

**AZERBAIJAN REPUBLIC**

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**ABSTRACT**

Of the dissertations for an academic degree  
Doctor of Philosophy in Medicine

**THE ROLE OF LAPAROSCOPY AND ANTI-ENDOMETRIAL  
ANTIBODIES IN THE DIAGNOSIS AND TREATMENT OF  
GENITAL ENDOMETRIOSIS IN WOMEN OF  
REPRODUCTIVE AGE**

**Specialization:** 3215.01 – Obstetrics and gynecology

**Field of science:** Medicine

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Dissertation work was performed in the clinical base of the II Department of Obstetrics and Gynecology of the Azerbaijan Medical University, in the maternity hospital No. 5 named after Sh. Alaskarova, and it was performed in the gynecology department of "UNIKLINIKA".

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## GENERAL CHARACTERISTICS OF THE WORK

**Relevance of the topic and degree of development.** In recent years, a lot of attention has been paid to women's reproductive health problems. Genital endometriosis in women of reproductive age ranges from 12-60% and the study of this problem is of special relevance and practical importance<sup>1</sup>. Despite the intensive and numerous studies conducted on various aspects of endometriosis, the pathogenesis of the disease, the features of the clinical course depending on the localization, as well as the modern informative diagnostics and treatment issues, which are of great practical importance, have not yet been studied to the end. The trend of increasing incidence of genital endometriosis, long-term and relapsing course, inhibiting the reproductive function and reducing the labor capacity of women has led to an increase in research conducted in this direction in recent years<sup>2,3</sup>. At present, laparoscopy is considered the most informative and indispensable method in the diagnosis of genital endometriosis. This method is not only limited to the diagnosis of patients with genital endometriosis, but is also important in cases of endocrine infertility of unknown origin and when conservative treatment is not effective.

Laparoscopy is also important in the treatment of genital endometriosis. Pathologies of small pelvic organs along with genital endometriosis of this method, The effectiveness of its application in pelvic adhesions and complex diagnostic situations such as fallopian tube obstruction is not in doubt. However, the lack of research conducted on this topic makes it difficult to determine the diagnostic severity. In our study, we want to evaluate the effectiveness of the laparoscopy method more accurately by conducting a systematic

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<sup>1</sup> Dubrovina S.O., Berlim Yu.D. Progestogens in the treatment of endometriosis // - Moscow: Obstetrics and Gynecology, – 2018. № 15, p.150–154.

<sup>2</sup> Kazachkova, E.A. Assessment of proliferative and antiproliferative properties of endometrial cells during endometrial hyperplasia associated with chronic endometritis / E.A. Kazachkova, A.V. Zatornitskaya, E.E. Voropaeva E.E. [ et al.] // - Moscow: Pathology Archive,- 2019. - № 6, - p. 41–48.

<sup>3</sup> Steiner, A.Z., Jukic, A.M. Impact of female age and nulligravidity on fecundity in an older reproductive age cohort. // Fertil. Steril., - 2016. - №6, p.1584–1588.

review of the studies conducted up to now, as well as investigate the pathogenetic mechanisms of genital endometriosis.<sup>4,5</sup> We believe that the parallel determination of antiendothelial antibodies with antimüllerian hormone, which is an indicator of ovarian reserve capacity, in determining the severity of endometriosis, in obtaining a more detailed characterization of the disease, in the clarification of development mechanisms, as well as it will be important in improving examination and treatment tactics in patients with genital endometriosis.<sup>6,7,8,9</sup> Taking into account the lack of precise and informative instructions for surgical treatment in patients with genital endometriosis, the importance of improving laparoscopic operations in such patients is not in doubt.

One of the existing hypotheses suggests the presence of autoimmune disorders in endometriosis, which is based on the increased production of autoantibodies in this pathology, which has been mentioned by many authors. As it is known, activation of B-

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<sup>4</sup> Tsitskarava, D.Z. Assessment of the content and pathogenetic role of peritoneal fluid cytokines in patients with deep infiltrative endometriosis / D.Z. Tsitskarava, M.I. Yarmolinskaya, A.V. Selyutin [et al] // - Moscow: Journal of Obstetrics and Women's Diseases, - 2017 - V. 66. - No. 1, - p.38–45.

<sup>5</sup> Paramonova, N.B. Morphological and molecular biological signs of impaired endometrial receptivity in infertile women suffering from external genital endometriosis. / N.B. Paramonova, E.A. Kogan, A.V. Kolotovkina [et al] // - Moscow: Archives of Pathology, - 2018, - No. 3, pp. 11–18.

<sup>6</sup> Markelova, E.V. Matrix metalloproteinases and their relationship with the cytokine system, diagnostic and prognostic potential / E.V. Markelova, V.V. Zdor, A.L. Romanchuk [et al.] // - Moscow: Immunopathology, allergology, infectology, - 2016. - No. 2, - p.11–22.

<sup>7</sup> Zondervan, K.T. Endometriosis / K.T.Zondervan, C.M.Becker, K.Koga [et al] // Nat. Rev. Dis. Prim., - 2018. - № 4, p. 56-64.

<sup>8</sup> Tong, R. Analysis of the guidance value of 3D ultrasound in evaluating endometrial receptivity for frozen-thawed embryo transfer in patients with repeated implantation failure. / R.Tong, Y.Zhou, Q.He [et al] // Ann. Transl. Med., - 2020. - № 8, - p. 942- 944.

<sup>9</sup> Takahashi, N. Factors associated with successful pregnancy in women of late reproductive age with uterine fibroids who undergo embryo cryopreservation before surgery. / N.Takahashi, M.Harada, R.Tanabe [et al] // Obstet. Gynaecol. Res., - 2018. - № 10, - p.1956–1962.

lymphocytes is the basis of the mechanism of increase in production of autoantibodies.

Evaluation of the phenotype and determination of the degree of differentiation of B-lymphocytes allows to assess the degree of activity of humoral immune reactions. However, studies devoted to the study of the nature of B-lymphocyte activity during endometriosis and related infertility are practically absent in modern times. In this regard, clarifying the characteristics of differentiation and activation of B-lymphocytes and determining the nature of the production of autoantibodies in patients with endometriosis and infertility at the same time is considered an urgent issue of both scientific and experimental importance. So, solving it will allow to clarify not only the development mechanisms of endometriosis and related infertility, it will also be the basis for the development of new criteria for the diagnosis of this disease<sup>10, 11, 12, 13</sup>.

