

Effectiveness of Combined Surgical and Hormonal Therapy in Treatment of Endometriomas

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Abstract

Background :Endometrioma is a specific form of endometriosis that develops in the ovaries and is characterized by the presence of the tissue similar to endometrium that forms cysts within the ovary.High rate of recurrence after surgical intervention presents a significant challenge in the management of this disease.

Aim of the study: Aim of the study was to review the literature to identify optimal methods of managing endometrial cysts in terms of preventing recurrences, achieving high rates of pregnancy and reducing pain intensity.

Material and methods: For this purpose following electronic databases were searched: Pubmed, Medline, Cochrane Library, Web of Science, EMBASE, Europe PMC, Science Direct, NCBI, Semantic Scholar, Natonal Library of Medicine, Springer.

Results: 129 articles were reviewed, 70 of them attracted our attention with their statistical significance and were analyzed and discussed in our article.

Conclusion: Heterogenous data obtained after the litarature data review do not allow to define the optimal method of treating endometrioma, which means that it is reasonable to continue research in this direction to improve the effectiveness of management of endometriomas. (TCM-GMJ December 2024; 9 (2): P13-P18)

Keywords: Endometrioma, recurrences, Dienogest, COC, Dydrogesterone, management of endometrioma .

Introduction

Endometriosis is a chronic progressive disease. Its pathological manifestations affect the quality of life of patients at the physical, mental and social levels. Endometriosis is characterized by the presence of the tissue similar to endometrium growing outside the uterus (15). It occurs in about 10-15% of women of reproductive age and is characterised by chronic pelvic pain, dysmenorrhea, dyspareunia, and infertility (15).

Symptoms of endometriosis are described in the oldest medical records dating back to around 4000 years ago (26). Chinese medicinal herbs have been used since ancient times to alleviate severe systemic symptoms associated with the menstrual period, when the pharmacological action of treating dysmenorrhea was still unknown (26,27). The first pathological description of endometriotic and adenomyotic lesions was made by Carl von

Rokitansky in 1860, but morphological characteristics and clinical manifestaions of these diseases was described only at the beginning of the 20th century byCullen (14).

In the 1920s, John Sampson gave the name "endometriosis" to this condition and proposed the "retrograde menstruation theory" to explain its pathogenesis. At that time conservative therapy for this condition was practically nonexistent, and severe pelvic symptoms were treated even in young women with aggressive surgical interventions such as hysterectomy and oophorectomy (14).

Early marriage and frequent childbirth were the first recommendations for the prevention of endometriosis (Meigs, 1953). Observing the positive effect of pregnancy in terms of improving symptoms of endometriosis, Kistner expressed the opinion that the process of decidualization can lead to necrosis of superficial ectopic implants and, therefore, their elimination fact, application of hormone therapy for symptomatic management of endometriosis began after the idea of inducing a " Pseudo pregnancy" condition was first introduced (28, 29). Thus, logical evidence for use of progesterone in management of endometriosis has been established (14).

Notably, by binding to progesterone receptors (PRs), progestins can induce anti-estrogenic, pro-apoptotic, anti-inflammatory and anti-neurogenic effects, leading to interrup-

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Received November 21, 2024; accepted December 18, 2024.

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tion of pain and pathogenic mechanisms in endometriotic lesions (30). Progestins can be taken by oral and vaginal preparations, intramuscular and subcutaneous injections, patches, subcutaneous implants, and intrauterine systems. Since the development of combined estrogen-progestin contraceptives in the 1960s, they have been widely used in endometriosis patients, with good rates of patient adherence and satisfaction (14, 31).

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.

Pathogenesis of endometriomas is complex and multifactorial, however, there are several theories to explain their origin:

1. Retrograde menstruation theory: This is the most widely accepted theory, according to which endometrial cells flow to the fallopian tubes during menstruation and can implant in the ovaries (33).
2. Coelomic metaplasia theory: According to this theory, epithelium of the peritoneum is transformed into tissue similar to endometrium (34).
3. Embryonic rest theory: According to this theory, endometriosis develops from remnants of the Müllerian duct left during embryo development (17).

