



Postoperative Hormonal Therapy - An Effective Way to Decrease the Risk of Endometriosis Recurrence

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Abstract

Endometriosis is a chronic disease that is associated with pelvic pain and infertility. It affects from 10 to 15% of women of reproductive age and is prone to recurrences. Combination of surgery with postoperative medicinal therapy is considered to be the most effective way to avoid endometriosis recurrence.

The Aim: This research was to study the causes of endometriosis recurrences and to evaluate the effectiveness of postoperative medicinal therapy options in the decrease of recurrence risk.

Materials and Methods: Actual and relevant publications in PubMed and eLibrary databases were studied.

Results: It was demonstrated that the risk of endometriosis recurrence can be significantly decreased by combination of surgery with postoperative therapy. Postoperative medicinal therapy should be prescribed even during pregnancy to increase the effectiveness of surgery. The prescription of the effective postoperative therapy taking into account individual characteristics of patients can help them to avoid self-refusal from the therapy decreasing the risk of recurrences.

Conclusion: The risk of the endometriosis recurrence can be significantly decreased by properly selected postoperative therapy. Dydrogesterone as a highly effective progestogen with a favorable safety profile approved for use in endometriosis postoperative therapy even during pregnancy is used to be the medicine of choice in endometriosis treatment.

Keywords: Endometriosis Recurrences; Hormone Therapy; Combined Oral Contraceptives (COC); Dydrogesterone; Gonadotropin-Releasing Hormone (GnRH) Agonists

Introduction

Endometriosis as it's described in ESHRE guidelines is a disease characterized by the presence of endometrium-like epithelium and/or stroma outside the endometrium and myometrium, usually associated with an inflammatory process. Endometriosis affects 10% of women of reproductive age and 40-50% of infertile women [1]. Despite a significant number of studies devoted to this disease, the solution of etiology, pathogenesis, diagnosis and treatment remains relevant.

Ovarian endometriosis is the "leader" among endometrioid heterotopias, so it is the most common among all localizations of external genital endometriosis: it affects 17-44% of the total number of patients [2]. The main symptoms of endometriosis are pain and infertility.

Surgical methods often do not bring a complete cure from endometriosis. Recurrence of endometriosis is a common occurrence among patients who have undergone surgery. For example, recurrence of the disease was noted in 5% of operated patients in

one year after surgery, in 5-14% - in 2 years after surgery, in 20-50% - in 5 years [3]. In this regard, one of the approaches to the endometriosis treatment is to combine surgery with subsequent medicinal therapy, where postoperative therapy by medicines provides a reduction in the likelihood of recurrence.

However, the recurrence of endometriosis can also be caused by the ineffectiveness of hormone therapy, the patient's refusal of treatment due to adverse events, and/or a lack of understanding of the postoperative medicinal treatment importance. According to a Swiss study, 39.3% of women with endometriosis stopped taking dienogest on their own due to adverse events or therapy ineffectiveness [4].

Properly selected therapy, as well as informing women before the start of treatment about the disease, the need for long-term therapy, possible adverse events when taking medicines and ways to solve these problems will reduce the risk of subsequent recurrences of endometriosis, including due to the self-refusal of patients to take medicines [5,6].

Medicinal therapy for endometriosis

Currently, progestogens, hormonal contraceptives, gonadotropin-releasing hormone (GnRH) agonists or antagonists are used to treat endometriosis [7-10]. The ESHRE Endometriosis Guideline (2022) notes the proven benefits of all these remedies.

However, after the study from 2018 showing anovulatory cycles occur with equal frequency in women with and without endometriosis the ability of COCs to suppress ovulation is already being questioned as a pathogenetic rationale for their use in endometriosis treatment [1,11,12]. In addition, significant number of findings confirming the insufficient efficacy of COCs in the treatment of endometriosis is appearing in the medical databases. In 2011 the results of an international survey of 441 patients with external genital endometriosis were published. The age range of the respondents was from 15 to 49 years. According to the data obtained, about 70% of patients indicated the fact of the necessity to change several COC types due to their insufficient effectiveness in relieving endometriosis-associated pelvic pain. At the same time, more than 40% of patients with external genital endometriosis are recommended from 3 to 10 different COCs to achieve a therapeutic effect [13].