At present, studies have been conducted to study the characteristics of the production of autoantibodies in endometriosis and associated infertility. It has been established for quite a long time that both in the blood serum of patients with endometriosis, also, the amount of anti-endometrial antibodies, as well as autoantibodies against phospholipids, annexin, and laminin in the peritoneal fluid increased. However, until now there is no consensus on their role in the pathogenesis of this pathology.

Scientific studies dedicated to the study of the characteristics of B-lymphocyte differentiation and activation during infertility

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<sup>10</sup>Tsitskarava, D.Z. Evaluation of the content and pathogenetic role of cytokines in the peritoneal fluid in patients with deep infiltrative endometriosis / D. Z. Tsitskarava, M. I. Yarmolinskaya, A. V. Selyutin [and others] // - Moscow: Journal of obstetrics and women's diseases, - 2017 - V. 66. - No. 1, - p. 38–45.

<sup>11</sup> Kovaleva, M. M. Surgical treatment of endometriosis (overview of literature) // - Moscow: Young student, - 2019. - № 4, -p.124-126.

<sup>12</sup>Abdel-Rasheed, M. microRNA expression analysis in endometriotic serum treated mesenchymal stem cells / M. Abdel-Rasheed, G.N. Eldeen, M. Mahmoud [et al] // EXCLI J, -2017. -T. 16, p.852–867.

<sup>13</sup> Alfer, J. Endometrial Dating Method Detects Individual Maturation Sequences During the Secretory Phase. / J.Alfer, A.Fattahi, N.Bleisinger [et al] // In Vivo, - 2020, - № 4, p.1951–1963

caused by various degrees of widespread endometriosis have not been carried out before. High incidence of endometriosis in women of active reproductive age, difficult selection of effective treatment methods and schemes, It is appropriate to preserve the ovarian reserve and to restore fertility in women who undergo operative intervention due to external genital endometriosis, prone to disease recurrence, effective and, at the same time, low-cost, makes the search for convenient methods for clinical practice extremely urgent.

Thus, in order to prevent genital endometriosis, which is considered one of the main medical and social problems in modern gynecology, modern informative diagnostics in women of reproductive age and there is a great need to conduct complex clinical-instrumental examinations with treatment methods.

### **The object and subject of the research**

100 women of reproductive age (18-38 years, average age  $29.5 \pm 8.5$  years) with external endometriosis were included in the study (main group). All patients in the main group were divided into 3 groups: Group I - patients with peritoneal endometriosis (n= 53); Group II - patients with extraperitoneal endometriosis (n=31); Group III - patients with common form of genital endometriosis (n=16). The control group consisted of 30 women who were considered conventionally healthy fertile and did not have endometriosis.

### **The purpose of the research**

The role of laparoscopic surgery and antiendometrial antibody in the diagnosis and treatment of genital endometriosis in women of reproductive age has been studied.

### **Tasks of the research work**

1. Assessment of somatic and reproductive health status of women with genital endometriosis.
2. Study of the characteristics of the clinical manifestation of genital endometriosis in patients with different localization, form and degree of severity of the pathological process and the main development patterns of the disease.
3. Justification of the spectrum of diagnostic procedures and their sequence in the comprehensive examination program of patients with genital endometriosis.

4. Study of the role of antiendometrial antibodies, TNF-alpha and IL-6 in the development of genital endometriosis.
5. Determining the possibilities of applying laparoscopy in the diagnosis and operative treatment of endometriosis.

#### **Methods of research work**

A number of modern examination methods were used in the conducted complex studies, including clinical, instrumental, immunological, sociological, computational, statistical and other methods.

#### **The main provisions defended:**

- The degree of severity of genital endometriosis depends on the manifestation of the general inflammatory process in the body.
- Autoimmune antibodies against endometrioid tissue are one of the main factors that lead to complications of endometriosis
- Determination of the activity of the inflammatory process in the body and the level of antiendometrial antibodies during laparoscopic surgery in the treatment of endometriosis can help to predict the reproductive function after surgery.

#### **Scientific novelty of the research**

Based on the results of complex clinical-laboratory, instrumental and sociological examinations conducted in Azerbaijan:

1. The role of IL-6, TNF-1alpha and antiendometrial antibodies in the pathophysiology of genital endometriosis has been studied.
2. Due to the severity of the inflammatory process in the body and the high level of antiendometrial antibodies, new definitions are given to the diagnostic criteria of genital endometriosis.
3. The effectiveness of laparoscopic treatment of genital endometriosis was evaluated depending on the level of IL-6, TNF-1alpha and antiendothelial antibodies.
4. Additional criteria for the application of the laparoscopic method in the diagnosis and complex treatment of genital endometriosis have been proposed.

#### **Practical and theoretical significance of the study**

The current study will provide important information to practicing obstetricians and gynecologists in determining treatment tactics for genital endometriosis in women of reproductive age. In

particular, the results of the present study can be used to more precisely determine the indications for laparoscopic surgery for the treatment of infertility. Also, the results obtained as a result of the study are of great importance in providing a prognosis after the treatment of genital endometriosis through laparoscopy.

### **Dissertation approval and application:**

The materials of the dissertation were discussed:

- Poster presentation at the 1st International Mother-Fetal Conference held in London, England (London, 2017).
- Report on the topic "The role of cytokine expression in the formation of genital endometriosis" at the Conference dedicated to the "Scientific Relevance of Medicine" organized by the Azerbaijan Medical University in 2023.

Dissertation materials at the inter-departmental meeting jointly held by profile chairs of Azerbaijan Medical University (Baku, 28.06.2022, protocol №.9), It was reported and discussed at the One-time Scientific Seminar of E 2.06 Dissertation Council operating under Azerbaijan Medical University (Baku, 2022, protocol No. 18). The materials of the dissertation are used in the teaching process of the II Department of Obstetrics and Gynecology of AMU, the proposed practical recommendations are applied in practice.

### **Name of the organization where the dissertation work was performed:**

The dissertation work was carried out on the basis of the Department of Obstetrics and Gynecology II of the Azerbaijan Medical University, in the clinical base located in the maternity hospital No. 5 named after Sh.Alaskarova and at the bases of the gynecology department of "UNIKLINIKA".

### **Publication of the provisions and results of the case.**

8 scientific articles and theses were published on the main provisions of the work. Among them, 5 articles were published in local press, 2 articles and 1 thesis were published in foreign press.

