# Effectiveness of Combined Surgical and Hormonal Therapy in the Prevention of Recurrences of Endometriomas

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**Abstract**

**Background:** : Endometrial cyst, or endometrioma develops in the ovaries and is characterized by the presence of the tissue similar to endometrium and forms cysts within the ovary. High rate of recurrence after surgical intervention presents a significant challenge in the management of this disease.

**Aim:** Aim of the study was to determine the effectiveness of surgical and combined (surgical and hormone therapy) therapy of endometrioma in terms of development of recurrences.

**Methods:** Study group consisted of 260 patients with endometrioma who underwent laparoscopic intervention with enucleation of endometrial cyst. Observation was carried out in the period up to 5 years after the surgical intervention. The study group was divided into the following groups: Group I - patients who were treated after surgical intervention with dienogest for 6 months continuously (n-57); Group II - patients who after surgical intervention were treated with combined contraceptives (COC) for 6 months cyclically 21 days from the 5th day of menstrual cycle (n-61); Group III - patients who after surgical intervention were treated with dydrogesterone for 6 months, cyclically 10 days from the 16th day of the menstrual cycle (n-44); Group IV - control group, patients who did not undergo postoperative drug treatment (n-98).

**Results**: At 5-year post-operative follow-up after treatment with Dienogest and Dydrogesterone, recurrence of endometrial cyst did not develop in any case, recurrence after administration of COC was observed in only 1 case (1.6%), and the rate of recurrence in the control group was 18.2% (n-18), $P<0.01$ , which is significantly higher compared to patients in each group of hormone therapy, however, no significant difference between the groups of hormone therapy was detected in terms of the development of recurrence ($P>0.05$).

**Conclusion:** After surgical treatment of endometrioma, in cases of using different hormonal drugs (Dienogest, COC, Dydrogesterone), the rate of recurrence of endometrioma is significantly low compared to treatment with surgical intervention only, and when assessing the effectiveness of individual hormonal medications (Dienogest, COC, Dydrogesterone) no significant difference was found in the rate of development of reccurencies. **TCM-GMJ December 2024; 9 (2): P8-P12)**

**Keywords**: Endometrioma, recidives, dienogest, treatment of endometrioma, COC, dydrogesterone, recurrence of endometrioma, treatment of recurrent endometriomas.

## Introduction

Endometrial cyst, or endometrioma, is one of the most common forms of endometriosis (16). It is a specific form of endometriosis that develops in the ovaries and is characterized by the presence of endometrial-like tissue that forms cysts within the ovary (32). Endometrioma often causes severe symptoms and requires continuous treatment, and high rate of recurrence after surgical intervention presents a significant challenge in the management of this disease.

Determination and identification of risk factors for the formation and recurrence of endometrial cysts is of vital importance in the effectiveness of pre- and post-surgical treatment (5).

Inflammatory processes, hormonal imbalance, and immune system dysfunction are thought to contribute to the development of endometrial cysts (35). Estrogens play an important role in the growth and development of endo-

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metriomas, which explains the effectiveness of hormone therapy in their treatment (36).

Endometrial cysts represent an important clinical problem for several reasons: pain syndrome, infertility, decreased ovarian reserve, risk of malignancy (19, 37, 38, 39, 40).

Currently, laparoscopy is considered as an approved and effective method of treatment of endometriomas due to its good tolerance, low risk of complications and acceptable cost (2).

However, the high probability of recurrence of endometrioma makes surgical treatment insufficiently effective (4). Many studies have analyzed the recurrence rate of endometriomas after laparoscopic surgery, which occurs in 11-30% of cases during 2-year follow-up (1, 4, 5,7, 8, 10) and 10-50% in the first 5 years after surgery (11,12, 13, 29, 31, 33).

Thus, in patients with endometriosis, the combination of conservative and surgical treatment is considered the most effective treatment tactic due to the low probability of recurrence and high rate of recieving pregnancy (3).

As mentioned above, progestins are used in the management of endometriomas. It is noteworthy that by binding to progesterone receptors (PRs), progestins can induce anti-estrogenic, pro-apoptotic, anti-inflammatory and anti-neurogenic effects, which leads to the cessation of pain and pathogenetic mechanisms in endometrial lesions (30).

Despite the above, surgical treatment of endometrial cysts remains the 'gold standard', especially for large (>3 cm) cysts (41). Due to the high risk of recurrence, it has become important to develop an effective post-surgical drug treatment strategy in the management of endometrial cysts (22).

Busacca et al. found recurrence of endometrioma in 24.6% of cases 4 years after surgery (4). According to a study conducted by Lara V et al. in 2014, 23.9% of cases had recurrence of endometrial cyst, of which 68.1% required reoperation and of which 28.1% required 2 reoperations and 18.8% - 3 reoperations due to new endometrial cyst (1). According to their study, patients who received post-surgical hormone therapy had significantly higher rates of recurrence of endometrial cyst than women who did not receive post-surgical hormone therapy. The recurrence rate in both groups increased dynamically after surgical intervention (1). Similar results have been obtained by Cheong et al., Sesti et al. (8,10).

