

# Comparison of the Effect on the Ovarian Reserve of Modern Methods of Treatment of Endometrioid Cysts



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## ABSTRACT

**Objective:** To compare the efficacy and safety of autologous platelet-rich plasma (PRP) therapy in laparoscopy and transvaginal sclerotherapy for the treatment of endometrioid cysts for maintaining ovarian reserve.

**Methods:** The study included 71 women under age 35 years with primary and secondary infertility. Twenty women underwent sclerotherapy of endometrioid cysts followed by autologous PRP injection into ovarian tissue, and 21 underwent laparoscopic cyst removal by stripping followed by autologous PRP injection. The control group consisted of 30 women who underwent laparoscopic cystectomy by stripping without autologous PRP injection. We assessed ovarian reserve for all patients before surgery as well 3 and 6 months after surgery by measuring serum anti-Müllerian hormone (AMH) levels and calculating antral follicle count using ultrasound.

**Results:** In the control group, AMH levels had decreased significantly at 3 and 6 months post-surgery, whereas levels in laparoscopy and PRP group remained almost unchanged from initial levels. In the sclerotherapy group, we observed a tendency towards increased AMH levels, but it was not statistically significant when compared with initial results. Follicle count changes were similar to AMH patterns.

**Conclusion:** In this study, sclerotherapy in combination with PRP therapy for ovarian endometriomas was associated with improved measures of ovarian reserve, and the combination of laparoscopic excision of the endometrioma with PRP therapy facilitated ovarian reserve preservation.

**Keywords:** endometrioma; anti-Müllerian hormone; ovarian reserve; laparoscopy; sclerotherapy; platelet-rich plasma

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## RÉSUMÉ

**Objectif :** Comparer l'efficacité et l'innocuité de l'injection de plasma riche en plaquettes (PRP) autologue en laparoscopie et de la sclérothérapie transvaginale pour le traitement des endométriomes en contexte de préservation de la réserve ovarienne.

**Méthodologie :** L'étude porte sur 71 femmes de moins de 35 ans atteintes d'infertilité primaire ou secondaire. De ce nombre, 20 ont reçu un traitement par sclérothérapie des endométriomes suivie d'une injection de PRP autologue dans le tissu ovarien, et 21 ont subi une kystectomie laparoscopique par *stripping* suivie d'une injection de PRP autologue. Les 30 femmes du groupe témoin ont quant à elles subi une kystectomie laparoscopique par *stripping* sans injection de PRP autologue. Nous avons évalué la réserve ovarienne de chaque patiente avant l'intervention ainsi qu'à 3 et 6 mois en postopératoire en effectuant le dosage sérique de l'hormone anti-mullerienne (AMH) et le compte des follicules antraux par échographie.

**Résultats :** Dans le groupe témoin, le taux d'AMH a diminué de façon significative à 3 et 6 mois en postopératoire, tandis qu'il est demeuré pratiquement inchangé par rapport au taux initial chez les femmes du groupe laparoscopie + PRP. Dans le groupe sclérothérapie, nous avons observé une tendance vers une augmentation du taux d'AMH, mais elle n'était pas statistiquement significative par comparaison aux résultats initiaux. Le profil de variation pour le compte des follicules était semblable à celui pour l'AMH.

**Conclusion :** Dans cette étude, le traitement combiné des endométriomes ovariens par sclérothérapie et injection de PRP a été associé à une amélioration des mesures de la réserve ovarienne, et le traitement combiné par excision laparoscopique et injection de PRP a facilité la préservation de la réserve ovarienne.

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## INTRODUCTION

Endometriosis is a chronic inflammatory disease that leads to chronic pelvic pain and infertility, and it occurs mainly in women of reproductive age. The most common sites for endometriosis are the ovaries, followed by the rectovaginal space, posterior leaves of broad ligaments, and sacro-uterine ligaments.<sup>1</sup> Many women with endometriosis suffer from infertility.<sup>2</sup> Even though laparoscopy is the standard of surgical treatment of ovarian endometriomas,<sup>3</sup> its negative effect on the ovary is expressed by a decrease in ovarian reserve.<sup>4</sup>

Sclerotherapy is also one of the promising treatments for ovarian endometriomas.<sup>5</sup> Its mechanism lies in the fact that the sclerosant, getting into the cavity of the cyst, damages its epithelial lining, followed by inflammation and fibrosis, which ultimately lead to obliteration of the cyst.<sup>6</sup> Sclerotherapy has been shown to be a cost-effective procedure for women with ovarian endometriomas.<sup>7</sup> Its effect on ovarian reserve is minimal or even absent in some studies.<sup>8–10</sup>

