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ASSESSMENT OF OVARIAN RESERVE AND ROLE OF ITS DETERMINING FACTORS IN PATIENTS WITH ENDOMETRIOMAS COMBINED WITH PELVIC INFLAMMATORY DISEASE

R. V. Bihun, N. I. Henyk

Ivano-Frankivsk National Medical University,
Department of Obstetrics and Gynecology named after I. D. Lanovyi

Abstract

Resume. Endometriosis affects from 10% to 50% of women of reproductive age and is one of the most common diseases in gynecology. One of its most common kinds – ovarian endometrial cysts – accounts from 17% to 44% of all patients. **The aim of the study** was to evaluate the parameters of the ovarian reserve in patients with endometriomas combined with pelvic inflammatory disease. **Research materials and methods.** Two groups of patients were formed: group I included 45 women with endometriomas combined with pelvic inflammatory disease; group II consisted of 45 patients with isolated endometriomas. Generally accepted criteria were used to assess the ovarian reserve: FSH level, AMH > 1.0 n/ml, number of follicles D, volume of both ovaries. Statistical calculations included the method of calculating the odds ratio (OR) and its 95% confidental interval (95% CI).

Research results and their discussion. The frequency of the decrease in main parameters of the ovarian reserve showed a deviation in two-thirds of cases in women of group I (68.9%), which is 2.2 times more common ($p<0.05$). AMH parameters showed a deviation by 3.6 times compared to the control group, and by 1.7 times compared to the

parameters of group II ($p<0.05$). The average level of FSH in blood serum of women in group I was 2.0 times higher than the control indicators, and 1.5 times higher than the indicators of patients in group II. The number of antral follicles < 5 in group II was in 22.2% of observations; and in group 1 – in 91.1% ($p<0.05$). The endometrioma itself demonstrated a significant influence on the parameters of the ovarian reserve: in the case of a significant share of multiple bilateral endometrial cysts (OR=5.65; 95% CI: (1.71-18.67); $p<0.05$), their large sizes (OR=7.94; 95% CI: (3.0-21.0); $p<0.05$), combination with pelvic inflammatory disease, (OR=29.42; 95% CI: (6.33 -146.72); $p<0.05$) and tubo-ovarian tumours (OR=6.96; 95% CI: (1.44-33.51); $p<0.05$), as well as aggressive consequences during surgical intervention on both ovaries (OR=8.26; 95% CI: (2.65-25.79); $p<0.05$). **Conclusions.** About half of the patients with endometriomas combined with pelvic inflammatory disease note a decrease in the ovarian reserve. Statistically reliable factors are multiple and large ovarian endometrial cysts, a combination with recurrent pelvic inflammatory disease, tubo-ovarian tumours and surgical interventions on the ovaries.

Key words: endometrioma; pelvic inflammatory disease; ovarian reserve.

Topicality. Endometriosis affects from 10% to 50% of women of reproductive age and is one of the most common diseases in gynecology [1-4]. One of its most common kinds – ovarian endometrial cysts (OEC) – accounts from 17% to 44% of all patients [1]. According to literature sources, asymptomatic ovarian endometriosis was detected in 12% of cases of surgical intervention for surgical and gynecological pathology; 15.4% of women underwent surgery to remove benign tumours of the appendages [1, 2]. The question of the pathogenesis of endometrioma is quite debatable. Local synthesis of estrogens and resistance to progesterone create prerequisites for the development of the disease and the formation of autonomy of endometrial heterotopias [4, 16]. Inflammation of the peritoneum, dominance of the inflammatory component, primarily enhanced by the combination with pelvic inflammatory disease (PID) and an imbalance in the work of the immune system are the main key components in the pathogenesis of OEC and pro-inflammatory predictors, as well as immunological dysfunction in the form of impaired immune surveillance of autologous tissue contribute to the progression of endometrial heterotopias, which ultimately forms a symptomatic picture of the disease [1-4, 9, 10].

