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Ovarian reserve after treatment of ovarian endometriomas by ethanolic sclerotherapy compared to surgical treatment

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Abstract. – OBJECTIVE: To preserve ovarian reserve, we treated ovarian endometriomas by ultrasound-guided aspiration followed by sclerotherapy of the cyst mucosa. We compared the results with laparoscopic cystectomy.

PATIENTS AND METHODS: We conducted a retrospective study of 96 women with ovarian endometriomas. In 54 of the women, ultrasound-guided aspiration of the contents was performed, followed by chemical sclerotherapy of the cyst plaque with ethanol. Laparoscopic cystectomy was performed in the remaining 42 women.

RESULTS: Statistical analysis of anti-Mullerian hormone (AMH) levels before and after the procedures showed a significant decrease in the case of cystectomy compared with ethanolic ovarian sclerotherapy (EOS).

CONCLUSIONS: Conservative treatment by echo-assisted puncture and sclerotherapy with ethanol proved to be a viable treatment for the removal of ovarian endometriomas. It is a simple procedure that does not affect ovarian reserve or fertility.

Key Words:
Ovarian endometrioma, Ethanol sclerotherapy, Cystectomy, Anti-mullerian hormone, Ovarian reserve.

Introduction

Endometriosis affects approximately 5-10% of the female population, with an even higher prevalence in women with infertility (20-30%)[1].

Ovarian endometrioma is the most common form of endometriosis. It occurs in about 17-46% of cases in which endometriosis is diagnosed[2].

Laparoscopic cystectomy is one of the most used surgical procedures for ovarian endometrioma. It has a recurrence rate of about 30% after 5 years but is also associated with damage to the ovarian reserve[3].

One study[4] shows that 6 months after surgery for ovarian endometriomas, the level of anti-Mullerian hormone (AMH) drops dramatically. This study should be considered when operating on a woman with minimal symptoms or low ovarian reserve. In attempts to remove endometriomas, it has often been reported that healthy ovarian tissue was removed. As a result, the ovarian reserve has been compromised[4-6].

Aspiration puncture and ethanol sclerotherapy have been shown to be effective in the treatment of thyroid, spleen, kidney, or liver cysts[7]. Chemical substances such as ethyl alcohol, methotrexate, or tetracycline are usually used in sclerotherapy of cysts.

Several studies[8-15] have described ethanol ovarian sclerotherapy (EOS) for the treatment of ovarian cysts, including endometriomas, with a recurrence rate of about 50%.

After EOS, pelvic pain seems to disappear without affecting ovarian reserve[13,16].

Other studies[17] have reported a better response to assisted reproductive techniques after EOS for ovarian endometriomas.

The present study was necessary because we wanted to compare the effect of ovarian sclero-

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therapy with laparoscopic cystectomy for preserving female fertility.

Patients and Methods

This observational retrospective study included 96 women in the fertile phase who were evaluated between January 2018 and September 2022. Demographic and clinical characteristics were recorded in all patients. We examined only ovarian endometriomas with a diameter of 3-8 cm, with no lesions suggestive of cyst malignancy.

We diagnosed the ovarian endometriomas by ultrasound. We used the criteria for ultrasound diagnosis established by the International Ovarian Analysis (IOTA): Cyst with thin capsule, with hypoechoic, homogeneous ultrasound content. Ultrasound diagnosis was performed using a Voluson S10 ultrasound machine equipped with a 7-MHz vaginal probe and a puncture aid (GE Medical Systems, Milwaukee, WI, USA). To confirm the diagnosis, we determined the serum level of Ca125.

To exclude cases with advanced extraovarian endometriosis and ovarian malignancy, we performed contrast magnetic resonance imaging (MRI) of the abdomen and pelvis in suspicious cases.

Inclusion Criteria

The inclusion criteria for the study were: age 20-35 years, ovarian endometrioma with definite features of ovarian endometrioma, size of ovarian endometrioma between 3-8 cm, unilocular cyst, serum Ca125 with levels between 35 and 200 U/ml, and signed informed consent.

Exclusion Criteria

The exclusion criteria were cysts with mixed structure (solid and liquid), dermoid cysts, cysts with intracystic septa, or signs that might indicate an increased risk of malignancy on ultrasound or MRI examination.

