

## AN ALTERNATIVE METHOD OF SURGICAL TREATMENT OF OVARIAN ENDOMETRIOMAS FROM THE STANDPOINT OF PRESERVATION OF THE OVARIAN RESERVE

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■ **Hypothesis/aims of study.** Ovarian endometriomas are a great danger to the female reproductive function. In addition to the negative impact of the disease itself on ovarian reserve, the reproductive capabilities of women are influenced by surgery on the ovaries and subsequent hormonal therapy. Ovarian reserve after cystectomy of the endometriomas suffers more than after removal of other benign ovarian tumors. The solution of the problem can be obtained using sclerotherapy during laparoscopy. The aim of this study was to assess the impact of sclerosing endometriomas during laparoscopy on the ovarian reserve.

■ **Study design, materials and methods.** The study involved 36 patients aged 25–35 years. Inclusion criteria were genital endometriosis, endometrioma of one of the ovaries with a volume of 15–100 cm<sup>3</sup>, and pregnancy planning. Exclusion criteria were uterine fibroids, endometrial hyperplasia, polycystic ovary syndrome, and the previous operations on the ovaries and uterine tubes. The main group consisted of 18 patients who underwent sclerotherapy of an endometrioma during laparoscopy with a 70% ethanol solution. The comparison group comprised 18 patients who underwent cystovariectomy with bipolar coagulation of the tumor lining. Within 4 months after surgery, gonadotropin-releasing hormone agonists were administered. An ultrasound examination of the pelvic organs and determination of anti-Müllerian hormone (AMH) level were performed before surgery, after surgery, and after hormonal treatment.

■ **Results.** In both study groups, AMH level decreased immediately after surgery: in the main group, it reduced by 1.4 times, in the comparison group by 2.4 times. After termination of therapy with gonadotropin-releasing hormone agonists and recovery of the menstrual cycle, AMH level increased slightly (it was  $2.9 \pm 0.40$  ng/ml in the main group, and  $1.8 \pm 0.24$  ng/ml in the comparison group). Within 12 months after surgery, pregnancy occurred in 44.4% of patients in the main group and in 33.3% of patients in the comparison group. Over 16 months of follow-up, not a single case of recurrence of the disease was subsequently detected.

■ **Conclusion.** Sclerotherapy of endometriomas during laparoscopy is supposed to be an effective and promising technique aimed at preserving the ovarian reserve in this category of patients.

■ **Keywords:** endometriosis; endometriomas; ovarian reserve; anti-Müllerian hormone; laparoscopy; endometrioid cyst sclerosis.

## АЛЬТЕРНАТИВНЫЙ МЕТОД ХИРУРГИЧЕСКОГО ЛЕЧЕНИЯ ЭНДОМЕТРИОИДНЫХ ОПУХОЛЕЙ ЯИЧНИКОВ С ПОЗИЦИЙ СОХРАНЕНИЯ ОВАРИАЛЬНОГО РЕЗЕРВА

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■ **Актуальность.** Эндометриоидные опухоли яичников представляют большую опасность для репродуктивных возможностей женщины. Помимо отрицательного влияния самого заболевания на овариальный резерв негативную роль играют и оперативные вмешательства на яичниках, и последующая гормональная терапия.

Овариальный резерв после цистовариоэктомии эндометриоидной опухоли яичника страдает сильнее, чем после удаления других доброкачественных опухолей яичника. Решением проблемы может стать методика склерозирования при выполнении лапароскопических вмешательств.

**Цель** — оценить влияние на овариальный резерв методики склерозирования эндометриоидных опухолей яичников при лапароскопических вмешательствах.

**Материалы и методы исследования.** Обследовано 36 пациенток в возрасте 25–35 лет. Критерии включения: наружный генитальный эндометриоз с наличием эндометриоидной опухоли одного из яичников объемом 15–100 см<sup>3</sup>, планирование беременности. Критерии исключения: лейомиома матки, гиперпластические процессы эндометрия, синдром поликистозных яичников, а также наличие в анамнезе операций на придатках матки. Основная группа — 18 пациенток, которым во время лапароскопии производили склерозирование эндометриоидной опухоли яичника 70 % раствором этилового спирта. Группа сравнения — 18 пациенток, которым выполняли цистовариоэктомию с биполярной коагуляцией ложа опухоли. В течение 4 мес. после операции назначали лечение агонистами гонадотропин-рилизинг-гормона. Ультразвуковое исследование органов малого таза и определение антимюллера гормона проводили до операции, после операции и после окончания гормонального лечения.

