особенностей заболевания не только на системном, органном и тканевом уровнях, а и с учетом клеточно-молекулярных особенностей функционирования организма. В связи с этим целью нашей работы являлось выявление эффективности применения различных схем лечения нерожавших женщин с опухолеподобными образованиями яичников с учетом особенностей иммунного статуса.

При исследовании иммунного статуса у нерожавших женщин с опухолеподобными эндометриоидными образованиями яичников (n=30) была выявлена несостоятельность фагоцитарной системы, дисбаланс Т- и В-клеточного иммунитета, дизиммуноглобулинемия. Основываясь на выявленных изменениях, пациенткам была назначена патогенетически обоснованная комбинированная терапия, включающая, помимо традиционной схемы лечения, назначение иммуномодуляторов и системной энзимотерапии. Результаты лечения свидетельствуют о полной нормализации показателей фагоцитарной, Т- и В-клеточной и, частично, гуморальной систем.

Ключевые слова: иммуномодулирующая терапия, нерожавшие женщины, опухолеподобные эндометриоидные образования яичников.

Despite the numerous stories of study of hyperproliferative diseases, in recent decades in the world there has been an increase of incidence of hyperplastic processes of endometrium, uterine and ovaries [1].

Analysis of the latest scientific evidence on the effectiveness of treatment for ovary endometriosis shows that there is no "gold standard" in this matter [2].

The most common treatment regimen of external genital endometriosis is a surgical removal of heterotopic lesions in the ovaries, but such treatment is not always possible to recover the specific functions of the female body [3], the more so now accumulated more and more evidence that surgical treatment of endometrial ovary cysts negatively affects ovarian reserve [4 - 8], and may cause relapse process [9].

Most clinicians prefer the combined therapy: the first stage is the surgical removal of foci of heterotopic endometrium, and the second step is the hormonal therapy aimed the suppression of the menstrual function [10, 11]. However, these

recent studies indicate that hormone replacement therapy is highly effective against pain, but not for women of the reproductive function [12, 13]. The results of treatment indicate a lack of effectiveness in reducing the frequency of relapses, as well as pregnancy [3], which indicates the need for new treatment.

The modern approach of treatment options and assessment of its effectiveness in nulliparous women with endometrial cysts is to build an optimal pathogenetically substantiated therapy based on features of the disease not only on the system, organ and tissue levels, and taking into the consideration the cellular and molecular features of the functioning of the body [13].

The aim of our work was to determine the effectiveness of various treatment regimens for nulliparous women with ovary tumor-like formations considering features of the immune status.

Materials and methods

We examined 80 women aged 17-40 years.

The first group (control group) consisted of 50 healthy non-pregnant women of reproductive age, who at the time of the examination had no signs of gynecological and chronic somatic pathology, administered to the facility for the choosing of contraception.

The second group (comparison group) formed of 30 women with established ovary endometriosis stage I-II, who did not give birth for various reasons (social, religious, unsettled personal life, etc.). Surgical and conservative treatment in this group have not been conducted.

Group 2 women were divided into two subgroups based on their ongoing therapy. Group 2A - consisted of 15 women who did not give birth to a variety of reasons, with a confirmed diagnosis of endometrioid ovary cyst treated with conventional hormone therapy with Dienogest.

Group 2B - consisted of 15 women who did not give birth to a variety of reasons, with a confirmed diagnosis of endometrioid ovary cyst treated with comprehensive treatment. Comprehensive treatment consisted of supplemental drugs with immunomodulating and metabolic action: Likopid and Vobenzim.

All patients were conducted physical examination, pelvic examination, transvaginal ultrasound of the pelvic organs and the immune status of the study.

For nonspecific immunological reactivity studies were conducted determination of phagocytic activity of blood monocytes and neutrophils, based on the method of determining the absorbent capacity and digesting them with respect to the microbial culture test after preincubation joint (according to H. Frimel) [14].

Determination of oxygen-dependent metabolism of neutrophils (NBT-test) and functional reserve of cells (stimulated NBT-test) was carried out by M.E. Viksman and A.N. Mayansky [15].