Autologous platelet rich plasma (PRP) is a platelet-rich blood substrate obtained by centrifugation of peripheral venous blood.<sup>11</sup> PRP has over 800 types of biologically active substances,<sup>12</sup> which make it a unique self-healing substrate in the body. Also, this unique environment can promote the activation of human folliculogenesis to the preantral stage.<sup>13</sup>

The aim of our work was to compare the efficacy and safety of endometriomas treatment for the preservation of ovarian reserve using PRP treatment in laparoscopy and transvaginal sclerotherapy.

## METHODS

The study was reviewed by the institutional ethics committee (obtained August 25, 2019; protocol N 17) and was

performed in accordance with the ethical standards described in an appropriate version of the 1975 Declaration of Helsinki, as revised in 2000.

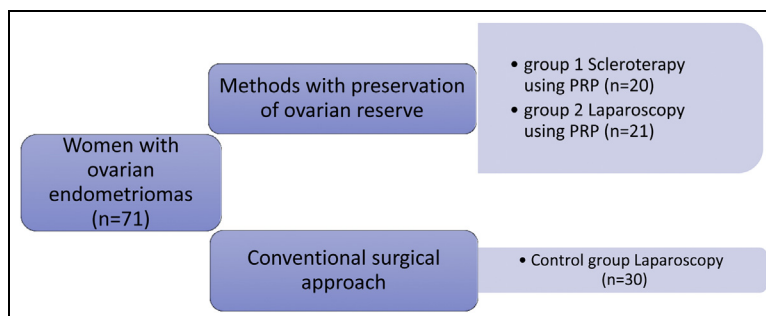
The study was carried out from 2018 to 2021. All surgeries were performed by one operator (M.M.). The study included 71 women (Figure 1) with primary and secondary infertility, of reproductive age under 35 years old, with unilateral or bilateral endometrial cysts, with a body mass index less than 30, with no history of human immunodeficiency virus or any significant disease that could significantly affect the results of the study.

All patients underwent a transvaginal ultrasound examination with an assessment of the ovarian cyst according to the recommendations of the International Ovarian Tumor Analysis (IOTA) group. All cysts were classified according to the Ovarian-Adnexal Imaging-Reporting-Data System (O-RADS) classification. Only patients with typical endometriomas (O-RADS 2) were included in the further stages of the current study.

Additionally, to decrease the risk of inadvertent ovarian cancer, specific biochemical tumour markers in the blood serum, such as CA-125 and human epididymis secretory protein 4, were checked using the Ovarian Malignancy Risk Algorithm (ROMA) calculator. The indication for the invasive treatment was endometrioma and associated infertility. The choice of one or another proposed treatment method was carried out after a detailed conversation about the expected benefits and potential risks of treatment methods with the patient and after the patient signed informed consent.

Before surgery and 3 and 6 months after, all women underwent an assessment of the state of the ovarian reserve by measuring anti-Müllerian hormone (AMH) on the third

Figure 1. Study design.



day of the menstrual cycle and by counting antral follicles during an ultrasound study on the same day.