In recent years, scientific studies supporting the significant impact of endometriosis both on the reduction of fertility and on the consequences of pregnancy have appeared [8, 12]. Of special interest is the question of the genesis of infertility, first of all, a decrease in the

ovarian reserve, which can be caused by the spectrum of a number of pathophysiological processes caused by endometrioma in the ovarian tissue, and are confirmed by a decrease in serum anti-Mullerian hormone, the number of antral follicles, a decrease in the response to controlled stimulation of the ovaries and the need for more high doses of gonadotropins used in programs of assisted reproductive technologies [5, 6, 8, 15].

The causes of infertility in women with endometriosis are multifactorial, as the cysts themselves, and a decrease in the ovarian reserve after surgery can become the initiator in the mechanisms of infertility. The existing possibilities of surgical and medical treatment of endometriosis help to get pregnant only in 15-25% of cases, and after surgical treatment the chances of getting a spontaneous pregnancy are reduced by 4% annually [5, 6, 8, 11, 15].

Ambiguous and debatable scientific statements regarding the negative impact of endometrioma on OR remain relevant and not fully structured. Scientists continue their disputes on scientific forums regarding the priority of the negative impact on ovarian function: the presence of the cyst or cystectomy, which maintains the relevance of further scientific research [11, 14].

The aim of the study was to evaluate the parameters of the ovarian reserve in patients with endometriomas combined with pelvic inflammatory disease.

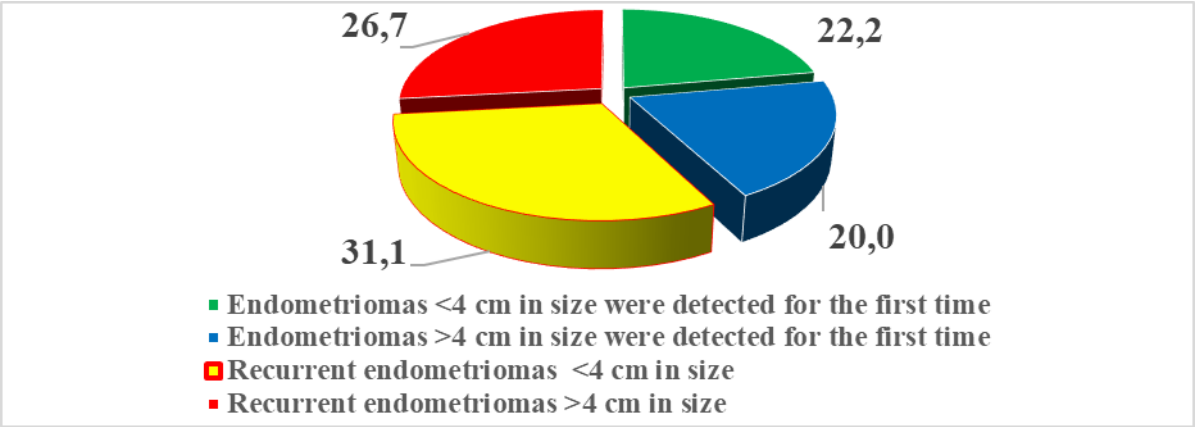
Research materials and methods. 90 patients with ovarian endometriomas who underwent a basic clinical and laboratory examination (assessment of family, obstetric and gynecological history, special gynecological examination), as well as an assessment of ovarian reserve parameters, took part in our study. In the process of scientific research, two groups were formed: group I consisted of 45 patients with endometriomas combined with pelvic inflammatory disease; group II included 45 patients with isolated endometriomas without comorbidity with clinically significant gynecological pathology. The control group (30 female patients) was formed in the same period of time from a group of conditionally healthy women who visited the doctor prophylactically for the purpose of annual medical examination. Randomization was carried out according to age, concomitant pathology, duration of the disease. The inclusion criteria were: age of patients from 18 to 40 years; a verified diagnosis of endometrioma against the background of a chronic inflammatory process or ineffective treatment of endometrioma; a burdened obstetric and gynecological anamnesis of chronic pelvic inflammatory disease; a medical history up to 5 years; absence of severe extragenital pathology; patient’s consent to participate in the study. Exclusion criteria were: patient general condition which does not allow participation in the study; a verified acute

specific sexually transmitted infection; uncompensated somatic pathology; aggravated allergy anamnesis; patients who refused to participate in the study.