### **Volume and structure of the case.**

Dissertation "Literature Review", written on 167 pages, "Materials and Methods", three chapters devoted to personal research, consists of a discussion of results, conclusions, practical



recommendations, a list of references, abbreviations, and a list of notations. The bibliography contains 206 sources (136 of them in English). The work is explained with 23 tables, 31 graphs and 12 photos. Dissertation from 212,618 symbols (Introduction – 13,827 symbols , Chapter I – 54,097 symbols , Chapter II - 22589 marks, Chapter III - 43673 symbols, Chapter IV - 23879 symbols, Chapter V - 19904 symbols, discussion of results - 30399 symbols, conclusions and practical recommendations - 4250 symbols).

## **MATERIALS AND METHODS OF RESEARCH**

The research work was carried out in 2015-2019 within the scientific program of the II Department of Obstetrics and Gynecology of the Azerbaijan Medical University in Baku. The study was carried out in the clinical base of the department located in Shamama Alaskarova maternity hospital No. 5 and in the gynecology department of "UNIKLINIKA". 100 women of reproductive age (18-38 years, average age  $29.5 \pm 8.5$  years) with external endometriosis were included in the study. These women formed the main group of those examined. The control group consisted of 30 women who were considered conventionally healthy fertile and did not have endometriosis. Based on clinical and laboratory examinations, all patients in the main group were divided into 3 groups.

Group I - patients with peritoneal endometriosis (n= 53);

Group II - patients with extraperitoneal endometriosis (n=31);

Group III – patients with common form of genital endometriosis (n=16);

Control group - women who are considered conventionally fertile and without endometriosis (n=30).

During the examination of patients, standard methods were used: visual examination, bimanual examination, during which the location, consistency, mobility, dimensions of the uterus and growths were evaluated, and USM was performed. Peritoneal endometriosis has been attributed to endometrioid lesions of the ovaries, fallopian tubes, and pelvic peritoneum. Extraperitoneal endometriosis such as vulva and vagina, vaginal part of the cervix, patients with uterine,

retrocervical endometriosis, as well as parametral, paracolpal endometriosis, which may or may not progress to the bladder and rectum, were taken. Patients with different forms of endometriosis are shown below by age. (table 1).

**Table 1**

**Age grouping of patients with different forms of endometriosis**

Age	I group n=53		II group n=31		III group n=16		IV group n=30		Cəmi n=130	
	obs	%	obs	%	obs	%	obs	%	obs	%
18-25	9	17,0	3	9,7	1	6,2	7	23,3	20	15,4
26-30	19	35,9	11	35,5	2	12,5	11	36,7	43	33,1
31-35	21	39,6	8	25,8	4	25,0	8	26,7	41	31,5
36- 38	4	7,5	9	29,0	9	56,3	4	13,3	26	20,0
Total	53	100	31	100	16	100	30	100	130	100

Patients with different forms of endometriosis were divided by age as follows: 20 people (15.4%) in the age group from 18 to 25 years old, 26-30 years old - 43 people (33.1%), 31-35 years old - 41 people (31.5%), 36-38 years old - 26 people (20.0%).

Group I - 9 people in the age group from 18 to 25 years old (17.0%) in the group of patients with peritoneal endometriosis, 26-30 years old - 19 people (35.9%), 31-35 years old - 41 people (39.6%), 36-38 years old - 4 people (7.5%).

Group II - 3 people in the age group from 18 to 25 years old (9.7%) in the group of patients with extraperitoneal endometriosis. 26-30 years old - 11 people (35.5%), 31-35 years old - 8 people (25.8%), 36-38 years old - 9 people (29.0%).

Group III - in the group of patients with a common form of genital endometriosis, there are 9 people (6.2%), 26-30 years old - 2 people (12.5%), 31-35 years old - 4 people (25,0%), 36-38 years old - 9 people (56.3%).

Control (control) group - in the group of women considered conventionally healthy fertile and without endometriosis - 7 people (23.3%) in the age group from 18 to 25 years old, 26-30 years old - 11 people (36.7%), 31-35 years old - 8 people (26.7%), 36-38 years old - 4 people (13.3%).

Primary infertility was found in 70 (81.4%) patients, and secondary infertility in 16 (18.6%) patients.

The reasons for the development of genital endometriosis have been determined. These included pelvic inflammatory diseases, operations, ovulatory dysfunction, etc. Extragenital diseases in the patient: respiratory, cardiovascular, urinary-excretory system, gastrointestinal tract diseases, endocrine pathologies, as well as varicose veins, liver, mammary gland diseases, etc. were detected and recorded. The characteristics of the newborn, childhood, and adolescence periods have been studied. The time of starting sexual life, the number of pregnancies (if any), their course and outcome were also considered. In cases of termination of pregnancy (spontaneous miscarriages, premature pregnancy), their duration and possible reasons were investigated, after which the patients were referred to specialist consultations. In order to quantitatively assess pain symptoms in patients with genital endometriosis, we used a visual-analog scale based on the recommendations of IMMPACT (Measurement method and pain assessment in clinical research initiative, 1998). We also used the scale MacLaverty S.M. and Shaw R.W. In addition to clinical examinations, the diagnostic criteria of endometriosis are based on the following examinations: standard gynecological examination and retrovaginal examination; colposcopy; smear for cytological examination from the cervical canal and vaginal part of the uterus; changes in the structure of the uterine wall, volume derivatives, as well as a transvaginal ultrasound examination of the small intestine, conducted to study the size of the uterus and growths; ultrasound examination of the kidneys in case of retrocervical endometriosis or parametrium infiltrate; possibility of urinary tract involvement in the process and urography (as indicated) in order to detect the pathological process. Colonoscopy or rectomanoscopy in the case of retrocervical endometriosis, analysis for biopsy in the case of damage to the distal part (as indicated); computer or magnetic resonance imaging - allows to assess the degree of invasion of heterotopia in the rectum, ureters, cervix, as well as narrowing of the intestinal orifice (as indicated). During the study, we determined the immune status of patients, especially the level of AEA, TNF- $\alpha$  and IL-6 indicators.

AEA, TNF- $\alpha$  and IL-6 concentration in peripheral blood Usco Life Science Inc. It was determined using reagent kits produced by the company. The amount of cellular regulators in blood serum and peritoneal fluid was determined by the IFA method, also the amount of sex hormone-binding globulin (SHBG) in peritoneal fluid and blood serum "Alkor-Bio" (Russia), Apo-AIV – Cloud-Clone Corp. (USA), complement S3 and S4-b components - «AssayPro» (USA), FASL and vascular endothelial growth factor (VEGF) - «Bender MedSystems» (Austria), DEBA-R- «R&Dsystems» (USA) microplate was determined in a Sunrise photometer (Tecan, Austria). The statistical processing of the research was carried out using the "SPSS STATIC 20" program. In all cases  $p < 0.05$ , the difference between groups was considered statistically significant.