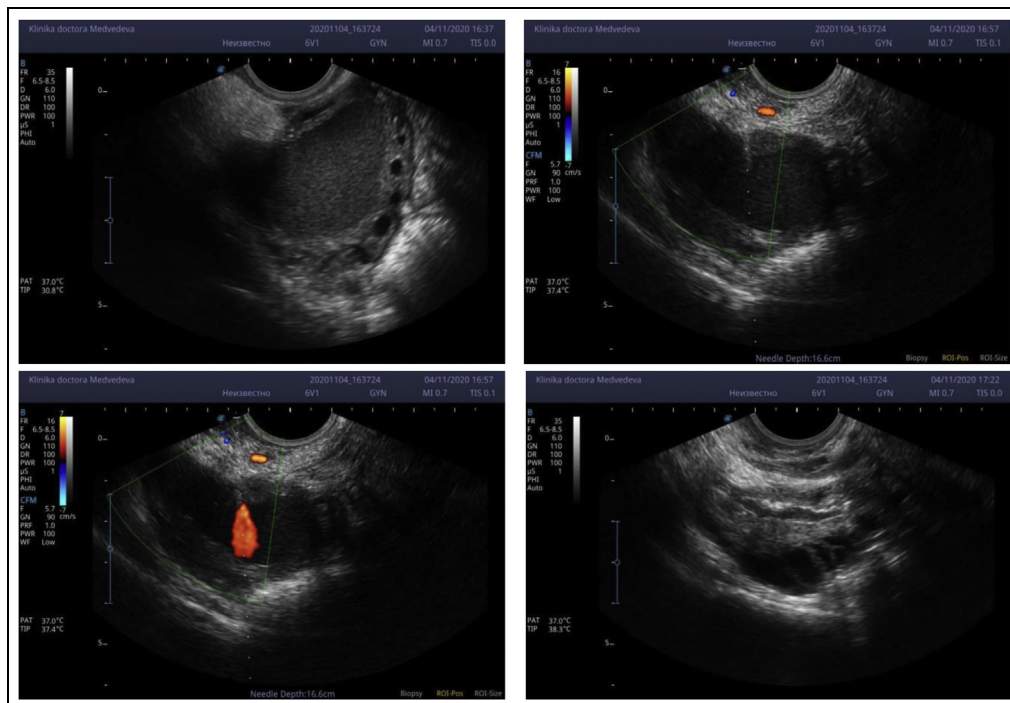
Treatment of endometriomas was carried out in 2 ways and based on this the patients were divided into study and control groups by flipping a coin. The control group consisted of 30 women who underwent laparoscopic cystectomy by stripping the capsule without the use of PRP. The study group was further randomized in the same manner by flipping the coin to decide who went into the following 2 groups: 20 women from group 1 underwent aspiration and sclerotherapy of the endometrioma with further application of PRP therapy to the ovarian tissue. To do this, under aseptic conditions, transvaginally under the control of ultrasound a fine-needle puncture of the ovarian endometrioma was performed; the "chocolate" content was aspirated into a container for cytological examination, after which the cyst cavity was washed out with a sterile saline solution in a volume of 200 to 400 mL on average. The amount of fluid inside the cyst at the same moment never exceeded its original volume to avoid cyst rupture and significant pain. Ethanol was injected into the cyst cavity for up to 80% of the aspirated fluid volume (but not more than 100 mL) for 15 minutes. After 15 min, ethanol was aspirated from the cyst cavity, and then it was washed out again with normal saline solution (Figure 2).

After that, a prepared autologous PRP in a volume of 4 mL was injected with a sterile puncture needle into the ovarian tissue. The procedure was performed under local anesthesia (lidocaine 2%, 4 mL injected directly to vaginal fornix) and nitrous oxide sedation was used on the patient's demand. General tolerability of the procedure was very high without any need for general anesthesia.

Autologous PRP was prepared intraoperatively using a vacuum tube for PRP treatment. For this, venous blood was collected to the mark indicated on the test tube (9 mL) and immediately centrifuged at a speed of 3200 rpm for 5 to 7 min according to manufacturer's instructions.

Twenty-one women from group 2 were treated with a typical laparoscopic approach: the capsule of the cyst was opened by a sharp method in the most thinned and distant place from the healthy ovarian tissue after complete adhesiolysis; the contents of the cyst were aspirated; the cyst capsule was removed by stripping with 2 clamps; bleeding vessels at the stripping site were identified under a stream of normal saline solution; hemostasis was carried out pointwise only for large bleeding vessels with bipolar coagulation with a power of 40 watts; and, if necessary, the ovary was sutured with a polyglactin suture number 2-0. Generally, suturing was performed in cases of large cysts

Figure 2. Ultrasound-guided ovarian endometrioma sclerotherapy.



or significant poorly controlled bleeding. After the main step, PRP in a volume of 4 mL was injected into the ovarian tissue under laparoscopic control using a puncture needle. The autologous PRP was injected inside ovarian tissue, not just instilled into the cyst's cavity, to prevent spillage.

All endometrioma capsules were sent for pathologic examination and were confirmed as endometriosis. Each aspirate obtained during the puncture of the endometrioma was sent for cytological examination and in no case were atypical cells detected. All patients with endometriomas were counselled about assisted reproduction techniques before undergoing surgery.

The results were statistically processed using Microsoft Excel. Using the Shapiro-Wilk criterion, normal distribution was assessed for all quantitative features. Nonparametric calculation tools were used for all cases where normal distribution was not present. To compare the numerical data of the 2 related groups, the Wilcoxon test of rank signs was used. For the numerical data of more than 2 groups, Kruskal-Wallis test and 1-way analysis of variance were used. The power analysis was performed with the calculation of the number of patients that should be included in the study. The critical value of the level of statistical significance for all types of analysis was  $P < 0.05$ .

