REVIEW ARTICLE

Pharmacological Management of Endometriosis-related Pain: The Expert Opinion

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Highlights

- Endometriosis treatment is still a challenge for modern medicine
- Therapy with combined oral contraceptives (COCs) may be reconsidered at least for some patients
- Progestogens may be an effective alternative to COCs when it comes to endometriosis-related pelvic pain

Abstract

Aim: The aim of this review article was to analyze and summarize the current treatment options of endometriosis-associated pain to provide additional information about treatment personalization for clinicians.

Background: Despite numerous studies being published, endometriosis is still one of the main challenges in gynecology. The etiology of endometriosis is unclear while its mechanism is believed to be connected to the peritoneal endometriotic lesions via retrograde menstruation, immunity abnormalities, and genetic, environmental, and lifestyle factors. Patients with endometriosis generally have to cope with chronic pelvic pain which definitely affects the quality of life. The disease is often characterized by a persistent recurrent course; therefore, when choosing a treatment, special attention should be paid not only to its efficacy, but also to long-term safety, tolerability, and compliance.

Review results: Actual and relevant publications in PubMed and eLibrary databases were studied. The authors highlight the pathogenic mechanisms of endometriosis and the current state of pharmacological management options. The available evidence on the use of combined oral contraceptives (COCs) for pelvic pain is critically assessed and the authors propose their opinion on the alternative treatment options with progestogens which seem to be an effective alternative to COCs with a more favorable safety profile.

Conclusion: Progestogens are an effective alternative to COCs in the treatment of endometriosis-associated pain; however, further well-conducted trials are needed in both types of therapy.

Clinical significance: The results of this literature review provide additional information to enable clinicians to personalize the treatment of endometriosis-associated pain.

Keywords: Combined oral contraceptives (COCs), Dienogest, Dydrogesterone, Endometriosis, Gonadotropin-releasing hormone (GnRH) antagonists and agonists, Norethisterone, Progestogens.

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Background

Endometriosis is a chronic gynecological disease of unknown etiology that affects 10% of women of reproductive age and 40–50% of infertile women.[1] Pain syndrome is one of the main problems associated with endometriosis. Although surgical treatment relieves the pain in approximately 80% of patients,[2] pain syndrome recurrence one year after surgery was reported in 40% of cases. At the same time, 20% of women are refractory to surgical treatment. The risk of decrease in ovarian reserve following cystectomy, however, significantly limits the indications for surgical treatment of endometriosis. After surgical treatment, the overall recurrence rate of endometrioma, e.g., in women without therapy was 23% at 3 years and 50% at 5 years.[3] Another view suggests that relapse-related symptoms one year postsurgery occur in the absence of medical treatment after surgical intervention.[4]

Review Results

Pathogenetic Mechanisms of Endometriosis and Current Treatment Options

Knowledge of pathogenetic mechanisms of endometriosis development could be a key to understanding its tendency of

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recurrence. Stem cell theory is becoming increasingly important in the etiology and pathogenesis of endometriosis.[5] At the same time, that theory does not conflict with other theories but rather unifies them by suggesting that bone marrow stem cells may contribute to the development of endometriotic lesions via lymphogenous dissemination and ectopic implantation in fetuses and males. Since mesenchymal stem cells do not express estrogen receptors, they are not responsive to hormonal treatment for endometriosis, establishing a hypoestrogenic environment. This treatment affects only estrogen-positive differentiated endometrial cells observed in most lesions. That could explain why treatment involving a prolonged hypoestrogenic state is capable of reducing symptoms of endometriosis but is rarely effective for disease eradication.[6]