In 54 of the women enrolled in the study, we used the evacuation technique by echo-assisted aspiration followed by chemical sclerotherapy of the cyst lining. In 42 women, we performed laparoscopic cystectomy (complete removal of the capsule).

In the evacuation and alcoholisation technique, we punctured the cyst with a 17G puncture needle, a device also used in the follicular aspiration technique of *in vitro* fertilization (Wallace® Single Lumen Oocyte Recovery Systems, CooperSurgical, Ballerup, Denmark). We performed echo-guided evacuation of the cyst contents using a suction pump (Origio Suction Pump, CooperSurgical, Ballerup, Denmark).

Procedure

Patient in gynecological position under intravenous short-term anesthesia with propofol (Fresenius Kabi Deutschland GmbH, Bad Homburg, Germany). Attachment of the sterile needle guide to the vaginal ultrasound probe. The vagina is disinfected with an antiseptic solution for mucous membranes. The ovarian endometrioma was identified and punctured. We tried to puncture the cyst in its central area. Aspiration of the cyst contents was done at a negative pressure of about 100-200 mmHG. We noted the amount of fluid aspirated from the cyst and then added about 60% of this amount in the form of 96% ethyl alcohol. We left this amount of alcohol in the cyst for about 7 minutes, after which the cyst contents were aspirated. When the cyst contents were thick, we diluted them with a saline solution. The extracted contents were sent for cytology.

After the puncture, patients were examined by ultrasound 3 months and 6 months after the procedure. Recurrence was defined as the appearance of an endometrioma on the same ovary with a size of at least 3 cm.

The laparoscopic procedure attempted to preserve the healthy ovarian tissue. In a few cases, electrocoagulation was required to stop bleeding, which was performed with monopolar or bipolar diathermy. All procedures were performed with laparoscopic devices (Karl Storz SE & Co. KG, Tuttlingen, Germany), under general anesthesia. In all cases, the level of AMH was determined before the procedure and 3 months after the procedure.

Statistical Analysis

We compared AMH levels between patients in the two groups. We compared the data of the group of patients treated with EOS with those of the group treated with laparoscopic cystectomy. We checked the continuous data of the two groups and the normality of their distribution with a Kolmogorov-Smirnov test, which showed that the distribution was normal. To determine whether the difference between the results of the two groups of patients was statistically significant, we used the paired *t*-test. $p < 0.05$ was considered

Table I. Patient characteristics.

	Interval, mean/ median
Age	20-35 (27.74)
BMI	20.07-32.37 (25.97)
Ethnicity	100% Caucasian
Menstrual pain	75 (78.1%)
Dyspareunia	30 (31.25%)
Regular menstrual cycle	80 (83.33%)
Urban environment	76 (79.1%)

statistically significant. StatsDirect 3 software (version 2.8.0, StatsDirect Ltd, Cambridge, UK) was used for power calculation and data analysis. The present study was approved by the ethics committee of the HitMed Medical Centre (decision number: 10/13, 2021).

Results

Patients included in the study had the following characteristics: age, BMI, ethnicity, menstrual pain, dyspareunia, regular menstrual cycle, and urban environment (Table I).

We studied a group of 96 female patients. 54 of them fulfilled the conditions for performing EOS. The remaining 42 cases were treated by laparoscopic cystectomy. Most of them were between 30 and 35 years old (Figure 1).

The size of endometriomas treated by laparoscopy or EOS ranged from 3 to 8 cm. 31.3% of all patients were found to have an ovarian endometrioma larger than 6 cm, and 68.7% of patients were found to have an ovarian endometrioma smaller than 6 cm. The painful complications that occurred during the EOS procedure were not significant, as all patients were sedated during the procedure. We had no cases of extravasation of ethanol into the pelvis. It is known that this chemical agent, when extracapsular, can cause chemical peritonitis. No other complications occurred during the EOS procedure. After the EOS procedure, only 6 cases (11.1%) complained of pelvic pain requiring the administration of non-steroidal anti-inflammatory drugs. No atypical cells were detected in the pathological-cytological results of the puncture fluid. The duration of the hospital stay was one day for sclerotherapy. Laparoscopic cystectomy requires a length of stay of 3-7 days.