**Результаты исследования.** В обеих группах сразу после операции было выявлено снижение уровня антимюллера гормона: в основной группе — в 1,4 раза, в группе сравнения — в 2,4 раза. После окончания терапии агонистами гонадотропин-рилизинг-гормона и восстановления менструального цикла уровень антимюллера гормона незначительно повысился (в основной группе он составил  $2,9 \pm 0,40$  нг/мл, в группе сравнения —  $1,8 \pm 0,24$  нг/мл). В течение 12 мес. после операции беременность наступила у 44,4 % пациенток основной группы, в то время как в группе сравнения — у 33,3 %. За 16 мес. наблюдения не было выявлено ни одного случая рецидива заболевания.

**Выводы.** Склерозирование эндометриоидных опухолей яичников при лапароскопических вмешательствах является эффективной и перспективной методикой, направленной на сохранение овариального резерва у данной категории пациенток.

■ **Ключевые слова:** эндометриоз; эндометриоидная опухоль яичника; овариальный резерв; антимюллеров гормон; лапароскопия; склерозирование эндометриоидной кисты.

## Introduction

One of the most common gynecological diseases in women of reproductive age is endometrioid disease, a chronic, benign, estrogen-dependent process based on the implantation, growth, and development of endometrial-like tissue outside the uterine cavity [1–8]. The incidence of endometriosis ranges from 5% to 10% [3, 4]. The disease is mainly manifested by pelvic pain syndrome and infertility [2]. Endometriosis constitutes approximately 50% of all cases of female infertility. The fertility rate in this disease is 0.02–0.10, while in healthy women, it is 0.15–0.20 [5–7]. The effect of endometrioid disease on fertility is multifactorial. However, the most significant is the decrease in the ovarian reserve, which is the functional reserve of the ovary and determines the ability to develop a healthy follicle with a full egg [9]. Endometrioid ovarian tumors are more dangerous for the ovarian reserve than other benign tumors. The cortical substance of the ovary surrounding the endometrioid cyst and forming its wall differs from healthy tissue in the low density of follicles and lower cortical specificity of the stroma [10]. With endometrioid cysts, surgical intervention is required. Also, they require the creation of a long-term treatment plan with the maximum use of drug therapy, which often harms the ovarian reserve [8]. Therefore, in addition to the negative impact of the disease itself, it is necessary to consider the effect of

surgical interventions on the ovaries and subsequent hormonal therapy on the reproductive capabilities of women [11–13]. According to available data, the ovarian reserve after cystovariectomy of the endometrioid ovarian tumor suffers more than after removal of other benign ovarian tumors, due to the greater loss of the ovarian cortex [11, 12, 14, 15]. In this regard, a recently formed opinion holds that it is inappropriate to conduct a cystectomy of endometrioid ovarian tumors with a maximum size of less than 3 cm in patients planning a pregnancy, with preserved spontaneous ovulation in the affected and contralateral ovaries [16, 17].

The key to preserving the ovarian reserve during cystovarioectomy of endometrioid ovarian tumors is the optimization of the surgical approach. It is well known that the use of electrocoagulation in laparoscopic interventions causes a microhemodynamic disorder around the follicles themselves and the redistribution of circulating gonadotropins both at the point of electrosurgical exposure and beyond [14, 15, 18, 19]. Electrocoagulation of the bed of the endometrioid tumor of the ovary when it is removed leads to a more pronounced decrease in the ovarian reserve than when hemostasis is achieved by other methods (individual sutures, use of hemostatic matrices) [20–23]. There is also evidence of the lack of difference in the level of anti-Mullerian hormone (AMH) in patients after laparoscopic

cystovariectomy of endometrioid ovarian tumors, regardless of whether the electrocoagulation of the tumor bed was performed [24, 25]. It is essential to understand that the AMH level reflects only the quantity and quality of the cohort that has entered into folliculogenesis and not the actual number of follicles in the ovary. If during the surgery, the ovarian tissue was not damaged, and the selection is performed from healthy primordial follicles, then the AMH level after surgery can be restored [26].

Techniques that minimize the negative impact of surgical intervention on the ovarian reserve include aspiration (sclerosing) therapy of endometrioid ovarian tumors under ultrasound guidance. This method of treatment is most often used in patients with relapses of the endometrioid tumor in a single ovary [27–29]. The results indicate that with sclerosing of endometrioid ovarian tumors under ultrasound control, it is possible to maintain an ovarian reserve, but the technique has a high relapse rate (from 1.8% to 62.5%). Such substantial differences in efficacy presented in the literature can be explained by different periods of monitoring of patients after surgery, the choice of hormonal therapy (gonadotropin-releasing hormone agonists, dienogest, oral contraceptives), and the fact that such a treatment option prevents coagulation and excision of endometrioid heterotopia in the pelvis [28, 29].