On the contrary, the mesothelial barrier which protects the underlying stroma from the endometrial transplants present in the retrograde menstrual fluid can be compromised by activation of the epithelial–mesenchymal transition (EMT) repair mechanism that leads to temporary loss of barrier integrity. If the mesothelial barrier is impaired, endometrial cells can more easily adhere to the underlying peritoneal stroma and establish endometrial lesions. The hypothesis is based on the clinical and experimental observations that correlate the location of the endometrial lesions with the areas of mesothelial damage together with genetic evidence that four genes (*WNT4*, *CDC42*, *VEZT*, and *ID4*) associated with endometriosis are direct regulators of the actin cytoskeleton, which coordinates mesothelial barrier integrity. It supports the previously disparate theories that endometriosis may be triggered by infection, mechanical damage, and inflammation since each of these mechanisms can induce EMT in the mesothelium. If the hypothesis is correct, inhibition of EMT in the mesothelial barrier may provide a novel paradigm for the prevention and treatment of endometriosis.[7]

Nevertheless, all modern scientific studies investigating the pathogenesis of endometriosis have not yet changed the opinion that hormone therapy is currently the principal conventional treatment option. That is why the effectiveness of various treatments is still a subject of study and discussion. According to Vercellini, the available hormone treatment options for endometriosis are symptomatic, differ in terms of their safety, tolerability, and cost, but exhibit similar pain relief effects and are not curative.[8] All pharmacologic treatments for endometriosis have their pros and cons. Justified the use of the most effective and safe treatment options in real clinical practice will allow improving the patients' quality of life significantly; however, the current data on some treatment options are limited.

Combined Oral Contraceptives in Treatment of Endometriosis

The inhibition of ovulation by combined oral contraceptives (COCs) was previously considered to be necessary for the treatment of endometriosis. In a study by Santulli et al., no difference was found in the rate of oligoanovulation between women with and without endometriosis. Therefore, these findings deny the intuitive belief that oligoanovulation may to some extent protect against endometriosis.[1]

In addition, it should be noted that the currently used monophasic estrogen–progestin contraceptives also include vaginal rings and transdermal patches. There were some reports that patients who used vaginal rings were more likely to be satisfied than those who used patches, albeit continuous use of both methods was linked to poor control of bleeding.[9]

Superficial endometriotic implants are considered to be "low-risk" lesions. These are more common in young women[10] who are often prescribed COCs.[8] Given the fact that endometrioma may originate from the corpus luteum with hemorrhage[11] and the inhibition of ovulation significantly reduces the recurrence rate of endometriomas after surgery, this appeared to be a reasonable approach for many years.[12]

In 2018, data from studies conducted by various authors evaluating the use of COCs for the treatment of endometriosis-associated pain were published.[13] COCs appeared to reduce to some extent the severity of pelvic pain; however, no evidence was found to suggest that one type of COC is more effective than another.[3] Reduced pain was observed in women using contraceptives compared with placebo, and this effect is comparable to that of progestogens.[13] The progestogenic component may be the main active ingredient of COCs. Various progestogens exert an approximately similar pain suppression effect. The low progesterone receptor level in ectopic endometrium is associated with an insufficient response to treatment with any types of progestogens.[14] It should be kept in mind that both primary dysmenorrhea and endometriosis-related pain can be responsive to any treatment method and that improvement of symptoms cannot exclude endometriosis.[15]

It should be taken into account that 5 mg of ethinylestradiol is suggested[16] to correspond to approximately 1 mg of micronized estradiol and 0.625 mg of conjugated equine estrogen. Consequently, the dose of ethinylestradiol in oral contraceptives exceeds the physiological dose of estrogen by several times. It is assumed that the use of high doses of estrogen and progestin is counterproductive, as it leads to a predominance of estrogen in the presence of progesterone resistance.[17]

According to the European Society of Human Reproduction and Embryology guidelines, doses of estrogen component in modern COCs are low enough not to reach the activating threshold of the disease.[18] Although there is evidence[19] that COCs may be effective in relieving endometriosis-associated dysmenorrhea, pelvic pain, and dyspareunia, reducing the risk of disease recurrence after surgery, and improving the quality of life, and combined hormonal contraceptives (CHCs) can be considered[18] by clinicians to reduce the above-mentioned symptoms and conditions, when prescribing COCs it should be taken into account that the estrogen component can be a source of additional risks for health in general and endometriosis progression in particular at least in some patients.