The average follow-up time after the procedure was 6 months, and we had a recurrence in 4 of the 54 patients with EOS (7.4%). Not a single patient with recurrence underwent surgical treatment, and we met the expectations in all cases. The symptoms (pain, discomfort) disappeared in 26 cases (48.1%) after sclerotherapy.

3 and 6 months after the EOS procedure, we observed a strong reduction of the endometrioma diameter EOS with a process of local fibrosis (Figure 2).

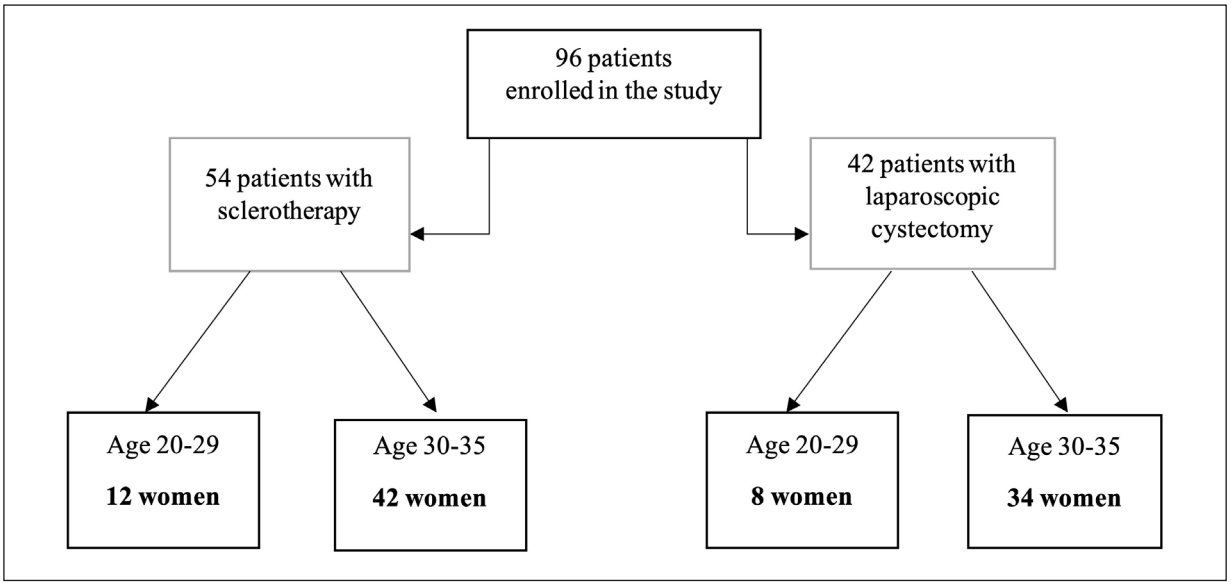

Figure 1. Distribution of patients by treatment and age groups.