In a 2009 study by Francesco Sesti and coauthors, they compared the incidence of postoperative endometrial cyst recurrence in women treated postoperatively with gonadotropin-releasing hormone agonists, low-dose monophasic oral contraceptives, dietary supplements, and placebo, after 18 months of follow-up, no significant difference was seen in endometrioma recurrence (10).

The opposite result of this study was obtained in a 4-year study of 523 women by Y Ota, Kurashiki et al.. In patients receiving Dienogest, endometrial cyst recurrence did not occur in any case. Recurrence occurred in 10% of cases in patients receiving COC, and in the control group recurrence occurred in 38% of cases (6).

In a study by Yap et al., there was a statistically significant benefit of hormone therapy in the development of endometrial cyst recurrence, but no advantage was found in pain and pregnancy rates when hormone therapy was compared with surgery alone (9).

Impact of post-surgical treatment on endometrioma remains unclear. The inconsistency of literature data may be caused by the different duration of post-operative follow-up of patients and unspecified criteria for the definition of recurrence.

For more than 60 years, progestins have been used with great success for the treatment of endometriosis, but in some cases, this therapy is still ineffective. Effect of progestins on target cells appears to depend on the expression of progesterone receptors (PR), but PR expression is often impaired in endometrial areas, and therefore the effect of progestins on target cells is impaired. In case of prescribing combined hormonal contraceptives, in addition to the above, the possible negative effect of the estrogenic component on endometriotic areas is added (14). Thus, understanding of the mechanisms of therapeutic success and failure is essential for clinical decision-making (14).

Dienogest is a fourth-generation progestin that has been developed specifically for the treatment of endometriosis (21). Its unique pharmacological profile includes high progesterone activity on the endometrium, anti-androgenic activity and moderate anti-gonadotropic effect (26, 27, 28). Dienogest acts against endometriosis by several mechanisms, namely, it causes atrophy of endometrial foci, reduces inflammatory processes, inhibits angiogenesis and increases apoptosis in endometrial cells (17, 18, 20).

Many studies confirm the effectiveness of Dienogest in the prevention of recurrence of endometrial cysts (22,23). In 2016, Takaesu et al. conducted a prospective study in which 568 patients were treated with Dienogest after laparoscopic surgery. Recurrence rate after 5 years was only 4%, which is significantly lower compared to no-treatment group (69%) (22). Similar results were obtained in a 2019 study by Ouchi et al. (17). A meta-analysis by Park et al. in 2019 compared Dienogest and GnRH agonists and found dienogest to be as effective in recurrence prevention with a better tolerability profile (32).

It is important to note that Dienogest has minimal effects on bone mineral density, making it an advantage over GnRH agonists for long-term use (34).

The mechanism of COC's action in the treatment of endometriosis includes suppression of ovulation, endometrial atrophy, reduction of prostaglandin production, and reduction of menstrual bleeding (24).

Many studies have also been conducted to determine the effectiveness of COCs in preventing the recurrence of endometrial cysts. A study by Cucinella et al. (2013) compared COCs and Dienogest. They found that both treatments were effective in preventing relapse, although Dienogest showed better results (relapse rate 9.8% vs 13.7% after 2 years). (26).

Dydrogesterone's mechanism of action includes stabilization of the endometrium, reduction of inflammatory processes and immunomodulatory effect (25). It is im-

portant to note that Duphaston does not have androgenic, estrogenic or glucocorticoid effects, which reduces the risk of side effects (25).

According to the studies available in the literature, Dienogest is most effective in preventing endometrial cyst recurrence (6, 17, 22,23, 26, 32). COCs are also effective, although less than Dienogest (35).

Since the results of the research conducted in these areas are contradictory in some cases, the continuation of the research is relevant and appropriate.

## Methods

A retrospective observational research design was selected for the study. In order to conduct the study, approval N6 of the Ethical Commission of the "Zhordania Medical Clinic" was obtained. Before inclusion in the study, all patients participating in the study were informed about the essence and aim of the study and written informed consent was obtained for inclusion in the study.

**Inclusion criteria:** Patients with histomorphologically established endometrioma after surgical intervention, patients with normal hormonal background, patients who did not take any hormonal drugs for 6 months before surgery, patients who did not have any surgical intervention on the genitals, patients who did not have abnormalities of the development of genital organs.

**Exclusion criteria:** Patients with adenomyosis, patients with impaired hormonal background, patients who had taken any hormonal drugs for 6 months before surgery, patients who had underwent surgical intervention on the genitals, patients who had abnormalities of the development of genital organs, history of reproductive organ tumors, women with tubal factor infertility, male factor infertility.