The fact of COCs inefficacy in the treatment of endometriosis was also confirmed in Casper R. study [14]. The results of the review demonstrated that once endometriosis was suspected or proven as the cause of chronic pelvic pain COCs couldn't be the best treatment option due to their low efficacy associated with mechanism of action. The authors conclusion suspects that the use of such ineffective therapy can lead to progression of the disease.

Later, in 2020, Yong et al. research was published, where the main purpose was to evaluate the efficacy of COCs and the frequency of their withdrawal due to the development of side effects in the treatment of patients with endometriosis-associated pain. As a result, it was shown that the ineffectiveness of COCs is associated with the persistence or worsening of chronic pelvic pain, in the genesis of which the myofascial or nervous system is involved [15].

Progestogens are the most used endometriosis therapeutics in Russian Federation since they belong to the first line of endometriosis treatment according to the ROAG recommendations (2020) and ESHRE (2022) as postoperative therapy or as recurrences prevention [7-10,16]. Progestogens can be taken in continuous and prolonged cyclic regimens to ensure atrophy of the glandular epithelium, decidualization of the stromal component and in a cyclic mode in the second phase of the cycle in patients with endometriosis planning pregnancy [10].

Dydrogesterone, norethisterone and dienogest are the most studied oral progestogens for the treatment of endometriosis, which have been the subject of many different studies and have been widely used in real clinical practice for a long time [10,14,17,18]. Although these molecules have demonstrated approximately the

same efficacy with different safety profiles. For example, norethisterone and dienogest have more potentially dangerous side effects, such as hyperlipoproteinemia and hypercholesterolemia, bone density rarefaction, hirsutism, etc [19-22]. Thus, the effect of dienogest on the reduction of bone mineral density (BMD) is comprehensively studied all over the world. The research by S.E. Kim et al. published in 2021 has shown that 79.5% of patients had a persistent decrease in BMD while taking dienogest for 3 years; a decrease in BMD in the lumbar spine was observed in 75.6% of patients and in the femoral neck in 69.4% of patients [23].

Dydrogesterone has been used in Russia for the treatment of endometriosis since the 1990s according to the instructions for medical use of the medicine. Its efficacy in endometriosis, was first discovered in the 1960s [24]. Since then, there has been a significant amount of research on dydrogesterone for the treatment of this disease [25-27]. One of the key advantages of dydrogesterone is that it does not affect the pituitary-adrenal axis of regulation of the female reproductive system, and that the concentration of progesterone in blood plasma does not decrease when it is used in the post-ovulatory period [28]. In addition, dydrogesterone does not suppress ovulation, which allows it to be the medicine of choice for women planning pregnancy, while increasing the chance of pregnancy in women with endometriosis-associated infertility [25,29-31].

Returning to the fact that endometriosis associated infertility is one of the, main reasons for patients to start the therapy its necessary to note, that according to the W.I.H. Johnston study 10 of 19 infertile patients became pregnant following dydrogesterone treatment [26]. The average duration of infertility of patients who conceived was four-and-a-half years with a range from eight months to eleven years. After the treatment course 7 healthy infants have been born, two first trimester abortions occurred and one patient has been pregnant to the moment of publication writing. Of 49 patients with endometriosis all but 5 had no subjective endometriosis symptoms after 9 months treatment.

As for regimens effectiveness the results of the observational open-label multicenter study on the use of dydrogesterone for the treatment of endometriosis in Russia (the ORCHIDEA study) showed that both dydrogesterone therapy regimens (continuous and prolonged cyclic) at approved doses for 6 months demonstrated a significant reduction in the severity of chronic pelvic pain and dysmenorrhea, as well as an improvement in quality of life and sexual satisfaction. In addition, a favorable safety profile of dydrogesterone in both therapy regimens was approved [32].

When selecting therapy for the treatment of endometriosis, it is necessary to take into account the fact that endometriosis is a chronic disease, and therefore therapy should be long-term, with proven long-term studies (12 months or more) of efficacy and risk-benefit profiles.

Effect of postoperative medicinal therapy on endometriosis recurrences

Despite the high recurrence rate of endometrioid ovarian cysts (EOC), to date, there is no much information in scientific publications about prospective follow-up of patients after endometrial surgery.