Thus, the optimal surgical approach for endometrioid ovarian tumors has not yet been determined. A promising solution to the problem of preserving the ovarian reserve and simultaneously preventing relapse can be the use of sclerotherapy of endometrioid ovarian tumors during laparoscopic interventions.

Our study aimed to assess the effect on the ovarian reserve of sclerosing the endometrioid ovarian tumors during laparoscopic interventions.

### Materials and research methods

The study included 36 patients aged 25 to 35 years who underwent treatment in the Department of Operative Gynecology of the D.O. Ott Scientific Research Institute of Obstetrics, Gynecology, and Reproduction. Criteria for inclusion in the study were external genital endometriosis with an endometrioid tumor of one of the ovaries sized from 15 to 100 cm<sup>3</sup> (the volume was calculated by the formula for determining the volume of ellipsoid bodies  $V = A_x B_x C_x 0.52$ ) and pregnancy planning. Exclusion criteria were uterine leiomyoma, hyperplastic endometrial processes, polycystic ovary syndrome, and a history of surgery in uterine appendages. All patients

underwent a standard preoperative examination. In addition, before surgical treatment on the days 2–3 of the menstrual cycle, all patients underwent an ultrasound examination to evaluate the anatomy of the pelvic organs. In addition, blood levels of AMH were determined, as well as the content of tumor markers Ca-125 and HE-4. The severity of pain was assessed using a visual analog scale in points from 0 to 10 before surgery and after hormone therapy.

Before surgery, patients were randomly divided into two groups, the study group and the comparison group. The study group consisted of 18 patients who underwent surgical treatment for external genital endometriosis with laparoscopic access in the volume of separation of adhesions, excision, and coagulation of pelvic peritoneal endometriosis foci and sclerosing of the endometrioid tumor of the ovary. In our study, the endometrioid tumor of the ovary was sclerosed according to the original method. After puncture of the ovarian endometrioid tumor capsule, its contents were aspirated and sent for cytological examination. Subsequently, a section of the cyst capsule 0.5 × 0.5 cm in size was excised and was sent for histological examination. Then, a 70% solution of ethyl alcohol was injected into the tumor cavity, which was evacuated after 2 min of exposure. The comparison group consisted of 18 patients who underwent surgical treatment for external genital endometriosis with laparoscopic access in the volume of separation of adhesions, excision, and coagulation of the pelvic peritoneal endometriosis foci, cystovariectomy, in which hemostasis was achieved by bipolar coagulation of the bed of the endometrioid ovarian tumor.

The severity of endometriosis (in points) was evaluated intraoperatively using R-AFS (revised classification of the American Fertility Society) [30]. During the surgery, patients of both groups underwent sonographic hydrotubation with a dye test with a 0.3% solution of indigo carmine to determine the patency of the fallopian tubes. After careful hemostasis and pelvic sanitation, an anti-adhesion barrier was applied to the patients of both groups. This barrier, which was a gel made of a highly purified sodium salt of hyaluronic acid (Antiadgesin, Nizhpharm, Russia), was put in the sites of separation of adhesions on the operated ovaries and the pelvic peritoneum. At the second stage, all patients were examined and underwent diagnostic hysteroscopy and endometrial biopsy.

Surgical interventions in all patients were performed in the first phase of the menstrual cycle using a set of equipment for endoscopic surgery manufactured by Karl Storz.

On day two after surgery, a controlled ultrasound examination of the pelvic organs was performed.

All patients were observed after discharge on an outpatient basis in the scientific and outpatient department of the D.O. Ott Scientific Research Institute of Obstetrics, Gynecology, and Reproduction within four months after surgery. The patients of both groups received treatment with gonadotropin-releasing hormone agonists (Buserelin-Depot, Pharm-Sintez, Russia) at a dose of 3.75 mg intramuscularly with an interval of 28 days. Before starting therapy, the level of AMH was repeatedly determined to assess the effect of surgery on the ovarian reserve.

After hormone therapy was completed, on days 2–3 of the menstrual cycle, the preservation of the ovarian reserve was re-evaluated in the second cycle after the restoration of menstruation. For this purpose, an ultrasound examination of the pelvic organs was performed, including the determination of the volume of the ovaries and the number of antral follicles, and the evaluation of the level of AMG.

Before the start of the study, all patients signed informed consent for participation. Statistical processing of the results was conducted using the software Statistica 8.0; the statistical significance level for all statistical tests was taken as 0.05.