Determination of the activity of myeloperoxidase (MP) of neutrophils was performed by the modified method cytochemically by R.P. Nartsissova [16].

Determination of cationic proteins (CP) in neutrophils was performed by a

bromophenol blue by M.G. Shubych [17].

Determination of subpopulations of lymphocytes was carried out by using monoclonal antibodies against antigens CD_3^+ (total number of T-lymphocytes), CD_4^+ (T-helper), CD_8^+ (T-suppressors), CD_{16}^+ (NK-cells), CD_{19}^+ (B cells) produced by NPO "Granum" (Kharkiv).

Determination of humoral immunity Ig A, Ig M, Ig G was performed by using monospecific serums against these immunoglobulins by the method of Manchini G. [18].

Statistical data processing performed using computer software package STATISTICA (StatSoftStatistica v.6.0).

Results of research

Study conducted by a number of authors point to the direct involvement of immune mechanisms in the pathogenesis of the ovaries, which coincides with our results [19, 20]. Thus, in the study of the immune status in nulliparous women with ovarian tumor-like formations, we have identified changes in the immune status, which were characterized by incomplete phagocytosis due to lower functional-metabolic reserve, reduced microbicidal capacity imbalance of cellular and humoral immunity (reduction in the number of T-lymphocytes and a sharp increase in the number of B-lymphocytes) disimmunoglobulinemy. In this regard, many authors point to the need for the complex treatment of immunomodulators, however, these drugs for various reasons are not always used, preferring the more traditional methods of treatment. One common cause of this approach is to apply the previously inadequate immunotherapy, leads to deeper disturbances.

Based on the above, we carried out a comparative analysis of the immune status of women treated with traditional and complex treatment, the main component of which is an immunocorrective therapy.

In assessing of functional parameters characterizing metabolic status of neutrophils in group 2A - showed an increase in the functional activity comparing with the control group up to 12 % (30 ') and 85 % (120'), whereas with respect to the comparison group - it was reduced by 10 % (30 ') and 19 % (120') accordingly (table 1).

Table 1

Condition of functional-metabolic status of neutrophils in nulliparous women with endometriosis, depending on the applied treatment

Me (75%Q – 25%Q = RQ)

Indicator, values	Group 1 (n = 50)	Group 2 (n = 30)	Group 2 A (n = 15)	Group 2 B (n = 15)
NPI on 30 min, %	67,5 (74,2 – 49,1 = 25,1)	60,1 (82,6 – 37,9 = 44,7)	62,7* (71,0 – 42,4 = 28,6)	64,5 (83,2 – 47,3 = 35,9)

NPN on 30 min, c.u.	3,1 (6,5 – 1,3 = 5,2)	3,9* (5,8 – 1,4 = 4,4)	3,5 (4,9 – 1,8 = 3,1)	3,2 (4,7 – 1,6 = 3,1)
NPI on 120 min, %	58,4 (68,3 – 39,8 = 28,5)	50,4 (75,1 – 30,8 = 44,3)	52,7 (62,1 – 29,8 = 32,3)	56,3** (67,2 – 31,6 = 35,6)
NPN on 120 min, c.u.	2,7 (4,8 – 1,9 = 2,9)	6,2* (7,2 – 0,9 = 6,3)	5,0*** (5,9 – 2,1 = 3,8)	3,7** (5,1 – 2,4 = 2,7)
NBTsp, c.u.	1,2 (1,3 – 1,0 = 0,3)	1,2 (1,5 – 0,9 = 0,6)	1,2 (1,7 – 0,6 = 1,1)	1,2 (2,2 – 0,5 = 1,7)
NBTst, c.u.	1,3 (2,2 – 0,8 = 1,4)	1,0 (1,9 – 0,5 = 1,4)	1,1 (1,8 – 0,4 = 1,4)	1,3 (2,1 – 0,6 = 1,5)
CP, c.u.	2,2 (3,0 – 1,4 = 1,6)	2,0 (2,8 – 0,7 = 2,1)	2,0 (2,6 – 0,6 = 2,0)	2,1 (2,9 – 0,7 = 2,2)
MP, c.u.	2,3 (3,4 – 0,7 = 2,7)	1,6* (2,0 – 0,3 = 0,7)	1,7* (2,3 – 1,0 = 1,3)	2,1 (2,8 – 0,6 = 2,2)

Notes: * - statistically significant differences ($p < 0,05$) relative to the control group, ** - Statistically significant differences ($p < 0,05$) relative to Group 2.