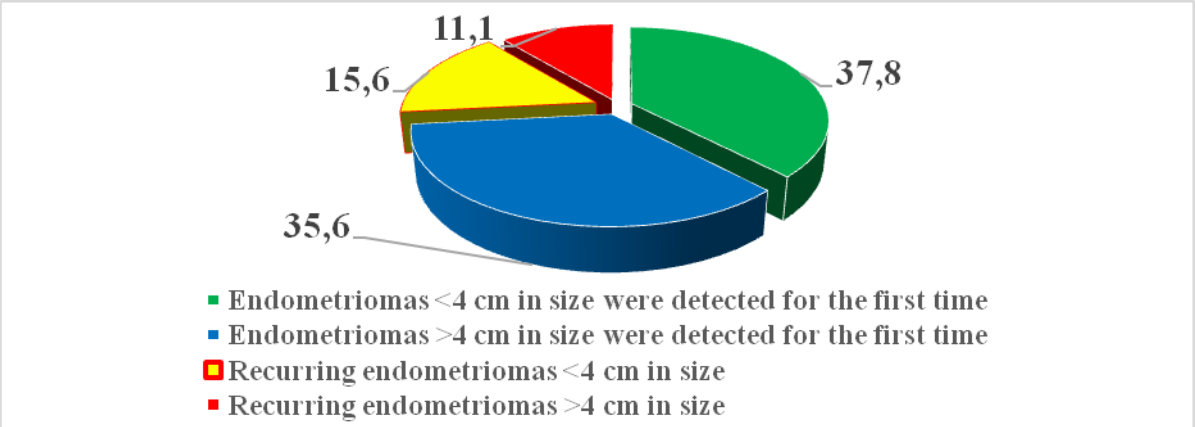
The concentration of protein hormones of the pituitary gland – follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin and steroid hormones: estradiol, progesterone, testosterone, anti-Mullerian hormone (AMH) and inhibin B in blood serum was carried out with the help of standard sets of Hema-Medyka reagents on analyzers "1420-Victor 2" according to the manufacturer's instructions. Generally accepted criteria were used to assess the ovarian reserve: FSH level (2^{nd} -3^{d} day of MC) < 10 IU/l, AMH level > 1.0 n/ml; thickness H 1.4 ± 0.4; the number of follicles D < 10 mm is not less than 10; the volume of both ovaries V, cm^3 is not less than 10. Sonographic examination of the pelvic organs was performed on an ultrasound device "ALOKA-SSD-1700" (Japan) using a vaginal sensor (7.5 MHz).

Statistical and mathematical processing of the research results was carried out according to the criteria of variational and statistical analysis with the calculation of average values (M), the error of the arithmetic mean (m) and using the Microsoft Excel computer program package. In order to identify risk factors for the reduction of OR, the method of calculating the odds ratio (OR) and its 95% confidental interval (95% CI) was used.

Research results and their discussion. The distribution of patients, taking into account the size and nature of endometriomas, showed a high proportion of recurrent OEC in patients with endometriomas combined with PID (57.8%), as well as two thirds of newly detected endometriomas in patients of group II (Figure 1).



a) group 1, p=45;



b) group 2, p=45;

Figure 1. Distribution of patients taking into account the size and nature of ovarian endometriomas, p=90, %.

The obtained results show an increase in the share of bilateral location of endometrioid cysts 2.4 times more often and multiple cysts 4.0 times more often in the case of a combination of endometrioma with PID, compared to the data of the group with isolated OEC ($p<0.05$).

In more than half of the observations, episodes of salpingitis, oophoritis in the anamnesis, signs of ecto-endocervicitis and vaginitis, as well as extragenital endometriosis were detected; in two-thirds of cases menstrual cycle disorders, ovarian retention formations and endometrial hyperplastic processes were found in every fourth case.