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 endometriomas, 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).

Considering the mentioned clinical importance, effective management of endometrial cysts, including prevention of recurrences, achieving high rates of pregnancy and reducing pain intensity is a significant challenge in modern gynecology.

Methods

For this purpose, following electronic databases were searched: PubMed, Medline, Cochrane Library, Web of Science, EMBASE, Europe PMC, Science Direct, NCBI, Semantic Scholar, National Library of Medicine, Springer. 131 articles were reviewed, 79 of them attracted our attention by their statistical significance and were analyzed.

Results and discussion

Current management of ovarian endometrioma depends on the size of the cyst and implies that surgery should not be performed in cases of cysts less than 3 cm in size (11). In studies investigating ovarian endometriomas in situ, it was found that the primary damage to the ovary was caused by progressive smooth muscle metaplasia and cortical fibrosis. Correlation between endometrial cyst and the degree of ovarian damage is not established, that means, it is simple presence of ovarian endometrioma that has damaging effect on follicular reserve of the cortical layer of the ovaries (11). Therefore, cystectomy in young women with endometrioma may partially damage the follicular reserve along with excision of the ovarian parenchyma, which is conditioned by diameter of the endometrioma (11).

Most commonly used surgical methods are (20):

- Laparoscopic cystectomy: This procedure involves removing the entire wall of the cyst while preserving the healthy ovarian tissue (42).
- Laparoscopic ablation/vaporization: with this method, cyst wall is broken by laser or electrocoagulation (43).
- Sclerotherapy: This less invasive method involves aspirating the contents of the cyst and injecting a sclerosing agent (43).

Although all of these methods are effective in cyst removal, each of them has its own advantages and risks. For example, cystectomy is associated with lower recurrence rate, but may result in a greater decrease in ovarian reserve. (45).

Also, despite successful surgical intervention, the risk of endometrial cyst recurrence remains a significant problem. According to various studies, the rate of cyst recurrence ranges from 10 to 50% during the first 5 years after surgery (46, 47, 48, 49, 50, 51). The risk of recurrence is influenced by several factors (7):

- Age: the risk of recurrence is higher at a younger age.
- Cyst size: Larger cysts are associated with a higher risk of recurrence.
- Bilateral cysts: Bilateral endometriomas increase the probability of recurrence.
- rAFS (revised American Fertility Society) stage: large size of endometrioma (>3 cm) is associated with a higher risk of recurrence after surgery.
- CA-125 level: High preoperative CA-125 levels may be predictive of recurrence.
- Surgical technique: Cystectomy is associated with lower recurrence rates compared to ablation.

Due to the high risk of recurrence, it has become important to develop effective postoperative drug treatment strategy in the management of endometrial cysts (22).

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, 8, 10) and 10-50% in the first 5 years after surgery (29, 31, 33, 43, 44, 45). 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 achieving 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 pathogenic 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).

As it is known, combined oral contraceptives contain a combination of estrogen and progestin. Their mechanism of action in the treatment of endometriosis includes suppression of ovulation, endometrial atrophy, reduction of prostaglandin produc-

tion, 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 is a synthetic progesterone that is structurally similar to endogenous progesterone (25). Its mechanism of action includes stabilization of the endometrium, reduction of inflammatory processes and immunomodulatory effect (25). It is important to note that Duphaston does not have androgenic, estrogenic or glucocorticoid effects, which reduces the risk of side effects (25).

Effectiveness of dydrogesterone in preventing the recurrence of endometrial cysts is less studied compared to dienogest and COCs.

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).

A number of studies have been conducted to determine the effectiveness of different hormonal medications for the pain syndrome associated with endometriosis. According to some researchers, Dienogest and Dydrogesterone are relatively more effective in managing chronic pain than COC (7, 11).