Indicators characterizing absorptive (30 ') and digestive (120') ability were reduced relative to the control group at 7 % and 10 %, and increased by 4 % and 4 % relative to the comparison group (which is statistically insufficient, but clinically significant). Indicators of NBTsp-test, characterize functional and metabolic reserve of neutrophils, did not change, whereas indicators of NBTst-test were reduced by 15 % relative to the values of the control group and increased by 24 % in relation to the values of the comparison group.

Indicators of microbicidal activity: cationic proteins (CP) and myeloperoxidase (MP) were reduced with respect to the values of the control group by 9 % and 26 %, CP indicators matched the values in comparison group, MP - were increased by 6 %, which is not statistically significant, but clinically significant.

When assessing cellular immunity in Group 2A women was shown a reduction of T-cell level: CD_3^+ , CD_4^+ , CD_8^+ , and NK-cells - CD_{16}^+ - 5 %, 11 %, 8 %, 9 %, relative values of the control group, and increased by 8 %, 6 %, 12 % and 4 % - relative to the values of the comparison group, in both cases, that is not statistically significant but clinically significant (table 2).

Assessing humoral immunity in Group 2A women shown an increase in the number of B-lymphocytes - CD_{19}^+ 16 % relative to a control group and a 6 % decrease relative to the comparison group (table 3).

The concentration of Ig A was reduced by 11 %, while the Ig M, Ig G – corresponded to the values of the control group. There was an increase of Ig A concentration by 33 %; reducing the concentration of Ig M by 15 %, while the

concentration of Ig G corresponded to the value of the comparison group.

Thus, the presence of immune disorders, remaining after conventional therapy by Dienogest, proved the necessity of using immunomodulators, which is pathogenetically substantiated in this case.

Table 2

Indicators of T-cell immunity in nulliparous women with endometriosis, depending on the applied treatment

Me (75%Q – 25%Q = RQ)

Indicator, values	Group 1 (n = 50)	Group 2 (n = 30)	Group 2 A (n = 15)	Group 2 B (n = 15)
CD ₃ ⁺ , %	63,7 (67,1 – 59,8 = 7,3)	56,2 (60,0 – 49,3 = 10,7)	60,7 (71,4 – 56,2 = 15,2)	65,3* (72,7 – 57,1 = 15,6)
CD ₄ ⁺ , %	38,7 (44,2 – 31,8 = 12,4)	32,4 (42,8 – 23,6 = 19,2)	34,4 (45,6 – 19,9 = 25,7)	37,2 (48,0 – 23,4 = 24,6)
CD ₈ ⁺ , %	25,6 (39,0 – 21,3 = 17,7)	20,9 (39,3 – 17,5 = 21,8)	23,5* (38,8 – 15,7 = 23,1)	24,9 (39,6 – 19,2 = 20,4)
CD ₁₆ ⁺ , %	16,5 (24,6 – 11,9 = 12,7)	14,3* (21,5 – 9,4 = 12,1)	15,0** (20,4 – 10,1 = 10,3)	16,0 (23,1 – 12,8 = 10,3)

Notes: * - statistically significant differences (p <0,05) relative to the control group,

** - Statistically significant differences (p <0,05) relative to Group 2.

Considering the features of the immune status of the study group of women, we found it necessary to extend the standard treatment, the purpose of immunoregulatory drugs, the main point of application which would serve as phagocytes, and then their action switched to the T-cell system.

In this case, the drug of choice was Licopid - a synthetic drug, which is the main structural component of the cell wall of almost all known bacterias, which met all the requirements set by us. The drug was administered at a dose of 10 mg 2 times a day sublingual for 21 days.