The analysis of gynecological, laboratory and instrumental examination data made it possible to present evidence and make a diagnosis of chronic pelvic inflammatory disease, although the verification of this diagnosis was not always accurate, reflecting the presence of PID to one degree or another (Figure 2).

Bimanual examination, along with the dominance of pain syndrome in the clinical symptomatology, confirmed a high share of cervical traction pain, limitation of mobility and painful appendages, an increase in appendages according to bimanual examination data (due to retention formations and endometriomas) and decrease in the volume of ovarian tissue according to ultrasound data which was confirmed in half of the observations; additional sonographic markers of pelvic inflammatory disease were also diagnosed, including changes in the sonographic picture of the uterine cavity, myometrium, endometrial echogenicity, etc., according to bacterioscopy – verification of STD.

The evaluation of characteristics of the reproductive function demonstrated its critically undesirable parameters in the case of OEC and its combination with PID with a

statistically significant dominance of the share of secondary infertility, an increase in the share of early spontaneous abortion by 2.4 times ($p<0.05$), as well as ectopic pregnancy by 2.0 times against the data of the group with isolated endometriomas, where preterm birth and miscarriage remained dominant (by 2.3 times, $p<0.05$).

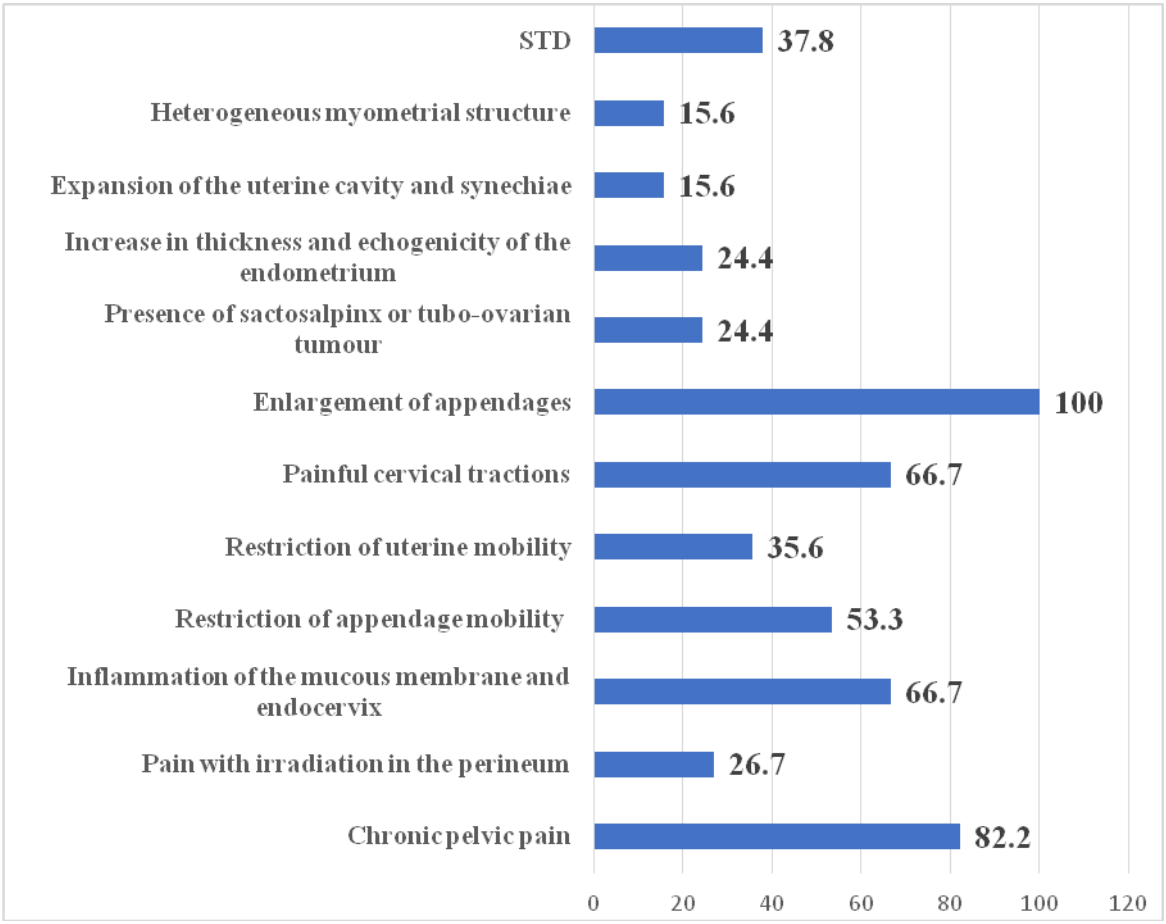


Figure 2. Peculiarities of clinical symptoms of PID in patients of group I, p=45, %

In the course of the study, a comparative evaluation of the hormone profiles of the examined groups was conducted and statistically significant differences were established in the main parameters characterizing the ovarian reserve (Table 1). First of all, it should be pointed out the different proportion of the reduction of the parameters of the OR in the studied groups: the frequency of the reduction of the main parameters showed a deviation in 31.1% of the observations in group II, and in two thirds of the cases in women with a combination of endometriomas with PID (68.9%) which is 2.2 times more frequent ($p<0.05$).

Average levels of AMH in patients with endometriomas against the background of PID were lower than in women with isolated endometriomas (1.8±0.1 ng/ml vs. 3.8±0.2 ng/ml, respectively ($p<0.05$)). In patients of group I, the level of AMH, as the earliest