## **RESEARCH RESULTS AND THEIR DISCUSSION**

The division of patients with genital endometriosis by group is described as follows: group I - patients with peritoneal endometriosis - 53%; group II - patients with extraperitoneal endometriosis 31% and group III - patients with mixed endometriosis -16%. Clinical-laboratory and diagnostic examination of patients made it possible to detect the following forms of genital endometriosis. Ovarian endometriosis is more common in patients with peritoneal endometriosis, 34% and 18.7% in groups I and III, respectively. Endometriosis of fallopian tubes is more common in patients with peritoneal endometriosis (58.5%), and in mixed form of genital endometriosis it is 31.3%. Retro-cervical endometriosis was recorded in 7 (22.5%) patients, and mixed form (ovarian and peritoneal endometriosis) in 1 (6.25%) patient corresponding to groups II and III. Pelvic endometriosis was found in 4 (7.5%) cases in group I and only 1 (6.25%) in group III. Endometriosis of the vaginal part of the cervix is more common in patients with extraperitoneal endometriosis (12.5%), and in the mixed form of genital endometriosis it is 12.5%. Comparative analysis of clinical and laboratory evidence shows that vulvovaginal endometriosis was observed in 6 (19.4%) cases of patients with extraperitoneal form of endometriosis, and in 2 (12.5%) cases in group III. Endometriosis of the vaginal part of the cervix was noted in 9

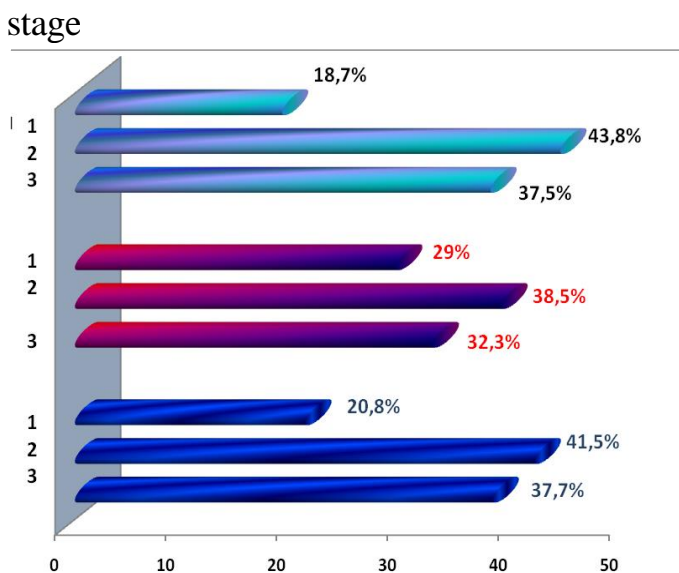
(29%) patients in the second group, and in 2 (12.5%) patients in the III group. Uterine endometriosis was detected in 6 (19.4) and 2 (12.5%) patients in groups II and III, respectively (table 2.).

**Table 2.**  
**Forms of location of endometriosis by groups in examined patients**

Forms of endometriosis (location)	Peritoneal endometriosis I group (n=53)		Extraperitoneal endometriosis Group II (n=31)		Mixed form of genital endometriosis Group III (n=16)		Total (n=100)	
	obs.	%	obs.	%	obs.	%	obs.	%
Ovarian endometriosis	18	34	-	-	3	18,7	21	21%
Endometriosis of the fallopian tubes	31	58,5	-	-	5	31,3	36	36%
Pelvic endometriosis	4	7,5	-	-	1	6,25	5	5%
Vulvovaginal endometriosis	-	-	6	19,4	2	12,5	8	8%
Endometriosis of the vaginal part of the cervix	-	-	9	29	2	12,5	11	11%
Uterine endometriosis	-	-	6	19,4	2	12,5	8	8%
Retrocervical endometriosis	-	-	7	22,5	1	6,25	8	8%
parametrial, para-colpal tissue endometriosis spreading to the bladder and rectum	-	-	3	9,7	-	-	3	3%
Total n=100	53	100%	31	100%	16	100%	100	100 %

It is important to note that the severity of endometriosis in patients

belonging to all groups was determined using the method of laparoscopy, R-AFR (1996) and AAGL (2006) classification. The ENZIAN (2012) classification, which accurately reflects the localization, development stages and depth of genital endometriosis, was also used. With the help of the ENZIAN classification, laparoscopic data were evaluated taking into account the area of endometrioid heteropathy and expressed in points: Stage I - minimal endometriosis (1-5 points) was found in 36 (36%) women, according to groups: 20 (37.7%) in group I, 10 (38.7%) in group II and 7 in group III (43.8%). II stage - mild endometriosis (6-15 points) 41 (41%) according to groups: in group I - 22 (41.5%), in group II - 12 (32.3%) and in group III - 6 (37.5 %). Stage III - endometriosis of moderate severity (16-40 points) in 23 (23%) patients: according to groups: in group I - 11 (20.8%), in group II - 9 (29.0%) and in group III - 3 ( 18.7%). Stage IV - severe endometriosis (>40 points) was not noted in any of the studied groups (Figure 1).



**Figure 1. Prevalence by groups according to stages of genital endometriosis in patients**

In addition, high risk of infection was observed in patients in the studied groups, the infection index was 3.1 for the groups, respectively;

3.2; Rated as 2.8. Most of the patients had 3 or more infectious diseases during the year. Various clinical signs were combined by us in 3 groups: pain syndrome 94 (94%); menstrual dysfunction 46 (46%) and infertility 87 (87%). It is important to note that in most patients - 69 (69%) symptoms of the disease were found in various combinations. The isolated form of clinical symptoms was observed in 31 patients, which is 31%.

A comparative analysis of anamnestic evidence related to the menstrual cycle showed that the onset of menstruation varied between 11 and 15 years of age. The above-mentioned average age of menarche was almost the same in all studied groups ( $13.0 \pm 2.1$  years;  $13.2 \pm 2.1$  years and  $13.3 \pm 1.7$  years, respectively). The duration of menstrual bleeding in most patients - 54 (54%) women was normal 4-6 days.