## Study results and discussion

The average age of the patients included in the study group was  $28.4 \pm 0.5$  years, and that of the patients in the comparison group was  $29.8 \pm 0.7$  years. Table 1 presents the results of a preoperative examination of patients of the groups under study. The Table shows that patients in both groups were comparable in the studied parameters.

Table 2 presents the average duration of the surgery and the amount of intraoperative blood loss. The duration of the surgery in patients in

the study group and the comparison group did not significantly differ. There were no significant differences in the volume of intraoperative blood loss, and there were no significant differences in the scoring of endometriosis severity by R-AFS.

During surgery, patency of the fallopian tubes was assessed in all the patients. Five patients (three from the study group and two from the comparison group) had a disorder of their patency. In two patients from the study group and one from the comparison group, this was because of adhesions in the ampullar section of the fallopian tubes. After their separation, the patency of the fallopian tubes was restored. Two patients (one from the study group and one from the comparison group) had the patency of the fallopian tubes in the interstitial section.

The postoperative period in all patients proceeded without complications. On the second day after surgery, an ultrasound examination of the pelvic organs was performed on them. In patients of the study group, during the ultrasound examination of the operated ovary, a homogeneous liquid formation was visualized, having a diameter of not more than 2.0 cm. The patients were discharged on days 4–6 after surgery. The duration of hospital stay after surgery did not depend on the approach. To assess the effect of the surgery on the indicators of the ovarian reserve, the AMH level was redetermined before the start of therapy with gonadotropin-releasing hormone agonists. In both groups, a decrease in the level of AMH because of surgical treatment was revealed. In the study group, the level of AMH decreased by 1.4 times and amounted to  $2.5 \pm 0.5$  ng/ml, whereas in the comparison group, it decreased by 2.4 times to  $1.3 \pm 0.4$  ng/ml.

Patients with intraoperatively detected obstruction of the fallopian tubes in the interstitial

Table 1 / Таблица 1

### Results of preoperative examination of patients in the study groups

#### Результаты предоперационного обследования пациенток исследованных групп

Indicators	Study group (n = 18)	Comparison group (n = 18)	Significance of differences, p
Volume of healthy ovary, cm <sup>3</sup>	$7.9 \pm 2.1$	$7.2 \pm 1.8$	N/S
Ovarian volume with tumor, cm <sup>3</sup>	$35.2 \pm 3.6$	$34.2 \pm 4.1$	N/S
Volume of endometrioid tumor, cm <sup>3</sup>	$26.8 \pm 3.8$	$24.6 \pm 3.0$	N/S
Number of antral follicles, pcs.	$15.3 \pm 1.5$	$16.4 \pm 1.4$	N/S
Anti-Mullerian hormone, ng/ml	$3.4 \pm 0.7$	$3.1 \pm 0.5$	N/S
CA-125, U/ml	$49.6 \pm 4.2$	$51.4 \pm 3.9$	N/S
HE-4, pmol/l	$32.8 \pm 3.1$	$34.2 \pm 2.6$	N/S

Note. N/S —not significant.



Table 2 / Таблица 2

**Characteristics of surgical treatment of patients in the study groups****Характеристика хирургического лечения пациенток исследованных групп**

Indicators	Study group (n = 18)	Comparison group (n = 18)	Significance of differences, p
Duration of the surgery, min	50 ± 7	48 ± 5	N/S
Amount of blood loss, ml	34.5 ± 6.0	40.3 ± 8.2	N/S
Evaluation of the severity of endometriosis by R-AFS, points	46.2 ± 2.6	44.8 ± 3.1	N/S

Note. N/S —not significant.

section (one in the study group and one in the comparison group) did not participate in the further stages of our study since they were recommended to plan pregnancy using assisted reproductive technologies. They were included in the super-long IVF protocol. Both of them became pregnant on the first attempt.

The remaining patients (17 from the study group and 17 from the comparison group) received therapy with gonadotropin-releasing hormone agonists (Buserelin) at a dose of 3.75 mg intramuscularly with an interval of 28 days for four months after the surgical stage of treatment. In two patients from the study group and one patient from the comparison group, after the end of therapy, pregnancy occurred without restoring the menstrual cycle. In the remaining 15 patients in the study group, the periods of menstruation recovery after the injection four of the gonadotropin-releasing hormone agonist amounted to  $70 \pm 3$  days. In 16 patients in the comparison group, the periods of menstruation recovery were  $64 \pm 2$  days (N/S). Table 3 presents the results of ultrasound and hormonal examinations conducted in the second cycle after the restoration of menstruation.