Previously, our research group has carried out the retrospective cohort study to compare the effectiveness of different hormonal therapy in endometriosis recurrence prevention [33]. Patients included in the study, were divided into two groups: group I consisted of 282 (88%) women with a history of primary EOC; group II-37 (12%) women with EOC recurrences. The age of the studied patients was in the range of 27-36 years. Median age, BMI, age of menarche, and data obtained from the analysis of reproductive function did not differ statistically in the two groups.

The results of the study have shown that there was a statistically significant difference in the use of such medicines as dydrogesterone, combined oral contraceptives (COCs) (without preference for any of the medicines) and gonadotropin-releasing hormone (GnRH) agonists. The incidence of dienogest use in women prior to primary or recurrent intervention did not differ. In group I, 169/282 (60%) of women received dydrogesterone before surgery, and in group II – only 4/37 (10%) of patients; GnRH was used in 34/282 (12%) patients with primary EOC, in 12/37 (32%) patients with endometrioid cyst recurrence. The largest number of patients in group II received COCs before surgery - 18/37 (49%), and in group I, the frequency of use of these remedies was 59/282 (21%).

During the study, statistically significant differences were obtained between the use of dydrogesterone, COCs and GnRH agonists in patients with primary EOC and with recurrence of this disease. According to the data obtained, the use of COCs or the absence of any therapy in women after surgery for EOC is likely to lead to repeated surgery for endometriomas recurrence. At the same time, therapy with dydrogesterone and GnRH agonists does not entail such consequences.

Modern choosing a treatment method tactics are based on complaints, the age of the patient, as well as the need to implement the reproductive function. However, the effectiveness of various types of hormone therapy in endometriosis treatment is still studying. In modern clinical practice, so-called symptomatic medications are used to treat endometriosis, which have their own advantages and drawbacks; have a different safety and tolerability profile, as well as economic availability [34]. However, it should be borne in mind that progestogens are the first line of therapy for endometriosis in both foreign and Russian guidelines. If their effectiveness is insufficient, physicians are resorted to second-line therapy-GnRH agonists. At the same time, the use of COCs in endometriosis treatment become less widespread due to the safety risks of women in general and the progression of the disease in each case.

Currently, dydrogesterone, as a medicine registered for the treatment of endometriosis, has several advantages due to its efficacy, favorable safety profile, and the possibility of individual selection of a therapy regimen for each patient, that is also confirmed by the results of our study described earlier [33].

Pregnancy influence on the risks of endometriosis recurrence

Initially progestogens using in the endometriosis treatment was based on the theory of “pseudopregnancy”. It is still considered that pregnancy has a positive effect on endometriosis. But in fact, pregnancy influence on the disease progression is ambiguous. Thus, sometimes endometriosis recurrences take place even during pregnancy.

In the last few years ovarian endometriosis became more widely spread among pregnant women: to the beginning of the century it has accounted only 5-6% of adnexal tumors detected during pregnancy [35,36], but recent six-year research (2004-2010) results have demonstrated that it became the lead reason for adnexal tumors occurrence and accounted for 39% of general number of cases [37]. As per this first large-scale description of consequences of pregnancy influence on endometriosis cysts size increase during pregnancy in 20% of cases, doesn't change in 28% of cases and decreases in 52% of cases [37].

Later literary review data demonstrated that from 8,8 to 39% of endometrioid cysts increased during pregnancy [38,39]. Benaglia., *et al.* research results have shown that in 8% of cases cysts increased during pregnancy, in 13% - decreased, in 33% cysts didn't change and in 46% of cases cysts were no longer identified during follow-up. For this phenomenon description different hypotheses were put forward. Menstrual cycles termination can be the factor potentially taking place in different endometrioid cysts “behavior” during pregnancy. Moreover, individual histological characteristics of each cyst can be probably related with variability of such “behavior” modifications during pregnancy since their decrease take place only in certain cases. It has been suggested that endometrioid cysts covered with endometrium more susceptible to decidualization, can be regressed and even disappeared [40].

Although some evidence supports an atrophic effect of pregnancy-related changes on endometriotic lesions, not all lesions demonstrate this effect [41]. Moreover, the same endometrioid cyst may demonstrate different growth dynamics under comparable conditions [41]. For example, a case of rapid growth with pronounced vascularization inside the cyst during the first pregnancy was described, while in the next 6 months after termination of pregnancy by curettage, the endometrioid cyst did not change, then regression in size and loss of growths inside the cyst were noted up to 15 weeks of gestation with subsequent pregnancy [42]. Different endometrioid cysts may exhibit different growth patterns during pregnancy: one case reported in the literature presented no change

in ultrasound findings in one ovary during pregnancy, while the other ovary showed intense changes during gestation [43].