Appointment of Vobenzym (a combination of high-protease) enhances the effectiveness of therapies and reduces the risk of adverse effects associated with hormonal drugs. The drug was administered 5 tablets three times a day orally for two months.

In assessing the indicators characterizing the functional and metabolic status of

neutrophils in Group 2B, - changes in the functional activity of neutrophils at 30' have been identified, while the 120' was an increase by 37 % on the value of the control group. With respect to the comparison group scores were reduced by 18 % and 40 %, respectively (table 1).

Showed a decrease absorptive (30') and digestive (120') ability of neutrophils relatively to the control group by 7 % and 5 % (which was not statistically significant, but clinically significant) and an increase by 7 % and 12 % relative to the comparison group.

The indicators characterizing the functional-metabolic reserve of neutrophils – NBTsp-test - to respect the values of the control group and the comparison group, the indicators NSTst test - corresponded the values of the control group, but higher than the value of the comparison group at 30 %, respectively.

Indicators of microbicidal system - CP and MP - were reduced relative to the control group by 4 % and 8 % (which was not statistically significant, but clinically significant) and increased relatively to the comparison group by 5 % and 31 %, respectively.

Number of T-lymphocytes with a phenotype: CD_3^+ , CD_4^+ , CD_8^+ , and NK-cells - CD_{16}^+ values substantially matched control, but values higher than the comparison group of 16 %, 15 %, 19 % and 21 % respectively (table 2).

The number of B-lymphocytes with CD_{19}^+ phenotype exceeds control values at 5 %, but was reduced by 15 % relatively to the values of the comparison group (table 3).

The concentration of Ig M and Ig A was reduced relatively to the control group and by 5 % to 9 % (which is not statistically significant but clinically significant), Ig G concentration was not different from control values. In relation to the values of the comparison group showed an increase in the concentration of Ig A by 42 % and reducing of the concentration of Ig M and G by 13 % and 4 %, respectively.

Table 3

Indicators of humoral immune system in nulliparous women with endometriosis, depending on the applied treatment

Me (75%Q – 25%Q = RQ)

Indicator, values	Group 1 (n = 50)	Group 2 (n = 30)	Group 2 A (n = 15)	Group 2 B (n = 15)
CD_{19}^+ , %	17,2 (23,1 – 15,6 = 7,5)	21,3* (32,9 – 17,1 = 15,8)	20,0* (30,1 – 16,8 = 13,3)	18,1** (26,4 – 14,7 = 11,7)
Ig A, g/l	1,8 (2,3 – 0,9 = 1,4)	1,2 (1,5 – 0,6 = 0,9)	1,6** (2,3 – 0,9 = 1,4)	1,7 (2,5 – 1,0 = 1,5)
Ig M, g/l	1,1	1,3	1,1	1,0

	(2,5 – 0,4 = 2,1)	(2,2 – 0,8 = 1,4)	(2,0 – 0,5= 1,5)	(2,1 – 0,4 = 1,7)
Ig G, g/l	10,2 (13,1 – 6,7 = 6,4)	10,7 (14,0 – 5,9 = 8,1)	10,5 (13,4 – 6,8 = 6,6)	10,3** (13,5 – 6,1 = 7,4)

Notes: * - statistically significant differences ($p < 0,05$) relative to the control group,
** - Statistically significant differences ($p < 0,05$) relative to Group 2.

Using the therapy proposed by us with Licopid and Vobenzym number of T-lymphocytes with a phenotype CD_3^+ , CD_4^+ , CD_8^+ recovered to physiological values, decreased the number of B-cells with the phenotype CD_{19}^+ , moreover was observed activation of neutrophils, increasing of phagocytic index, completeness of phagocytosis, a gradual increase in the concentration of Ig A.

Thus, the effect of the proposed method of treatment achieved by exposure to one of the major factors in the pathogenesis of tumor-like endometrioid ovarian formations and by appointment of Licopid combined with Vobenzym, that led to the normalization of immune status and allowed to recommend the scheme for the treatment of nulliparous women with endometrioid tumor-like ovary formations.