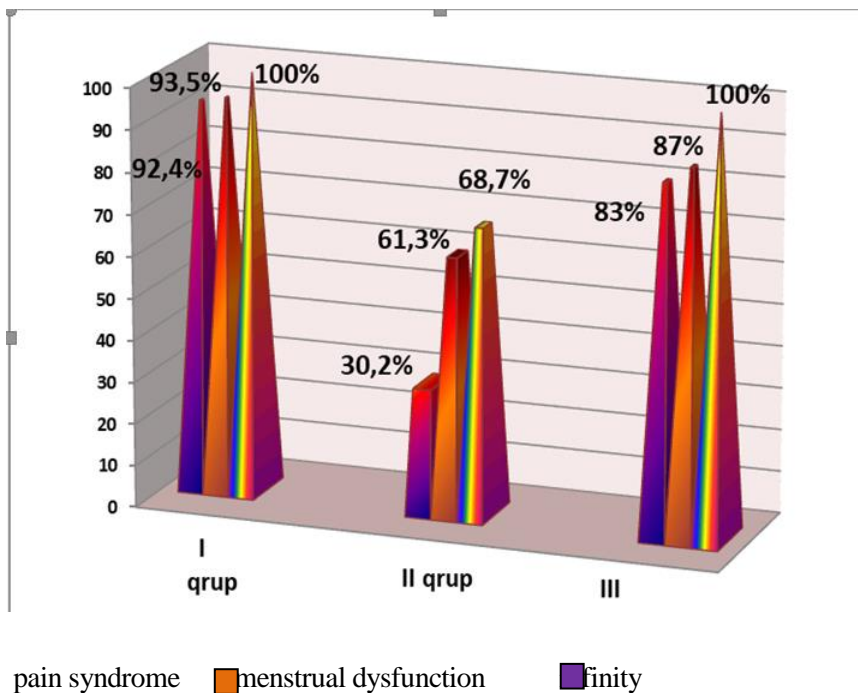
Among the extragenital diseases, the first place is occupied by endocrine diseases in 29 (29%) cases, among which high-grade diabetes mellitus was noted in 11 (11%) cases, and thyroid gland diseases in 18 (18%) cases. Urinary system diseases - 21 (21%) of which 9 (9%) are pyelonephritis are in the second place.

Gastrointestinal diseases were also recorded in 20 (20%) patients, anemia in 19 (19%), arterial hypertension in 17 (17%), and hypotension in 32 (32%) cases. Depending on its localization, the clinical signs of endometriosis showed that the pain syndrome in group I was observed more often in patients with ovarian endometriosis.

Dysmenorrhea was more common in patients with ovarian endometriosis in 12 (66.6%) cases compared to other localizations. Dysmenorrhea was found in 5 (55.6%) patients with mixed endometriosis in group II, 29 (54.7%) in peritoneal form, and only 5 (16.1%) in retrocervical form. Dyspareunia (painful coitus) was found mostly in endometriosis of fallopian tubes - 5 (16.1%) and endometriosis of ovaries - in 3 (16.7%) patients.

Disorders of the menstrual cycle in 7 (11.3%) cases are manifested in the form of bloody discharge before and after menstruation. Hyperpolymenorrhea was observed in 13 (21.1%) patients. Changes in the menstrual cycle were 44.4% in mixed endometriosis and 33.3% in ovarian endometriosis. Infertility was observed in 53 (85.5%) patients. The frequency of leading symptoms (pain syndrome and menstrual

dysfunction) did not differ significantly in individual groups. According to the study, pain syndrome was observed in all forms of endometriosis - in 94 (94%) cases, dysmenorrhea in 55 (55%) cases, dyspareunia in 16 (16%) cases, and chronic pelvic pain unrelated to menstruation in 23 (23%) cases. pains were found (Figure 2).



**Figure 2. Frequency of clinical signs in patients with genital endometriosis by study group**

The obtained data show that most of the patients with external genital endometriosis had normal dimensions of the uterus. In the case of peritoneal endometriosis, a tumor-like derivative in the growth area - dense elastic consistency, smooth surface, limitation of movement and painful palpation was characteristic in 25 (47.2%) cases. In 14 (26.4 %) patients, unilateral endometrioid cysts were noted, and in 11 (20.7 %) bilateral endometrioid cysts. During the vaginal examination, only 3 patients with peritoneal



endometriosis (5.7%), 2 patients with extraperitoneal endometriosis (6.5%) and 1 patient with mixed form (6.25%) did not observe these or other changes. There was no patient in the studied groups whose platelet count in peripheral blood was higher than normal ( $180-450 \times 10^9/l$ ). On the contrary, patients with platelets below the norm were significantly more frequent in the group of patients with endometriosis both before treatment ( $\chi^2=9.28$ ;  $p<0.05$ ) and after treatment ( $\chi^2=11.22$ ;  $p<0.05$ ) they came.

As for monocytes, their number was not outside the lower limit of the norm before or after treatment in any case in the studied groups. However, at this time, the number of patients with the number of monocytes in the peripheral blood was higher than the upper limit of the norm in the endometriosis group and the control group neither before treatment ( $\chi^2=0.86$ ;  $p=0.3457$ ) nor after treatment ( $\chi^2=2.48$ ;  $p=0.092$ ) was not significantly different. At different localizations of endometrioid heterotopias, statistically significant differences were found in the number of platelets before treatment compared to the control group. In patients with endometriosis, the number of platelets remained below normal. In patients with endometriosis, there is a moderate positive correlation between platelet and monocyte counts in peripheral blood, which disappears after treatment. In turn, the number of peripheral blood monocytes was significantly higher in patients with endometriosis and other gynecological diseases.

It is known that chemokines (chemotaxic cytokines) are involved in the development and exacerbation of endometriosis, which occurs through the regulation of leukocyte function. Here, 2 representatives of the  $\beta$ -chemokine family have a special place: monocyte chemoattractant protein-1 (MCP-1) and chemokine expressed and produced by T-cells during activation (RANTES). In addition to the activation of monocytes and macrophages, MCP-1, which interacts with T-lymphocytes, natural killer cells, and barrier cells, was found in endometrial cells, and its expression changes to an uncontrolled form during endometriosis. [25]. Patients with endometriosis also had an increase in the amount of RANTES and CRP in peripheral blood compared to the control group, but the

difference did not reach a statistically significant level ( $p=0.16$  and  $p=0.26$ , respectively).