and most informative marker of ovarian reserve, was reduced in 31.1% of observations, and its parameters showed deviations 3.6 times more often compared to the control group, and 1.7 times compared to the indicators of group II ($p<0.05$). It should be emphasized that the level of AMH in blood serum of women of group I was significantly lower than the threshold level (according to the Bologna criteria) and was 1.8±0.1 ng/ml (compared to 3.8±0.2 on average in group II).

The second marker, no less important marker of OR, is inhibin B, the decrease of which was most strongly noted in group I (59.6±4.3 pg/ml), which is statistically significant not only with control parameters, but also with indicators in group II (66.3±3.2 pg/ml, $p<0.001$).

Table 1

Parameters of the ovarian reserve according to the data of hormonograms, M±m, p=120

Parameters	Group 1, p=45	Group 2, p=45	Control group, p=30
AMH, ng/ml	1.8±0.1*	3.8±0.2*	6.5 ± 0.3
Inhibin B, pg/ml	59.6 ± 4.3*	66.3 ± 3.2	79.5 ± 0.5
FSH, IU/l	16.6 ± 1.2*	10.4 ± 0.7°	7.8±0.5
LH, ME/l	14.5±1.2*	8.6 ± 0.4°	6.2 ± 2.3

Notes:

1. * – the difference is significant against the data of the control group, $p<0.05$;
2. ° – the difference is significant against the data of group I, $p<0.05$.

There are also significant differences between both groups in the level of FSH in blood serum; in 37.8% the FSH level was within the normal range. The average level of FSH in blood serum in group I was 2.0 times higher than that in the control group, and 1.5 times higher than that in group II (10.4 ± 0.7 IU/l, $p<0.005$).

Thus, the level of the studied hormonal markers of OR in both groups shows indicators characterizing its low status, while the most informative marker should be the parameters of AMH, which shows statistically significant differences. The assessment of the concentration of inhibin B and FSH should not be excluded, while LH and estradiol in terms of information are not so significant.

The data on the hormonal examination of the OR state correspond to the parameters of the ultrasound examination, demonstrating a direct relationship between the level of AMH and the number of antral follicles (Table 2).

In patients of group I, the average ovarian volume was 3.1±0.3 cm^3, which is 2.9 times less compared to the control patients (9.1±2.1 cm^3), ($p<0.05$). Antral follicle count in the section, which is also one of the important parameters of OR, made it possible to demonstrate the lowest number in patients of group I, where indicators of normal reserve were found only in 8.9% of observations. The number of antral follicles < 5 in group II was in 22.2% of observations; in group I – in 91.1% ($p<0.05$).