Conclusions

1. On the pre-treatment stage in nulliparous women with endometrioid tumor-like ovary formations were identified changes in the immune system, manifested by failure of phagocytic system (incomplete phagocytosis and functionally deficient metabolic reserve), an imbalance of T- and B-cell units, disimmunoglobulinemy, that indicated a direct participation of immune mechanisms in the pathogenesis of the disease.

2. Normalization of cellular and humoral parameters of innate and adaptive immunity, occurring after a comprehensive therapy, confirms the validity of pathogenic inclusion in the traditional regimen of drugs with immunomodulative and antioxidant effects, which will significantly improve the quality of life of patients.

Reference in original

1. Адамян Л. В. Эндометриозы / Адамян Л. В., Кулаков В. И., Андреева Е. Н. – [2-е изд.]. – М.: Медицина, 2006. – 416 с.

2. Костючек Д. Ф. Анализ эффективности дооперационной консервативной гормональной терапии при эндометриозе яичников / Д. Ф. Костючек, Е. Н. Дурасова, В. А. Печеникова // Актуальные проблемы медицины и биологии: материалы научно-практической конференции. – СПб, 2010. – С. 49 – 50.

3. Павлов Р. В. Иммунологические критерии раннего прогнозирования рецидивов наружного генитального эндометриоза / Р. В. Павлов, М. С. Кундохова // Медицинский вестник Северного Кавказа. – 2011. – № 1. – С. 39 – 43.

4. Серебренникова К. Г. Современная медикаментозная терапия опухолевидных образований и ретенционных кист яичников / К. Г. Серебренникова, Е. П. Кузнецова // *Фундаментальные исследования*. – 2011. – № 5. – С. 218 – 223.
5. Impact of ovarian endometrioma on assisted reproduction outcomes / S. Gupta, A. Agarwal, R. Agarwal [et al.]. // *Reprod. Biomed. Online*. – 2006. – № 13. – С. 349 – 360.
6. Garcia-Velasco J. A. Management of endometriomas in women requiring IVF: to touch or not to touch / J. A. Garcia-Velasco, E. Somigliana // *Human Reprod.* – 2009. – № 24 (3). – С. 496 – 501.
7. The effect of surgical treatment for endometrioma on in vitro fertilization outcomes: a systematic review and meta-analysis / L. Tsoumpoul, M. Kyrgiou, T. A. Gelbaya [et al.]. // *Fertil. Steril.* – 2009. – № 92. – С. 75 – 87.
8. Влияние эндометриальных кист яичников на фертильность женщин репродуктивного возраста / А. В. Ширинг, Н. В. Ермолова, В. И. Орлов [и др.]. // *Мать и дитя: IV регион. науч. форум: тезисы докл.* – Екатеринбург, 2010. – С. 335 – 337.
9. Современные подходы к диагностике и лечению кистозных образований яичников / Л. И. Кудрявцева, В. В. Дурасова, Т. В. Полякова [и др.]. // *Мать и дитя: V российский форум: тезисы докл.* – Москва, 2003. – С. 371 – 372.
10. Тактика лечения бесплодия при наружном генитальном эндометриозе / И. Б. Манухин, М. Л. Геворкян, Л. Б. Студеная [и др.]. // *Мать и дитя: IX Всероссийский науч. форум: тезисы докл.* – Москва, 2007. – С. 455 – 456.
11. Адамян Л. В. Эволюция гормональной терапии эндометриоза (обзор литературы) / Л. В. Адамян, А. К. Осипова, М. М. Сонова // *Проблемы репродукции*. – 2006. – Т. 12, № 5. – С. 11 - 16.
12. Прогнозирование эффективности хирургического лечения бесплодия у женщин с малыми формами наружного генитального эндометриоза / А. К. Красильникова, А. И. Малышкина, Н. Ю. Сотникова [и др.]. // *Акушерство и гинекология*. – 2013. – № 7. – С. 39 – 45.
13. Євдокимова В. В. Імунологічне дослідження крові пацієнток, хворих на ендометріоз. Сучасні принципи лікування геніального ендометріозу імуномодуляторами / В. В. Євдокимова // *Практична медицина*. – 2011. – Т. XVII, № 4. – С. 67 – 78.
14. Фримель Н. Иммунологические методы / Н. Фримель. – М.: Медицина, 1984. – 472 с.
15. Виксман М. Е. Способ оценки функциональной активности нейтрофилов человека по реакции восстановления нитросинего тетразолия: метод. рекомендации / М. Е. Виксман, А. Н. Маянский. – Казань: Казанский НИИЭМ, 1979. – 21 с.
16. Нарциссов Р. П. Цитохимические исследования лейкоцитов / Р. П.