Thus, even though pregnancy is often associated with endometrioid cysts decrease and positive effect on the disease, recurrences of endometriosis also can occur during this period of woman's life. In some cases, the need for surgical endometriosis treatment during pregnancy is explained by the threat of complications from the tumor due to the rapid growth of the tumor and severe pain. And clinical situation like this is one more case when the best possible condition for prolonging pregnancy is the use of progestogens, namely dydrogesterone, in postoperative therapy⁴⁴. From this point of view, possibility of using in postoperative therapy during pregnancy is additional advantage of dydrogesterone [45].

One way or another, all specialists in the field of endometriosis treatment recognize the need for postoperative hormonal treatment. The prescription of dydrogesterone for endometriosis is due to the antiproliferative effect and stimulation of apoptosis in the foci [46]. It is worth noting that according to the instructions, dydrogesterone can be used not only in pregravid preparation after surgical treatment of various forms of endometriosis, but also in the subsequent use at least until the 20th week of pregnancy, which makes this medicine universal in pregnancy after surgical treatment of endometriosis.

Patients self-refusal from postoperative therapy as the reason for endometriosis recurrence

Often, the relapse of endometriosis occurs as a result of patients' self-refusal from therapy. The main reason for patients' self-refusal from the prescribed therapy is the occurrence of adverse reactions. For example, with continuous intake of progestogens, irregular bleeding is possible in the first 3 months of treatment in 20% of patients [47], which negatively affects their adherence to therapy.

Nowadays there are a few methods to protect patients from therapy self-refusal. It is necessary to inform patients about the need of long-term treatment to avoid recurrence of the disease. Moreover, patients have to know about possible adverse events to be ready for that and not to doubt the effectiveness of therapy if they occur. And in addition to informing patients about possible adverse events in order to prevent possible self-withdrawal from therapy, it is also possible to change the type of progestogen or dosage to increase compliance.

To help practicing physicians in 2023 the collective of authors from Russia published "Algorithms for the management of patients with endometriosis", which describes in detail the algorithm for switching from one progestogen to another in the development of adverse events, as well as the mechanism for changing the dosage [48]. The algorithms present 6 main portraits of patients, an algorithm for transferring patients from GnRH agonists to progestogens, and algorithms for menstrual bleeding managing. Person-

alization of therapy for women with endometriosis is presented using the example of dydrogesterone as progestogen that has several registered regimens of use, which makes it possible to manage therapy, select the necessary dosages (10-30 mg), regimens (cyclic, prolonged cyclic and continuous) and increase patient compliance. Dydrogesterone makes it possible to demonstrate algorithms for managing patients in various clinical situations. However, these algorithms are applicable to any progestogens with registered appropriate regimens of use.

For example, it is possible to minimize the risk of developing an adverse medication reaction, such as "uterine bleeding", due to the recorded prolonged cyclic regimen from the 5th to the 25th day of the menstrual cycle and different dosages of dydrogesterone. Thus, in a large-scale multicenter study on the use of dydrogesterone in patients with endometriosis ORCHIDEA (2018-2020), no cases of uterine bleeding were noted in the group of prolonged cyclic regimen 0/273 (0.0%) [49].

Conclusion

Endometriosis is a chronic disease that need a long-term medication support. The effectiveness of surgical methods decreases without postoperative treatment. This therapy is an integral part of the treatment of endometriosis, allowing to achieve long-term remission. While preoperative medicinal therapy is usually used to treat existing endometriosis lesions, postoperative medicinal suppression is used to prevent recurrence after surgical removal. The use of medication is expected to improve the outcome of treatment compared to surgery by itself, regardless of the treatment duration.

Nowadays progestogens are the first line treatment in endometriosis, in the case of their ineffectiveness physicians use the second line therapy - GnRH agonists. But before that it's possible to change the regimen, the dosage and the type of progestogen to achieve the best result of therapy and good patient compliance. COCs are prescribed ever less for endometriosis treatment due to the high risks of adverse events and the disease progression in each specific case.

Dydrogesterone as medicine registered for endometriosis treatment has several advantages in efficiency, safety and the possibility of individual selection of the regimen for each woman.

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