Examination of the level of proteins by subgroups showed that the level of MCP-1 in the peritoneal fluid of patients with endometrioid cysts is much higher than the similar indicator in patients in other groups, and in women with mild forms of the disease, the value of this indicator is close to the indicator in the control group. In general, the amount of MCP-1 in the peritoneal fluid in patients with endometriosis is higher than in the control group, but this difference is statistically insignificant ( $p=0.8$ ). This can probably be explained by the implantation of endometrial cells into the abdominal cavity and the exacerbation of the disease.

However, further studies are needed to test this hypothesis - whether MCP-1 levels can act as a marker of disease severity or progression. Regarding the values of RANTES and CRP in peritoneal fluid, no intergroup differences were found in these parameters. The level of RANTES in the peripheral blood of patients with superficial and deep infiltrative endometriosis compared to the control group ( $p=0.22$  and  $p=0.16$ , respectively), as well as the levels of CRP in patients with endometrioid cysts and deep infiltrative endometriosis ( $p=0$ , respectively) 26 and  $p=0.22$ ) increase was found.

The level of RANTES in the peripheral blood of patients with superficial and deep infiltrative endometriosis compared to the control group ( $p=0.22$  and  $p=0.16$ , respectively), as well as the levels of CRP in patients with endometrioid cysts and deep infiltrative endometriosis ( $p=0$ , respectively) 26 and  $p=0.22$ ) increase was found. It is hypothesized that CRP can be used as a marker of endometriosis, but this hypothesis needs to be fully investigated.

Data from our study show that changes in the immune system during external genital endometriosis are characterized by increased levels of pro-inflammatory chemokines. Immunological processes involving macro-phages probably play an important role in the development and exacerbation of external genital endometriosis. A positive correlation was found between the levels

of MCP-1 ( $p=0.05$ ) and C-reactive protein ( $p=0.47$ ) and the severity of endometrioid disease, indicating the presence of defective function of peritoneal macrophages in widespread forms of endometriosis. Indicators of the level of MCP-1 and C-reactive protein in peripheral blood can be used as markers of endometriosis activity. It should be noted that in the development of genital endometriosis, not only the violation of the completeness of the immune balance, but also the formation of a complete immune response during known pathology plays an important role, which is especially important in preventing relapses and complications.

In this regard, the state of the immune system of the patients with endometriosis studied by us, the levels of anti-inflammatory cytokines - TNF- $\alpha$  and IL-6 were studied. The level of TNF- $\alpha$  in patients with a mixed form of endometriosis (group III) increased more honestly than in the control group ( $p<0.05$ ). In terms of the spread of the process in the studied patients, a greater increase in the level of TNF- $\alpha$  was characteristic of the III and II stages (respectively,  $65,431 \pm 9,2$  pg/ml;  $64,212 \pm 7,5$  pg/ml), however, results close to II and III stages ( $62,345 \pm 9,4$  pg/ml) were obtained in stage I of endometriosis. As can be seen from table No. 4.1.2, the level of TNF- $\alpha$  in the 4th stage of genital endometriosis was significantly reduced and statistically significantly different compared to the 3rd stage. The level of TNF- $\alpha$  was  $61,321 \pm 5.8$  pg/ml in stage IV.

The comparative analysis also showed that in women with endometriosis, the level of TNF- $\alpha$  increased in the III stage of the spread of the pathological process, while in the IV stage, a statistically significant decrease of this indicator was noted ( $p<0.05$ ).

Therefore, the increase in the concentration of TNF- $\alpha$  corresponds to the stage of development of the known disease. According to the obtained results, the concentration of IL-6 in patients belonging to groups III and I ( $19,6000 \pm 2,18$  pg/ml and  $15,58 \pm 0,98$  pg/ml, respectively) was lower than that of control group IV ( $11,1700 \pm 2.85$  pg/ml) increased relatively honestly ( $p<0.05$ ). For women belonging to group II, a slight increase in the level of IL-6

was observed compared to group IV ( $13.5742 \pm 2.46$  pg/ml and  $11.1700 \pm 2.85$  pg/ml, respectively).

A greater increase in the level of IL-6 is noted in the II stage, and a smaller increase in the IV stage of the pathological process ( $p < 0.05$ ), which indicates the development of a violation of intercellular communication, deficiencies in the immune balance. The status of antiendothelial antibodies was also evaluated by us. According to the obtained results, high concentration of AEA among patients with genital endometriosis was observed in group II and III ( $73225,80 \pm 27099,45$  pg/ml vs  $56562,50 \pm 40890,04$  pg/ml) and was statistically significantly higher than that of women in the control group. In women belonging to group I, this indicator ( $19733,96 \pm 16153,63$  pg/ml) is slightly higher than in the control group ( $7980,00 \pm 2762,60$  pg/ml), but the difference is not statistically honest. In the III and II stages of the spread of the pathological process, anti-endometrial antibodies are close ( $40876 \pm 4982$  pg/ml and  $35632 \pm 2634$  pg/ml, respectively), In stages I and IV, almost the same results ( $22081 \pm 1367$  pg/ml and  $21232 \pm 2089$  pg/ml, respectively) were recorded. Progression of endometrioid heterotopia is observed in stage III of the disease. Accordingly, AEA can be used to detect and grade endometriosis this is of particular importance for the selection of modern and effective treatment tactics.

As a result of the research work, the correlation dependence between antiendometrial antibodies and TNF- $\alpha$  and IL-6 was evaluated in different groups of patients with genital endometriosis. Based on the obtained results, it was determined that there is a statistically significant positive correlative relationship between markers such as AEA, TNF- $\alpha$  and IL-6, which reflect the activity of the immune system. Rather, the dysfunction of cytokines (TNF- $\alpha$  and IL-6) directly depends on the level of AEA, a very small imbalance that exists causes significant changes in the immune system of patients with endometriosis. Taking all this into account, it is possible to evaluate

AEA as one of the sensitive markers in the occurrence of endometriosis, which is important in gynecological practice. As tests for replacement during diagnostic surgery in a research study

and for sorting when deciding on surgical interventions for endometriosis blood biomarkers were evaluated as tests. Specific objectives include: to provide a comparative assessment of the diagnostic accuracy of blood biomarkers as a benchmark for the diagnosis of peritoneal, ovarian and deep infiltrating pelvic endometriosis compared to surgical diagnosis. Compared with the control group, the serum level of sex hormone-binding globulin (SHBG) also increases during disease progression: 73.1% – during the I-II stage ( $p=0.01$ ) and 51.1% – during the III-IV stage ( $p=0.034$ ). During the III-IV stages of endometriosis, the level of the C3 component in the blood serum increases by 22.3% compared to the indicators in the control group ( $p=0.016$ ). It should be noted that in the early stages of the disease, there is a tendency to increase the level of this protein in the blood serum ( $p=0.05$ ).