## RESULTS

The age of all women ranged from 20 to 34 years, with a mean of 28.6 (SD 3.48) years. In group 1, the mean age was 29.2 (SD 3.45) years, in group 2 it was 28.6 (SD 4.0) years, and in the control group it was 28.2 (SD 3.13) years without significant difference among groups ( $P > 0.05$ ).

Monolateral endometrioma was the most common endometriosis presentation in all groups: 16 (80%) in group 1, 17 (81%) in group 2, and 27 (90%) in group C. The diameter of the cysts ranged from 30 to 84 mm, on average 46.3 (confidence interval [CI] 95% 42.6; 50) mm: in group 1 it was 49.2 (CI 95% 44.3; 54.1) mm, in group 2 it was 43.7 (CI 95% 37.8; 49.6) mm, and in group C it was 42 (CI 95% 37.8; 46.2) mm without a statistically significant difference ( $P > 0.05$ ).

Ovarian cancer tumour markers were within the normal range, with a slightly increased level in group 1, which had a mild statistically significant elevation for cancer antigen 125 (CA-125), which was likely to have no clinical significance (Table 1). As presented in Table 2, anti-Müllerian hormone levels and antral follicle counts before invasive endometrioma treatments did not differ statistically significantly. Three and 6 months after the treatment, markers of the ovarian reserve were reevaluated to compare the effect of the performed minimally invasive treatment on ovarian reserve (Table 2).

In group 1, the level of AMH after 3 and 6 months after the sclerotherapy almost did not change from the initial level. In group 2, the change was slightly different, where AMH decreased at the beginning and after 6 months the indicators increased almost to the initial level, as it was before the operation without a statistically significant difference with the initial level. In the control group, AMH levels decreased by 1.7 ( $P < 0.001$ ) and 1.8 ( $P < 0.001$ ) times after 3 and 6 months, respectively. Unlike the second group, a significant decrease in its level was not restored after 6 months, once again proving the negative effect of laparoscopic treatment on ovarian reserve.<sup>4,14,15</sup> Further analysis using the pairwise comparison procedure showed that the median AMH level in groups 1 and 2 was higher

**Table 1. Tumour marker levels and risk of ovarian cancer**

	Group; mean (SD) <sup>a</sup>			P value
	1 - Sclerotherapy	2 - Laparoscopic cystectomy	Control	
CA-125, U/mL, median (95% CI)	42.19 (32–51.3)	29 (21–35)	31.15 (28.14–42.29)	0.024 <sup>b</sup>
HE4, pmol/L, mean (SD)	37.47 (9.24)	36.69 (8.09)	40.01 (8.01)	0.19 <sup>c</sup>
ROMA percent	4.46 (0.56)	4.05 (0.37)	4.8 (0.38)	0.46 <sup>c</sup>

<sup>a</sup>Unless otherwise specified.

<sup>b</sup>Kruskal-Wallis criterion (H).

<sup>c</sup>One-way analysis.

AMH: anti-Müllerian hormone; CA-125: cancer antigen 125; HE4: human epididymis secretory protein 4; ROMA: ovarian malignancy risk algorithm.

**Table 2. Changes in ovarian reserve indicators over time, before surgery, and 3 and 6 months after surgery**

	Before surgery			3 months			6 months			
	Group 1	Group 2	Control	Group 1	Group 2	Control	Group 1	Group 2	Control	
AFC (number of follicles calculated by ultrasound)	10 (9;12)	9 (9;12)	10 (9;12)	10 (10;12)	9 (8;11)	6 (5;9)	11 (10,75;13)	10 (10;12)	7 (7;9)	<i>P</i> value < 0.001 <sup>b</sup>
AMH (ng/mL)	2.94 (2.28–3.31)	2.89 (2.5–3.5)	3.25 (2.7–3.56)	2.82 (2.35–3.53)	2.76 (2.15–3.02)	1.89 (1.62–2.13)	2.92 (2.33–3.52)	2.78 (2.2–3.28)	1.75 (1.4–2.06)	0.00064 <sup>b</sup>

Note: Group 1 – sclerotherapy, n = 20; group 3 – laparoscopic cystectomy, n = 21; control group, n = 30.  
<sup>a</sup>Equality of variances according to Leuven's test.  
<sup>b</sup>Kruskal-Wallis criterion (H).  
AMH: anti-Müllerian hormone.

than in the control group by 1.49 and 1.46 times, respectively, after 3 months, and after 6 months it was higher than in the control group by 1.67 and 1.59 times, respectively.