Vercellini et al. (2008) in a meta-analysis assessed the effectiveness of COCs in the treatment of pain associated with endometriosis and concluded that COCs significantly reduce pain and improve quality of life (13). In 2007 Trivedi et al. conducted a randomized controlled trial comparing Duphaston (Dydrogesterone) and placebo in patients with endometriosis. They found that Duphaston significantly reduced symptoms and improved quality of life (40). Similar results were obtained by Overton et al. and Tsai et al. (12). In a 2017 study, Duphaston and Dienogest were compared. They concluded that both treatments were effective in reducing pain associated with endometriosis, although dienogest showed better results (42). Thus, in the management of endometriosis, it is necessary to use individual approaches and make decisions based on the needs of patients.

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

As Dienogest is used long-term for treatment of endometriomas, its effect on the lipid profile is an important issue, as hormone therapy may affect cardiovascular risks.

Studies show that the use of Dienogest can cause changes in the lipid profile, such as changes in the concentration of fatty acids and an increase in the levels of LDL (low-density lipoprotein). A study by Makarov et al. shows that Dienogest may affect metabolism of fatty acids in the body, which in turn affects the lipid profile (79). A study by Vang et al. shows that Dienogest may decrease HDL levels, which is associated with an increased risk of heart disease (78).

Hormonal changes caused by Dienogest may affect liver function and lipid synthesis. A study by Beregovski et al. (2019) describes that hormonal changes caused by Dienogest are associated with altered lipid metabolism (77).

According to the data available in the literature, Dienogest has a neutral or slightly positive effect on the lipid profile. Strowitzki et al. (2010) conducted a 52-week study in which Dienogest did not cause significant changes in total cholesterol, LDL-

cholesterol, HDL-cholesterol, or triglycerides (76). However, some studies point to potential risks, in particular Ott et al. (2008) found a small but statistically significant increase in triglycerides with the use of Dienogest (75). Klipping et al. (2012) studied the effect of a combination of Dienogest and ethinyl estradiol and found small but statistically significant increases in HDL-cholesterol and decreases in LDL-cholesterol (74). According to the meta-analysis conducted by Grandi et al. (2016), Dienogest-containing contraceptives do not cause negative changes in lipid profile (73).

Some studies have shown that Dienogest does not have a significant effect on the overall lipid profile even with its long-term use. For example, Grant et al. (2017) concluded in their study that long-term use of Dienogest generally does not change LDL and HDL levels, but may cause small changes in some cases (72).

Although most studies show that Dienogest has a neutral or slightly positive effect on the lipid profile, additional long-term studies are needed to fully explore these effects.

It is known that hormonal drugs often affect bone mineral reserves (bone structure) and, therefore, the risk of developing osteoporosis. Thus, it is very important to study the effect of Dienogest on bone mineral change (BMD). In a review of the literature, effect of Dienogest on bone mineral change is assessed in different studies. In general, hormones like progesterone can affect bone mineral reserve and bone density. A study by Williams et al. (2016) shows that short-term use of Dienogest does not produce statistically significant changes in bone mineral density, but long-term use may affect bone tissue in the vertebral and hip bones (71). However, according to Peixoto et al. (2018) study results, Dienogest may cause small changes in bone mineral change in the first months of its use, although this effect is less evident in cases of long-term use (70).

A study by Quinn et al. (2017) suggests that short-term use of Dienogest may cause a small decrease in bone density, but that this effect is more likely to be related to other hormonal changes and clinical factors (69).

Based on clinical trials and observational data, for example in the study by Barnes et al. (2019), long-term use of Dienogest may cause changes in bone density, but its effect on bone structure is generally believed to be relatively small (67, 68).

As mentioned above, effect of Dienogest on bone mineral change is different during short-term and long-term use. Although general clinical studies indicate that Dienogest may cause small changes in bone density, this effect on bone structure is relatively small compared to other hormonal drugs, which requires additional studies in this direction to evaluate the effect of long-term use of Dienogest on bone mineral change.

According to different studies, the effect of Dienogest on glucose levels is not uniform. Some studies have shown that Dienogest does not cause significant changes in glucose levels or insulin secretion. However, there is data that in some cases it can affect glucose metabolism.