Нарциссов // Лабораторное дело. – 1964. – № 3. – С. 150 - 151.

17. Шубич М. Г. Выявление катионного белка в цитоплазме лейкоцитов с помощью бромфенолового синего / М. Г. Шубич // Цитология. – 1974. – №10. – С. 1321- 1322.

18. Mancini G. Immunochemical quantitation of antigens by single radial diffusion / G. Mancini, A. Carbonare, J. Henemans // Immunochemistry. – 1965. – № 2. – P. 235.

19. Кондратюк В. К. Сучасні уявлення щодо патогенетичних механізмів ушкодження репродуктивної системи у жінок з пухлиноподібними ураженнями яєчників (огляд літератури) / В. К. Кондратюк // Педіатрія, акушерство та гінекологія. – 2006. – № 6. – С. 93 – 97.

20. Шаповал О. С. Состояние клеточного и гуморального звеньев иммунной системы у женщин репродуктивного возраста с опухолеподобными образованиями яичников / О. С. Шаповал, Л. Л. Воронцова // Патология. – 2014. – № 3. – С. 53 – 59.

Reference in transliteration

1. Adamyan LV, Kulakov VI, Andreeva EN. E'ndometriozy [Endometriosis]. М.: Medicina 2006.

2. Kostyuchek DF, Durasova EN, Pechenikova VA. Analiz e'ffektivnosti dooperacionnoj konservativnoj gormonal'noj terapii pri e'ndometrioze yaichnikov [Analysis of efficiency of of preoperative conservative hormonal therapy for ovarian endometriosis]. Aktual'nye problemy medicyny i biologii: materialy nauchno-prakticheskoy konferencii [Actual problems of biology and medicine: Materials of scientific practical Conference]. Sankt Peterburg 2010; 49-50.

3. Pavlov RV, Kundohova MS. Immunologicheskie kriterii rannego prognozirovaniya recidivov naruzhnogo genital'nogo endometrioza [Immunological criteria for early prediction of recurrence of external genital endometriosis]. Medicinskij vestnik Severnogo Kavkaza 2011; 1: 39-43.

4. Serebrennikova KG, Kuznecova EP. Sovremennaya medikamentoznaya terapiya opuholevidnyh obrazovanij i retencionnyh kist yaichnikov [Modern drug therapy tumor formation and retentive of ovarian cysts]. Fundamental'nye issledovaniya 2011; 5: 218-23.

5. Gupta S, Agarwal A, Agarwal R et al. Impact of ovarian endometrioma on assisted reproduction outcomes. Reprod Biomed Online 2006; 13: 349-60.

6. Garcia-Velasco JA, Somigliana E. Management of endometriomas in women requiring IVF: to touch or not to touch. Human Reprod 2009; 24 (3): 496-501.

7. Tsoumpoul L, Kyrgiou M, Gelbaya TA et al. The effect of surgical treatment for endometrioma on in vitro fertilization outcomes: a systematic review and meta-analysis. Fertil Steril 2009; 92: 75-87.

8. Shiring AV, Ermolova NV, Orlov VI i dr. Vliyanie e'ndometrial'nyh kist yaichnikov na fertil'nost' zhenshin reproduktivnogo vozrasta [Influence of

endometrial ovarian cysts on fertility of women of reproductive age]. Mat' i ditya: IV region. nauch. forum: tezisy dokl. [Mother and Child: IV region. scientific. Forum: Theses of reports]. Ekaterinburg 2010; 335-37.