At the local level, similar dynamics of the amount of these proteins were preserved. So, compared to the corresponding indicators in the control group, the level of ApoAIV in the peritoneal fluid was 26.8% ( $p=0.001$ ) in stage I-II of external genital endometriosis, an increase of 23.3% ( $p=0.030$ ) was determined in stage III-IV. The amount of sex hormone-binding globulin in the peritoneal fluid during the I-II stages of the disease was 28.9% ( $p=0.032$ ) and in the III-IV stages – increased to 39.5% ( $p=0.032$ ).

In the III-IV stages of endometriosis, compared to the indicators in the control group, the amount of S3 increased to 73.2% ( $p=0.001$ ), however, during the I-II stages of EGE, its level did not change honestly. No statistically significant changes were detected in the concentration of vascular endothelial growth factor in peritoneal fluid in patients with EGE stage I-II. However, in the III-IV stages of the disease, the local level of vascular endothelial growth factor increased by 57.8% ( $p=0.022$ ) compared to the indicators in the control group.

FAS-induced apoptosis of CD95-positive cells plays an important role among the main mechanisms of disruption of apoptotic processes during endometriosis. It has been shown that endometrial cells of patients with endometriosis are resistant to

cytokine-induced apoptosis. In stages I-II of EGE, the concentration of sFASL in the blood serum was 43% lower than in the control group ( $p=0.040$ ). However, the level of this protein in blood serum did not change in larger stages ( $p>0.05$ ).

The amount of sFASL in the peritoneal fluid in the group of patients with stages III-IV of EGE was 41% lower than the data in the control group ( $p=0,003$ ). Statistically significant changes of the local level of sFASL during the early stages of EGE were not determined. It is known that the surgical method in the treatment of external genital endometriosis is the only method that removes the morphological substrate of endometriosis. The indications for planned hospitalization in the women included in the present study were: endometrioma larger than 4 cm in size; unbearable pain syndrome or clinical ineffectiveness of conservative therapy for 6 months; infinity. In total, 73 (73.0%) patients underwent planned endosurgical operation. Indications for urgent surgery were severe pain syndrome that could not be prevented by drugs, rupture of endometrioid cyst. In total, 27 (27.0%) emergency operations were performed.

Thus, 100 patients were not only given diagnostic laparoscopy to detect and determine the extent of endometriosis, the following types of operations were also performed: endocoagulation of endometrioid heteropathies - 22 (22.0%), exclusion of endometrioid heteropathies - 28 (28.0%), cystectomy - 54 (54.0%). Unilateral tubectomy with exclusion of endometrioid heteropathies ( $n=24$ ) - 5 (20.8%) and adhesiolysis - 4 (16.7%) operations were performed. In no case was there any complication during the operation or after the operation.

Thus, by us ( $n=73$ ), endosurgery was applied to 29 (21.27%) women included in the first group: Endometriosis of ovaries in 11 (37.9%) patients, peritoneal in 8 (27.6%) patients, 3 women (10.3%) also had retrocervical endometriosis and 7 (24.2%) women had a common form of endometriosis (ovarian endometriosis + peritoneal endometriosis). Out of 21 (21.0%) patients with ovarian endometriosis, 14 (66.7%) women underwent cystectomy by stripping the capsule, In the remaining 7 (33.3%) cases, taking into

account that the size of the endometrioid foci is less than 0.5 cm, pathological areas were removed.

In case of retrocervical endometriosis, endometrioid heteropathies were excluded. According to the R-AFS classification, the first stage of endometriosis was 36 (36.0%), the second stage was recorded in 41 (41.0%), and the third stage in 23 (23.0%) patients. Pain syndrome in 94 (94.0%) women before treatment; menstrual cycle disorder in 46 (46.0%) patients; Infertility was observed in 86 (86.0%) women.

Depending on the stage of activity of the pathological process, pain syndrome was present in 49 (92.4%) of 53 patients in the first group of endometriosis before treatment, it was recorded in 29 (93.5%) of 31 women in the second group, and in all women in the third group - 16 (100%). After treatment, pain disappeared in most patients of all groups of endometriosis.

These complaints occurred in 21 (39.6%) of 53 patients in the first group of the disease, it was kept in 10 (18.86%) women in the second group, and in 8 (15.09%) women in the third group. The decrease in the frequency of pain depended on the degree of pain of the endometrioid process: pain in the first degree of the disease decreased by 2.1 times, in the second degree by 1.24 times, and in the third degree by 2.0 times. After laparoscopy surgery (n=100), 62 women (62.0%) recovered reproductive function and pregnancy was recorded. In 19 (19.0%) women, pregnancy did not occur naturally and extracorporeal fertilization was requested. Depending on the recovery of reproductive functions after laparoscopy, different indicators were obtained when examining the level of inflammatory and autoimmune markers.

The level of alpha-tumor necrosis factor in peripheral blood was significantly higher in women applying for Extracorporeal Fertilization ( $p=0.001$ ). The IL-6 indicator did not differ statistically between the compared women ( $p=0.058$ ). Not only the level of anti-endometrial antibodies, but also the indicators of anti-thyroid peroxidase antibodies and anti-thyroglobulin antibodies of the peripheral blood were detected at a sufficiently high level in women who were unable to conceive naturally. The difference between the compared women of all 3 indicators was recorded at a statistically significant level.

This shows that even if it is not against the background of any autoimmune disease, the disruption of immune regulatory functions in the body plays an important role in the pathogenesis of genital endometriosis, and also significantly affects the outcome of treatment.

The results of the study show that it is important to assess the severity of the inflammatory process in women who are indicated for laparoscopy to restore reproductive functions. Of course, it is impossible to evaluate any local and specific inflammatory process in the body based on the level of alpha-tumor necrosis factor. In addition to the high level of anti-endometrial antibodies depending on the recovery of reproductive function after laparoscopy in women with genital endometriosis, the statistically honest specificity and sensitivity of this indicator were determined. In these cases, prevention of autoimmune processes and selection of Erstra Corporal Fertilization as an alternative to restore women's reproductive functions can be considered appropriate.