According to Bendtsen, L. et al. (2001), the authors suggest that some types of hormonal contraceptives, including drugs containing Dienogest, may have some effect on glucose metabolism, but this effect varies between individuals (65).

A study by Sjöberg, L. et al. (2013) showed that Dienogest did not cause significant changes in glucose levels, although in some cases there may be an increase in blood glucose levels (64).

According to study by Jansen, F. et al. (2006), Dienogest and similar hormones should be used with caution, especially in cases where it is known in advance that the patient has disturbances in glucose metabolism (63).

Since the effect of Dienogest on the blood glucose level may vary from individual to individual, it is necessary to monitor the glucose values in specific cases.

Dienogest is a 19-nortestosterone derivative progestin used in the management of patients with endometriosis. Against the background of its use, bloody discharge can occur in various ways, which can affect the quality of life of patients.

According to the literature, frequency and intensity of bleeding after taking dienogest may vary from individual to individual. On the background of taking Dienogest, presence of a small amount of bloody discharge is more common, which is mainly observed in the first months of treatment, although some patients may develop abnormal bleeding from the uterus, which may be indication to stop hormonal therapy.

A 2008 study by Matsuzaki, Y. et al. showed that Dienogest significantly reduced the frequency of endometriosis-induced bleeding, although brown discharge may occur in 20-30% of cases during the first months of treatment. (62). Similar results were obtained by Heinemann, L. et al. (2008), Wang, L. et al. (2014) and Gonzalez, M. et al. (2017) (59, 60).

There are studies in the literature showing that amenorrhea may persist for some time after Dienogest has been discontinued. Generally, according to the literature data, menstruation resumes in the majority of women within 1-3 months after discontinuation of Dienogest, although in some cases amenorrhea may remain (persistent form). In these cases, the patient requires a thorough assessment to exclude other causes, such as pregnancy, hypothalamic or pituitary, or other endocrine disorders (56, 57, 58). Amenorrhea may develop in 10-20% of women with Dienogest use, especially when the drug is used for a long period of time. This percentage may vary depending on individual factors, length of treatment, and other factors (60, 61, 62). In such cases, full consultation and revision of treatment if necessary is recommended.

Dienogest is known for its influence on the menstrual cycle and the structure of the endometrium. By disrupting ovulation and changing the structure of the endometrium, Dienogest can affect fertility. Thus, it is important to understand how its discontinuation affects reproductive health in women planning pregnancy after treatment.

Infertility may develop in 5-10% of women with Dienogest use, although it may be temporary and depends on individual factors and duration of treatment. In most cases, fertility is restored after completion of the treatment (53, 54, 55).

As mentioned above, dienogest acts similarly to Progesterone, causing cessation of ovulation and changes in the structure of the endometrium. With long-term use, this can cause ovarian function disorders and menstrual cycle disturbances. After discontinuation of the medication, hormonal balance is gradually restored, but the period of its restoration may vary in different cases, and recovery of fertility may take some time (52, 53, 57, 58).

Most studies report that normal ovulation and menstrual cycles are usually restored within 1-3 months of discontinuation of the medication, although in some women this process may take longer. Factors such as length of Dienogest use, underlying reproductive health conditions, and individual hormonal balance play an important role in these cases. (52, 57, 58).

In the literature, data on the effect of Dienogest on body weight are heterogenous. In a review of the literature, studies generally do not demonstrate significant changes in body mass with Dienogest intake. However, some patients report small changes in body weight while taking Dienogest. These changes may be temporary and depend on a variety of factors, including

water retention from hormone medications and other factors such as diet, physical activity, and individual metabolism.

According to a study by Matsuzaki, Y. et al. (2008), the majority of patients did not experience statistically significant changes in body weight with intake of Dienogest, although some women reported slight changes in weight, which may have been the result of individual patient response (62). Similar results were reported by Sjöberg, L. et al. in 2013 (21).

Conclusion

Heterogenous data obtained after the review do not allow to define the optimal (best) method of treating endometrioma, which means that it is advisable to continue research in this direction to improve the effectiveness of management of endometriomas.

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