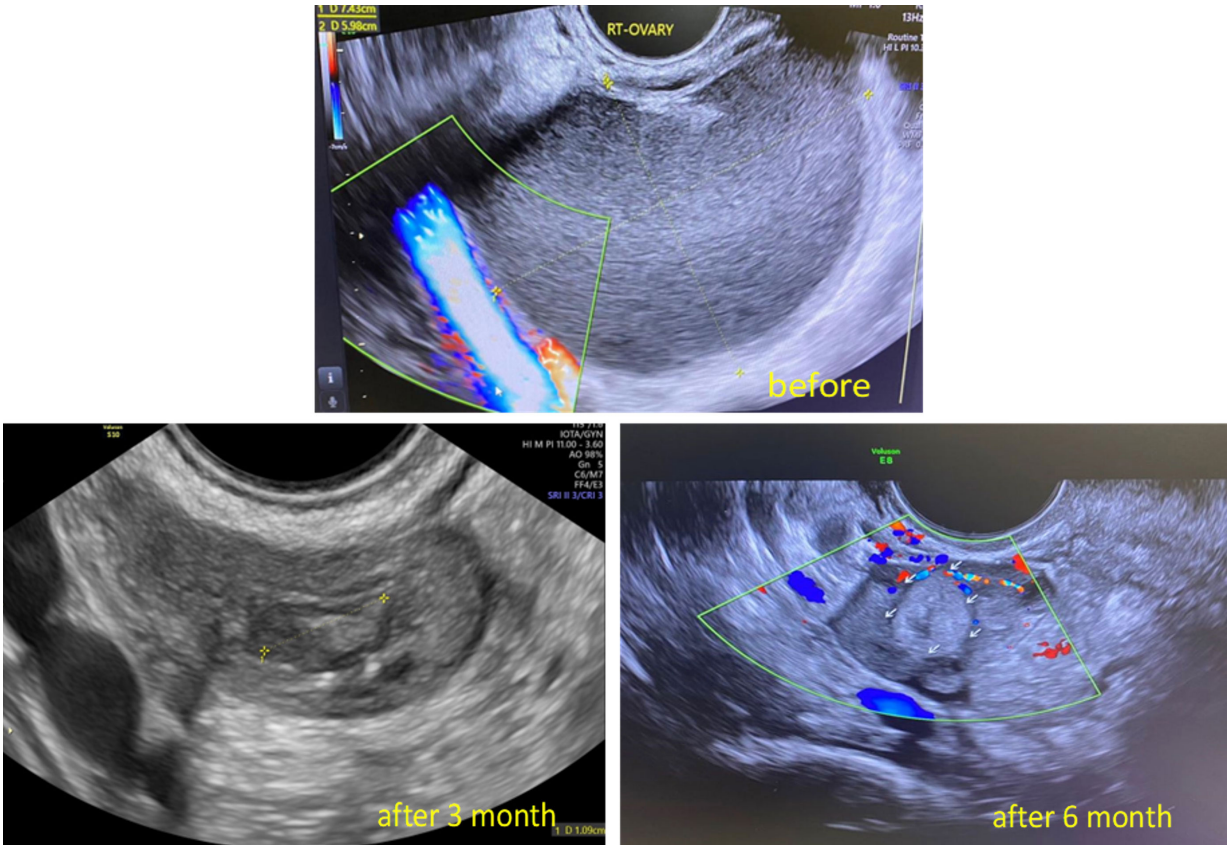

Figure 2. Ultrasound images before sclerotherapy and after sclerotherapy. A considerable reduction in the size of the ovarian endometrioma can be observed (from 8 to 1 cm).

AMH hormone levels were determined before the procedure and 3 months after the procedure. Two groups of patients were formed depending on the type of procedure performed:

– Group 1 - AMH in women who underwent EOS (54 patients).
– Group 2 - AMH in women who underwent laparoscopic cystectomy (42 patients).

The average AMH level by age group was as follows (Table II and Table III):

Statistical analysis showed us that there was no statistically significant difference between AMH

Table II. Group 1: 54 female patients with EOS.

Age	Number of cases	AMH before EOS mean value	AMH 3 months after EOS mean value
20-29 years	12	3.24 (1.89-4.59)	3.05 (1.51-4.58)
30-35 years	42	2.26 (1.1-3.42)	2.18 (1.08-3.28)

Table III. Group 2: 42 patients with laparoscopic cystectomy.

Age	Number of cases	AMH before cystectomy mean value	AMH 3 months after cystectomy mean value
20-29 years	8	3.18 (1.83-5.3)	1.62 (0.74-3.08)
30-35 years	36	2.38 (1.14-3.42)	1.16 (0.26-2.17)

levels before and after EOS in both age groups: 20-29 years ($p = 0.1873$) and 30-35 years ($p = 0.2029$).

Compared to the surgically treated patients, a statistically significant decrease in AMH levels was observed in both age groups ($p < 0.001$). This group of patients showed a greater decrease in ovarian reserve after surgery (≈ 49%).

Discussion

Ovarian endometriomas are often associated with infertility and pelvic pain. Conversion of an ovarian endometrioma to a malignant tumor occurs in less than 1% of cases[18]. However, as the latest classification WHO indicates, it is important to make a differential diagnosis between ovarian endometriomas and other serous ovarian tumors before any therapeutic decision is made[19].

MRI of the pelvis and the sequences used are of particular importance in ruling out malignant genital pathologies[20].

Recently, new serum biomarkers such as circulating tumor DNA, circulating extracellular vesicles and non-coding RNAs have been identified in the differential diagnosis of ovarian neoplasia, in addition to the classic circulating serum proteins HE4 and Ca125[21,22].

Most of these markers, determined by molecular analysis, mainly based on next-generation sequencing, have already found their way into clinical routine for many tumor types[23].