Study group consisted of 260 patients with endometrioma who underwent laparoscopic intervention with enucleation of endometrial cyst in 2016-2022 yy. Observation was made 5 years after the surgical intervention.

The study group was divided into the following groups:

**Group I** - patients who were treated after surgical treatment with Dienogest for 6 months continuously (n-57);

**Group II** - patients who were post-operatively treated with combined contraceptives (COC) for 6 months cyclically 21 days from the 5th day of menstrual cycle (n-61);

**Group III** - patients who were post-operatively treated with Dydrogesterone for 6 months, cyclically 10 days from the 16th day of the menstrual cycle (n-44);

**Group IV** - control group, patients who did not undergo postoperative drug treatment (n-98).

In order to determine the recurrence all participants underwent an ultrasound examination of small pelvic organs on the 2nd–3rd days of the menstrual cycle. Ultrasound was performed with VOLUSON E10 (produced by General Electric, USA).

**Statistical analysis:** The obtained data were processed using statistical analysis software SPSS 24.0 (Statistical Package for Social Sciences, version 24) using $Chi^2$ test.

## Results

The mean age of the patients participating in the study was 30.01 ± 4.5 years. Mean age of patients in each group did not differ significantly (P>0.05) (**table 1**).

In our study we assessed the rate of post-operative recurrence of endometriomas in women who received hormonal drug therapy (Dienogest, COC, Dydrogesterone) and compared with a control group, where no drug therapy was administered post-operatively. It was found that no recurrence developed after taking Dienogest and Dydrogesterone. After taking the COC, it was found only in 1 case (1,6%). The rate of recurrence in the control group was 18.2% (n-18), which is significantly higher than the indicators of the each group of hormone therapy, although no significant difference was detected between the groups of hormone therapy in terms of the development of recurrences (**Table 2**).

**Table 1. Mean age in groups.**

| Groups | Mean age | P |
|---|---|---|
| Group I (n-57) | 29,2±3.9 | P>0.05<br>$P^1$>0.05<br>$P^2$>0.05 |
| Group II (n-61) | 30,4±2.8 | P>0.05<br>$P^3$>0.05 |
| Group III (n-44) | 28,8±4.5 | P>0.05 |
| Control group (n-98) | 31.5±2.4 | |

P – Comparison of Groups I, II and III vs control group

$P^1$ – Comparison of Groups I vs Group II

$P^2$ - Comparison of Groups I vs III

$P^3$ - Comparison of Groups II vs III

**Table 2. The rate of recurrence by groups after 5 years of surgery**

| Group | Rate of recurrence | P |
|---|---|---|
| Group I (n-57) | 0 | P<0.01<br>$P^1$>0.05<br>$P^2$>0.05 |
| Group II (n-61) | 1,6 % (n -1) | P<0.01<br>$P^3$>0.05 |
| Group III (n-44) | 0 | P<0.05 |
| Control group (n-98) | 18,2% (n-18) | |

**P – Comparison of Groups I, II and III vs control group**

**$P^1$ – Comparison of Groups I vs Group II**

**$P^2$ - Comparison of Groups I vs III**

**$P^3$ - Comparison of Groups II vs III**

## Discussion

Endometrioma is characterized with severe symptoms and requires ongoing treatment, and high rate of recurrence after surgical intervention presents a significant challenge in the management of this disease.

According to the data of our study, no recurrence developed after taking Dienogest and Dydrogesterone. After taking the COC, recurrence was found only in 1 case (1,6%). The rate of recurrence in the control group was 18.2% (n-18), which is significantly higher than the indicators of each group of hormone therapy. No significant difference was detected between each group of hormone therapy in terms of the development of recurrences of endometrioma.

Results of our study obtained in the control group are consistent with the results of a number of studies in the literature (1, 4, 5, 8, 10). There are data in the literature that in patients who underwent post-operative hormonal therapy with various hormonal medications, endometrial cyst recurrence developed at a significantly higher rate compared to women who did not receive post-operative hormone therapy (1,8,10). These data contradict the data of our study and the data of a number of studies available in the literature (6, 17, 22,23, 26, 32, 35,43).

Thus, in patients with endometriomas, the combination of hormonal and surgical treatment is considered the most effective treatment tactic due to the low probability of recurrence. However, the types of conservative treatment require clarification, as the existing literature data in this area is quite scarce and inconsistent. It is necessary to use individual approaches and make decisions based on the needs of patients.

## Conclusion

After surgical treatment of endometrioma, in cases of using different hormonal medications (Dienogest, COC, Dydrogesterone), the rate of recurrence of endometrioma is significantly low compared to treatment with surgical intervention only, and when assessing the effectiveness of different hormonal medications (Dienogest, COC, Dydrogesterone) no significant difference was found in rate of development of endometrioma recurrences.

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