Table 2

Parameters of the functional state of the ovaries, p=120, ABV, %.

Parameters	Group 1, p=45	Group 2, p=45	Control group, p=30
Right ovary volume, cm^3	3.3±0.2*	6.2±0.2°	9.3±0.2
Left ovary volume, cm^3	2.9±0.2*	5.4±0.3°	8.8±0.4
The number of antral follicles			
up to 5 follicles, ABV, %	41–91.1*	10–22.2*°	1–3.3
5-10 follicles ABV, %	4–8.9*	31–68.9°	22–73.3
10-15 follicles, ABV, %	0*	4–8.9*°	7–15.6

Notes:

1. * – the difference is significant against the data of the control group, $p<0.05$;
2. ° – the difference is significant against the data of group 1, $p<0.05$.

The assessment of risk factors determining OR in women of the examined groups made it possible to establish probable reasons for its decrease. Taking into account the data of literary sources published in recent years regarding the sharp reduction of the pool of primordial follicles after 36 years (up to 25,000) [3, 5, 6], we also established a greater proportion of older patients with OEC in group I (33.8±2.9 years compared to 30.2±3.7 years in group II, respectively). According to generally accepted statistics, women aged 20-30 are able to perform their reproductive function, but by the age of 40, only 50% of fertility reserves are preserved, and after 43, even in the absence of menopause, the physiological limitations of OR lead to its loss [3, 5, 6].

The features of a patient's "perinatal portrait" should be considered decisive; the comparative analysis of the value of the risk ratio of the factors demonstrated that placental dysfunction and preeclampsia in the examined patients' mothers had a fairly high prognostic significance for OR reducing, the risk exceeded by 10.7 times (OR=10.71; 95% CI: (3.44-

33.33); p<0.05), the premature birth factor (OR=13.79; 95% CI: (1.79-106.23); p<0.05), fetal hypotrophy (OR=6.75; 95% CI: (0.86-53.10); p<0.05), burdened heredity regarding reproductive function (OR=4.96; 95% CI: (1.39-17.65); p<0.05), etc. A long-term nicotine addiction (from puberty) played also a significant role (OR=2.38; 95% CI: (0.82-6.84); p<0.05).

The study of the somatic history made it possible to establish the role of extragenital diseases, namely thyroid pathology (OR=4.26; 95% CI: (0.94-19.39); p<0.05): hypothyroidism and autoimmune thyroiditis which initiate autoimmune damage not only in the endocrine system, but also in the reproductive sphere and ovaries. Thus, hypothyroidism was diagnosed in 12 (13.3%) cases, and autoimmune thyroiditis was revealed in 7 (7.8%) women.

Endometrioma itself, as a proliferative disease, demonstrated a significant influence on OR parameters. The obtained statistical calculations made it possible to note a considerable influence on the OR parameters in the case of a significant share of multiple bilateral endometrioid cysts (OR=5.65; 95% CI: (1.71-18.67); p<0.05), their large sizes (OR=7.94; 95% CI: (3.0-21.0); p<0.05), proliferative endomyometrial processes (OR=3.43; 95% CI: (1.42-8, 32); p<0.05). It should be emphasized that PID has the significant impact, especially chronic recurrent salpingo-oophoritis (OR=29.42; 95% CI: (6.33-146.72); p<0.05) and tubo-ovarian tumours (OR=6 .96; 95% CI: (1.44-33.51); p<0.05) as well as the predictive role of sexually transmitted infections (OR=5.45; 95% CI: (2.21-13 .43); p<0.05).

The most aggressive factor determining the decrease in the ovarian reserve was the factor of surgical intervention on the ovaries (ovarian resection); almost every third patient (31 women, 34.4%) had it. Risk analysis, taking into account the volume of surgical intervention, established a predominant role in surgical intervention on both ovaries – by 8.3 times (OR=8.26; 95% CI: (2.65-25.79); p<0.05).