9. Kudryavceva LI, Durasova VV, Polyakova TV i dr. Sovremennye podhody k diagnostike i lecheniyu kistoznyh obrazovanij yaichnikov [Current approaches to diagnosis and treatment of ovarian cysts]. Mat' i ditya: V rossijskij forum: tezisy dokl. [Mother and Child: V Russian Forum: Theses of reports]. Moskva 2003; 371-72.

10. Manuhin IB, Gevorkyan ML, Studenaya LB i dr. Taktika lecheniya besplodiya pri naruzhnom genital'nom e'ndometrioze [Tactics infertility treatment for external genital endometriosis]. Mat' i ditya: IX Vserossijskij nauch. forum: tezisy dokl. [Mother and Child: IX Russian scientific. Forum: Theses of reports]. Moskva 2007; 455-56.

11. Adamyan LV, Osipova AK, Sonova MM. E'volyuciya gormonal'noj terapii e'ndometrioza (obzor literatury) [Evolution of hormone therapy for endometriosis (review)]. Problemy reprodukcii 2006; 12 (5): 11-6.

12. Krasil'nikova AK, Malyshkina AI, Sotnikova NYu i dr. Prognozirovaniye e'ffektivnosti hirurgicheskogo lecheniya besplodiya u zhenshin s malymi formami naruzhnogo genital'nogo e'ndometrioza [Predicting the effectiveness of surgical treatment of infertility in women with small forms of external genital endometriosis]. Akusherstvo i ginekologiya 2013; 7: 39-45.

13. Evdokimova VV. Imunologichne doslidszhennya krovi pacientok, hvorih na endometrioz. Suchasni principi likuvannya genial'nogo endometriozu imunomodulyatorami [Immunological studies of blood of patients suffering from endometriosis. Modern principles of treatment of endometriosis brilliant immunomodulators]. Praktichna medicina 2011; XVII (4): 67-78.

14. Frimel' H. Immunologicheskie metody [Immunological methods]. M.: Medicina 1984.

15. Viksman M, Mayanskij A. Sposob ocenki funkcional'noj aktivnosti nejtrofilov cheloveka po reakcii vosstanovleniya nitrosinego tetrazoliya: metod. rekomendacii [Way of estimating the functional activity of human neutrophils by the reduction reaction of nitroblue tetrazolium: method. recommendations]. Kazan': Kazanskij NIIE'M 1979.

16. Narcissov R. Citohimicheskie issledovaniya lejkocitov [Cytochemical researches of leukocytes]. Laboratornoe delo 1964; 3: 150-1.

17. Shubich M. Vyyavlenie kationnogo belka v citoplazme lejkocitov s pomoshh'yu bromfenolovogo sinogo [Identification of cationic protein in cytoplasm of leukocytes with bromophenol blue]. Citologiya 1974; 10: 1321-2.

18. Mancini G. Immunochemical quantitation of antigens by single radial diffusion / G. Mancini, A. Carbonare, J. Henemans // Immunochemistry. – 1965. – № 2. – P. 235.

19. Kondratyuk VK. Suchasni uyavlennya shhodo patogenetichnih mehanizmiv ushkodzhennya reproduktivnoï sistemi u zhinok z puhlinopodibnimi urazhennyami

yachnikiv (oglyad literaturi) [Current understanding of the pathogenic mechanisms of damage the reproductive system in women with ovarian tumor-like lesions (literature review)]. *Pediatrics, akusherstvo ta ginekologiya* 2006; 6: 93-7.

20. Shapoval OS, Voroncova LL. Sostoyanie kletchnogo i gumoral'nogo zven'ev immunnoj sistemy u zhenshin reproduktivnogo vozrasta s opuholepodobnymi obrazovaniyami yaichnikov [Cellular and humoral immune system in women of reproductive age with tumor-like formations of ovaries]. *Patologiya* 2014; 3: 53-9.