## RESULTS

1. Clinical-laboratory and diagnostic examination of patients made it possible to detect forms of genital endometriosis: patients with peritoneal endometriosis -53%; patients with extraperitoneal endometriosis 31% and patients with mixed endometriosis -16%. Endometriosis of the fallopian tubes was found in 58.5% of patients, and endometriosis of the pelvis was found in 7.5% of patients [1].
2. According to the study, pain syndrome was observed in all forms of endometriosis - 94% of cases, 55% had dysmenorrhea, 16% had dyspareunia, and 23% had chronic pelvic pain unrelated to menstruation. Depending on its localization, the clinical signs of endometriosis showed that pain syndrome in group I was observed more in patients with ovarian endometriosis; this symptom was 100% in pelvic and mixed forms of endometriosis; in the case of endometriosis of uterine tubes, this percentage was 87.1%. Dysmenorrhea was more characteristic of patients with ovarian endometriosis in 66.6% cases compared to other localizations. Dysmenorrhea in patients with mixed endometriosis 55.6%, in the form with endometriosis of the fallopian tubes - 42.1%, it was found in 25.0% of cases with pelvic endometriosis. Dyspareunia was found mostly in fallopian tube endometriosis - 22.7% and ovarian endometriosis - in 16.7% of patients [2,3].
3. Symptoms of immunodeficiency and autoimmunity have been observed in patients with genital endometriosis, which leads to



weakening of immune control. In the course of our research, it was discovered that patients with genital endometriosis have an active pathological process, which, in turn, creates conditions for the implantation and development of functional foci of the endometrium in localizations that are not normal for them. Accordingly, the occurring pathological process is characterized by morphological, hemodynamic, vascular and connective tissue changes at the cellular level, which ensures the progression of the endometrioid focus and the emergence of adhesion phenomenon [3].

4. Antiendometrial antibody levels increase in patients with genital endometriosis as disease severity increases, suggesting that antiendometrial antibody levels increase during progression of endometrioid heterotopy. High concentration of AEA among patients with genital endometriosis was observed in group II and III ( $73225.80 \pm 27099.45$  pg/ml and  $56562.50 \pm 40890.04$  pg/ml) and was statistically significantly higher than that of women in the control group. In all 3 study groups, the level of alpha-tumor necrosis factor was statistically significantly higher than in the control group. However, in patients belonging to group III, the level of alpha-tumor necrosis factor significantly increased compared to groups II and I (respectively,  $57.0189 \pm 4.31$  pg/ml;  $62.7097 \pm 4.57$  pg/ml and  $67.8750 \pm 5.93$  pg/ml), while in the control group this indicator changed to  $48.9667 \pm 7.51$  pg/ml. The concentration of IL-6 in patients belonging to groups III and I ( $19,6000 \pm 2,18$  pg/ml and  $15,58 \pm 0,98$  pg/ml, respectively) was higher than that of the control group ( $11,1700 \pm 2,85$  pg/ml). ml) increased relatively honestly ( $p < 0.05$ ) [4,6,7].
5. Women with genital endometriosis with high levels of autoimmune antibodies were significantly less likely ( $p < 0.05$ ) to recover reproductive functions after laparoscopy. In women with genital endometriosis with high levels of antiendometrial antibodies, in vitro fertilization after laparoscopic surgery is a more effective treatment method for infertility [5,6,8].

## PRACTICAL RECOMMENDATIONS

1. The obtained information on the diagnosis and treatment of genital endometriosis provides a basis for more effective treatment of patients.
2. The use of laparoscopy as an effective, informative and specific method for genital endometriosis of various degrees of severity in women of reproductive age leads to a decrease in infertility.
3. When the autoimmune process is active in the body, especially in women with genital endometriosis with a high titer of anti-endometrial antibodies, it is more appropriate to perform in vitro fertilization after laparoscopic surgery for the treatment of infertility.
4. In patients with suspicion of external genital endometriosis, it is recommended to determine the amount of globulin combining apolipoprotein-AIV and sex hormones in the blood serum. If the level of apolipoprotein-AIV in the blood serum is lower than 44.17  $\mu\text{g/ml}$ , and the globulin binding sex hormones is lower than 70.57  $\text{nmol/l}$ , then the diagnosis of external genital endometriosis is not confirmed. If the level of apolipoprotein-AIV in blood serum is higher than 44.17  $\mu\text{g/ml}$ , and globulin binding sex hormones is higher than 70.57  $\text{nmol/l}$ , then external genital endometriosis is diagnosed. For the differential diagnosis of the stages of external genital endometriosis, it is necessary to calculate the sex hormone-binding globulin/apolipoprotein-AIV ratio and when its value is lower than 2.7, the stage I-II of external genital endometriosis is detected, and when its value is greater than 2.7, the stage III-IV of the disease is detected.

## **LIST OF PUBLISHED SCIENTIFIC WORKS ON THE TOPIC OF THE DISSERTATION**

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## LIST OF ABBREVIATIONS

Apo-AIV - apolipoprotein-AIV  
anti-Tg - anti thyroglobulin antibodies  
anti-TPA - thyroid peroxidase antibodies  
SHBG -sex hormone binding globulin  
VEGF - vascular endothelial growth factor  
ECF - extracorporeal fertilization  
IL - Interlinkin  
Ig G, M, A – immunoglobulin G, M, A  
MALT — mucosa associated lymphatic tissue  
MCP-1 - monocyte chemoattractant protein-1  
RANTES - A chemokine expressed and produced by T-cells  
ROC curve - receiver operating characteristic  
St - infinity  
17P-OSD - 17p-oxysteroid hydrogenase  
TGF- $\beta$ 1 – transforming-  $\beta$ 1  
TNF-alpha - tumor necrosis factor - $\alpha$   
EGE - external genital endometriosis  
TNF – tumor necrosis factor  
VEGF - vascular endothelial growth factor





The defense will be held on « 12 » January 2024 at «      » at the meeting of the Dissertation council ED 2.06 of Supreme Attestation Commission under the President of the Republic of Azerbaijan operating at Azerbaijan Medical University.

Address: AZ1022, Baku city, A. Gasimzade st. 14, (conference hall).

It is possible to get acquainted with the dissertation work in the library of Azerbaijan Medical University.

The electronic version of the dissertation and abstract is posted on the official website of the Azerbaijan Medical University ([www.amu.edu.az](http://www.amu.edu.az)).

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