Laparoscopic surgery has been considered the treatment of choice for ovarian endometriomas. The European Society of Human Reproduction and Embryology (ESHRE) guidelines[24] published in 2015 even reported spontaneous pregnancies after the excision of endometriomas larger than 4 cm.

It should be noted that the presence of an endometrioma in the ovary displaces healthy ovarian tissue, and laparoscopic cystectomy may further compromise ovarian reserve. Coagulation of the vessels that bleed during laparoscopic cystectomy leads to a reduction in the vascularity of healthy ovarian tissue with the development of local inflammation that affects the ovarian cortex and eventually lowers AMH levels[5,25].

To avoid damage to the ovarian reserve, some authors recommend postponing laparoscopic surgery even for cysts larger than 3 cm[26].

Several previous studies[4,27-30] in which laparoscopic surgery was performed reported a significant decrease in AMH levels after cystectomy: 30% after unilateral surgery and up to 44% after bilateral surgery. In this sense, our study also found a statistically significant decrease in AMH levels after the removal of the endometriotic cyst by laparoscopy ($p < 0.001$).

Laparoscopic cystectomy has a recurrence rate of between 5-12%, and after 5 years, a recurrence rate of about 30% was found in a sample of 1,200 women[31-33].

Some studies[34,35] advise against puncture or ultrasound-guided aspiration for diagnosis or treatment because the recurrence rate is as high as 97%, and there is also an increased risk of infection of the punctured cyst. There are numerous articles in the literature showing that the recurrence rate decreases significantly when intracystic alcohol is introduced[8,9,11,15,36].

In a study[37] of recurrent ovarian endometriomas after laparoscopic surgery, patients who underwent sclerotherapy had a final recurrence rate of only 13%.

One study reported that IVF procedures retrieved more eggs in the sclerotherapy group than in the laparoscopic cystectomy group, but the pregnancy rate was relatively the same in both groups[38]. Another study[39] published in 2020 concluded that sclerotherapy of ovarian endometriomas prior to IVF treatment resulted in higher live birth rates.

In our study, EOS was performed as an outpatient procedure under intravenous anesthesia. No major complications occurred during the procedure. Antibiotic prophylaxis was not required before or after the procedure.

We were able to show that sclerotherapy with 96% alcohol should be considered, especially in young patients who want to preserve their fertility potential. In fact, AMH levels were not significantly affected after ovarian sclerotherapy compared to laparoscopic surgery ($p < 0.001$ *vs.* $p > 0.18$). In this study, we were able to show that ovarian reserve was not affected after sclerotherapy in any age group.

In addition, the length of hospital stay was one day with sclerotherapy compared to 3-7 days with laparoscopic cystectomy.

Most of our patients with endometriomas treated with EOS participated in the IVF procedure. The study overlapped with the COVID-19 pandemic, which negatively impacted fertility and assisted reproductive technology[40].

Under these conditions, the less invasive technique, shorter procedure duration, and post-procedure recovery, as well as reduced contamina-

tion, represented advantages for the medical team that favored the subsequent IVF procedure. Nevertheless, the ovarian reserve was only marginally affected.

Limitations

A limitation of this study was the small sample of patients. Another limitation was the short duration of follow-up after the procedure.

Conclusions

Sclerotherapy for the treatment of endometriomas up to 8 cm in size is a simple procedure with a significantly lower risk of recurrence and without compromising ovarian reserve. In comparison, laparoscopic cystectomy is a procedure associated with the resources, costs, and risks of any surgical procedure. In addition, the ovarian reserve is more severely affected, and the fertility of the operated patient is reduced. Sclerotherapy is suitable for patients who want to undergo IVF treatment.

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Conflict of Interest

The authors declare that there are no conflicts of interest.

Ethics Approval

This study was approved by the HitMed Medical Centre Ethics Committee (Decision Number: 10/13, 2021).

Informed Consent

Informed consent was obtained from all subjects involved in the study.

Availability of Data and Materials

The data sets generated and/or analyzed in this study are available on request from the corresponding author.

Authors' Contributions

CCV (conceptualization, methodology, and writing of the original draft); LD and ACV (investigation, data maintenance, formal analysis) AMG and AMO (methodology, writing, review and editing); CCV and MAS (monitoring, project management, validation). All authors have read and agreed to the published version of the manuscript.

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