Surgical treatment had a stronger effect on the volume of the affected ovary in patients in the comparison group. A noticeable decrease in the number of antral follicles was also registered. After surgical treatment, the number of antral follicles in patients in the comparison group was significantly less than in the study group. If a homogeneous fluid formation was visualized immediately after surgical treatment in patients in the study group on the operated ovary, having a diameter of not more than 2.0 cm, then after treatment with gonadotropin-releasing hormone agonists and restoration of the menstrual cycle, the ovary acquired a normal acoustic structure in all patients.

In patients in the study group, a decrease in the level of AMH remained, which, nevertheless, was statistically insignificant ( $3.4 \pm 0.7$  ng/ml before surgery,  $2.5 \pm 0.5$  ng/ml after surgical treatment,

and  $2.9 \pm 0.4$  ng/ml after hormonal treatment ( $p \leq 0.05$ ). In the comparison group, the decrease in the AMH level was more pronounced ( $3.1 \pm 0.5$  ng/ml before surgery,  $1.3 \pm 0.4$  ng/ml after surgical treatment, and  $1.8 \pm 0.24$  ng/ml after hormonal treatment ( $p \leq 0.05$ ). Moreover, the AMH level in the comparison group was significantly lower than that in the study group.

After treatment, the severity of pain decreased in both the study group and the comparison group (Table 4).

Pregnancy in the natural cycle was planned in 34 patients (94.4 %). Over the follow-up period of 12 months, spontaneous pregnancy occurred in 14 patients, which amounted to 43.8 %. The distribution of patient groups is presented in Table 3.

After treatment, pregnancy occurred in almost half of the patients of the study group, whereas in the comparison group, pregnancy occurred in only a third of patients (33.3 %) within 12 months after the surgery. No cases of spontaneous abortion were registered among these patients (Table 5).

In general, the follow-up period for patients was approximately 16 months. During this time, not a single case of disease recurrence was detected.

## Conclusion

The results showed that the method of sclerosing endometrioid ovarian tumors during laparoscopic interventions enables the reduction of the negative effect on the ovarian reserve of the ovaries, compared with electrosurgery to achieve hemostasis of the tumor bed during cystovarioectomy. Comparing the data of our study with the results of using hemostatic matrices during laparoscopic interventions on the ovaries for endometrioid tumors, we can equate them according to the criteria of efficacy to preserve the ovarian reserve and ensure safety [22, 23]. Moreover, the lower cost of the sclerotherapy method is its indisputable advantage.

In our study, there was not a single case of disease recurrence over 16 months of follow-up.

Table 3 / Таблица 3

## Results of examination of patients in the study groups after surgical and hormonal treatment

## Результаты обследования после хирургического и гормонального лечения в исследованных группах

Indicators	Study group (n = 15)	Comparison group (n = 16)	Significance of differences. p
Volume of healthy ovary. cm <sup>3</sup>	7.3 ± 2.3	6.7 ± 1.5	N/S
Volume of operated ovary. cm <sup>3</sup>	5.9 ± 0.8	3.0 ± 0.6	N/S
Number of antral follicles. pcs	13.8 ± 1.5	9.1 ± 1.4	≤0.05
Anti-Mullerian hormone. ng/ml	2.9 ± 0.4	1.8 ± 0.24	≤0.05

Note. N / S —not significant.

Table 4 / Таблица 4

## Results of assessing the severity of pain syndrome using a visual analogue scale before and after treatment in the study groups

## Результаты оценки выраженности болевого синдрома по визуально-аналоговой шкале до и после лечения в исследованных группах

Evaluation timeframe	Study group		Comparison group	
	n	points	n	points
Before surgical treatment	18	5.2 ± 0.8	18	5.9 ± 0.9
After treatment (after the restoration of the menstrual cycle)	15	0.4 ± 0.3	16	0.7 ± 0.6

Such optimistic results are probably because of laparoscopic access, unlike cyst puncture under ultrasound guidance that enables the surgeon to perform salpingoovariolysis, assess the extent of endometriosis, perform the excision, coagulation of its foci on the peritoneum, and sclerotherapy of the cyst capsule under visual control, and confirm the diagnosis histologically. Thus, in contrast to the already proven method of sclerotherapy of endometrioid, ovarian tumors under ultrasound control [27–29], our study shows the need for their sclerosing precisely during laparoscopic interventions, which in this case, provides complete surgical treatment of patients with external genital endometriosis.

## Additional information

The authors declare no conflict of interest related to the study and publication of this article.

Table 5 / Таблица 5

## Frequency of pregnancy after treatment in the study groups

## Частота наступления беременности после лечения в исследованных группах

Study group n = 18		Comparison group n = 18	
n	M ± m, %	n	M ± m, %
8	44.4 ± 11.7	6	33.3 ± 11.1

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