The antral follicle count (AFC) in group 1 (sclerotherapy group) practically did not change after 3 months and even significantly increased after 6 months from the initial one. In group 2 the AFC decreased after 3 months, but, surprisingly, after 6 months it recovered to the initial values as it occurred with AMH levels in this group (Table 2). In the control group, AFC after 3 months decreased almost 2 times and remained decreased after 6 months, once again confirming the negative effect of the laparoscopic excision on ovarian reserve.

## DISCUSSION

Endometriosis is a common disease and one of the leading causes of female infertility.<sup>1,2</sup> One of the most common localizations of endometriosis is the ovary, in which endometrioid cysts form. The negative impact of both the endometrioid cysts themselves and the surgical treatment of these cysts on the ovarian reserve is well known and widely described in the literature.<sup>3,4,9</sup>

In this regard, today much attention is paid to medical approaches aimed at maintaining the ovarian reserve in women with endometrioid cysts. One such approach is the use of 96-degree ethanol sclerotherapy. Another approach is to use modern surgical energies and ovarian tissue care during laparoscopy.<sup>7,8,10,16</sup>

Unfortunately, today we do not have effective medical methods that would allow us to influence the reduced ovarian reserve in the direction of its increase. One of the potentially effective methods of positively influencing the ovarian reserve is the use of autologous PRP therapy. Despite the lack of publications in the available literature on the use of autologous PRP in women with ovarian endometriosis, we have chosen this technique based on the availability of data on the possible positive effects of PRP on ovarian regeneration and follicular reserve. There are a fairly large number of publications devoted to the use of this technique that showed promising results in thin and nonreceptive endometrium in women with infertility and unsuccessful in vitro fertilization (IVF) attempts. To date, there are even systematic reviews that have demonstrated the successful use of autologous PRP to improve ovarian reserve, pointing out that this technique has the prospect of improving the regeneration of an injured ovary during surgery. Also, PRP can be utilized as a separate technique

that can be used in women with low ovarian reserve, regardless of the reasons that have led to this point.<sup>13,17</sup>

A slight increase in the level of CA-125 in the blood serum in patients of the first study group was most likely caused by random fluctuations of this marker, which tends to increase in women with endometriosis. Despite a statistically significant increase in this parameter in the first group, we do not regard this as a clinically significant event. It's well known that all CA-125 has a very low specificity for ovarian cancer, therefore this marker is not recommended for malignancy risk assessment to date. Its use in our study is more a reflection of policy in our hospitals than a real scientific need.

It is well known that endometriosis and surgery for ovarian endometriosis are risk factors for reduced ovarian reserve, so the use of autologous PRP may eventually become a standard step in the minimally invasive treatment of this localization of endometriosis.<sup>18–20</sup>

The worst values of the ovarian reserve were in the group in which laparoscopy was used with stripping the capsule of the endometrioma and selective coagulation of ovarian tissue. The ovarian reserve indices have changed less with traditional laparoscopy with the use of PRP therapy. Laparoscopy was performed in a standard manner by one operator, so it can be assumed that the differences in parameters obtained between the groups were rather due to the use of PRP treatment than differences in the surgical technique. This suggests that the use of PRP therapy improves the postoperative risks of reducing the ovarian reserve. The best result is even an improvement in the AFC index, which was noticed in the group where sclerotherapy with PRP therapy was used. Thus, sclerotherapy is an even more preferable treatment for endometrioid cysts in terms of preserving ovarian reserve and can be recommended in situations where there is an opportunity to not perform surgical treatment.

### Limitations

Limitations include lack of previous research studies on PRP use in ovarian endometrioma; lack of long-term outcomes such as pregnancy rate, IVF success rate, and live birth rate; no long-term assessment of ovarian function including the average age of menopause; a suboptimal method of randomization (tossing a coin); and the inability to conduct a completely blind study. Taking into account the last 2 points, we believe that from a scientific point of view, this study should be considered as a cohort.

### CONCLUSION

Sclerotherapy with PRP therapy is the most optimal method for treatment of ovarian endometriomas for the preservation of ovarian reserve according to obtained data. Laparoscopic stripping of the endometrioma capsule with the additional introduction of PRP into the ovarian tissue prevents the negative effect of this surgical intervention on the ovarian tissue in the postoperative period, thereby preserving the ovarian reserve. Further studies are needed to clarify if these approaches impact the live birth rate.

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