Discussion. More and more scientific researchers prove the negative impact of OEC on the functional state of the ovaries and the quality of oocytes; they confirm their point of view in domestic and foreign research works [1-5]. Their conclusions are based on echographic, histological, as well as biochemical criteria: a decrease in the number of follicles in women with OEC, a greater number of atretic follicles, changes in the intrafollicular environment and granulosa cells, an increase in the level of intracellular free radicals, etc. [17, 18]. The authors demonstrate that the change in the status of oxidative stress partially explains the decrease in the number of follicles and oocytes developing in IVF cycles in women with bilateral endometriomas, the decrease in the rate of spontaneous ovulation in the ovaries

containing OEC [5, 8, 11]. At present, according to the results of the studied literary sources, it should be noted that endometriomas lead to damage of the surrounding tissues of the ovary, regardless of the size of the cyst [15, 18]. OEC contains biologically active substances, proteolytic enzymes and inflammatory mediators, ten times higher than the concentration in blood serum, which causes the alteration of tissues surrounding the ovary [13, 15, 18]. Such patients are recommended to be included in the high-risk group for the development of premature ovarian failure due to the need for surgical treatment and the possibility of recurrence.

In a systematic review, Sanchez A. et al. [17] demonstrated that the presence of an endometrioma leads to the ovarian damage, primarily due to its mechanical stretching, regardless of the size of the cyst.

According to other authors, the reduction of the ovarian reserve is most pronounced in patients with bilateral cysts, with a decrease in the number of primordial follicles by 60-80%, and antral follicles by 80-90% [6]. Surgical removal of intact tissue adjacent to the capsule reduces the number of oocytes, where each millimeter of intact tissue leads to a decrease in the number of antral follicles by 1.06 [16]. According to the results presented in the available literature sources, the total analysis of the number of antral follicles in the operated ovary with endometrioma is significantly lower than in the contralateral one [15].

A meta-analysis of anti-Müllerian hormone evaluation in 17 studies (968 women with OEC and 1874 control patients) demonstrated low levels of AMH even in isolated endometrioma [15], and its level does not depend on the volume of the removed intact ovarian tissue [14]. Another prospective study showed that endometriosis, like endometrioma, does not lead to a decrease in AMH; its level is affected only by surgical treatment [13]. At the same time, the adverse effect of laparoscopic cystectomy on ovarian reserve indicators depended on the size and location of the endometrioma [8, 9].

Surgical treatment is accompanied by a chain of risks, including tubo-peritoneal infertility, reduction of OR, premature ovarian insufficiency, anesthetic and infectious complications [7, 9]. A systematic review of 11 studies demonstrated a reduction in AMH levels after ovarian surgery, which is more significant in bilateral lesions, as well as a reduction in ovarian response to gonadotropin stimulation in controlled ovulation induction programs after cystectomy [9, 11]. The results of the research prompted the European Society of Human Reproduction and Embryology (ESHRE) to propose a refusal of surgical intervention and removal of endometriomas before IVF programs [8, 9, 11].

Thus, the processed literary sources allowed to confirm that even isolated endometriomas, as such, have a significant impact on the condition of the ovarian reserve and the reproductive function of a woman.

Conclusions. Thus, about half of patients note a decrease in OR, primarily in the group with endometriomas combined with PID. Statistically reliable factors for the reduction of OR are: age of a patient, pathological puberty, thyroid dysfunction, nicotine addiction; the dominant and determining prognostic factors are multiple and large ovarian endometrioid cysts, a combination with recurrent PID, tubo-ovarian tumours and surgical interventions on the ovaries, and also a high infectious status with the dominance of sexually transmitted infections.

Undoubtedly, it is not always possible to prevent a decrease in OR, but the awareness of practicing obstetricians and gynecologists about the factors that determine it in patients with endometriomas allows forming risk groups, calculating reproductive plans, correcting reproductive behaviour and developing rehabilitation directions for this category of patients, and it creates a perspective for further scientific research.

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