The increased risk of venous and arterial thrombosis should be taken into account in women over 35 years of age who smoke and are overweight.[20] The picture is not so clear with the management of pain syndrome by COCs in adolescents. Adolescents with endometriosis are more likely to experience migraines than adolescents without endometriosis.[21] Moreover, the estrogen component of COCs may cause headache by exacerbating the existing migraine.[20] Although data from randomly assigned trials support estrogen–progestin therapy to reduce endometriosis-associated pelvic pain,[22] one meta-analysis concluded that the evidence was insufficient to make a final judgment about COCs.[23] Several studies[24] have shown that up to a quarter of patients stopped using CHCs. More severe chronic pelvic pain was associated with long-term CHC ineffectiveness while a lower quality of life was associated with CHC discontinuation due to side effects.

Studies conducted in 2011 and 2017 have shown that women who had previously been exposed to COCs for primary dysmenorrhea had an increased risk of deep infiltrative

endometriosis,[25] and high doses of estrogens in COCs may contribute to the progression of the disease into a more invasive type.[17,26] Therefore, it is suggested to avoid the prescription of COCs due to their estrogen component and to use progestogens as the first-line treatment in patients with deep infiltrative endometriosis. It is important to keep in mind that despite the recognized antigonadotropin activity of progestogens and the anovulatory state generally associated with their use, women should be formally advised to use barrier contraception.[8]

Several international guidelines recommend the use of oral contraceptives for relieving endometriosis-related pain.[18] However, it should be noted that Russian guidelines do not recommend using COCs for endometriosis treatment, as they are not indicated to treat this. This position corresponds to current data concerning the advisability of limiting the use of COCs in patients with endometriosis available.[26] The Russian clinical guidelines classify progestogens as the first-line hormonal treatment, which can be prescribed in endometriosis in accordance with the procedure governing the provision of medical care in obstetrics and gynecology of the Russian Ministry of Health.

GnRH Antagonist and Agonist Therapy in Endometriosis

Gonadotropin-releasing hormone (GnRH) antagonists are indicated for patients with inadequately treated pain or progestin resistance.[13] GnRH agonists and antagonists may be used for a few months before starting progestogens[27] or intermittently during progestogen treatment in case of insufficient pain relief or prolonged bleeding, in combination with add-back therapy in nonresponders to progestogens who are unwilling to undergo surgery due to high surgical risk.

Adverse effects of GnRH agonist and antagonist therapy are subjective vasomotor symptoms and objective findings, such as loss of bone mineral density. The bone loss induced by GnRH agonists and antagonists is greater than that of after natural menopause, averaging 1% per month during 6 months of treatment. The use of add-back therapy can help alleviate the side effects of GnRH agonists and antagonists without reducing its efficacy as long as the add-back regimen does not involve high doses of estrogen. Basically, adequate doses of sex steroids (estrogens + progestins) are provided to prevent significant bone demineralization, but not enough to stimulate the growth of endometriotic tissue. This approach is based upon the "estrogen threshold hypothesis," i.e., low levels of circulating estradiol are associated with regression of estrogen-sensitive tissues (e.g., endometriotic implants). Adding back small amounts of estrogen will increase circulating levels enough to maintain the integrity of some tissues, such as bone, with a relief of vasomotor symptoms, while causing other tissues (e.g., endometriotic lesions) to remain in a state of regression.

The analysis of published comparative data on the use of various treatment options resulted in the conviction that cyclic[28] and continuous[29] use of COCs, GnRH receptor antagonists,[30] and progestins[29] suppress endometriosis-related pain. Since the relapse of symptoms occurs when medications are discontinued, long-term treatment should be planned in women who do not want to become pregnant. All treatments led to a clinically significant pain reduction compared with placebo. The magnitude of this therapeutic effect is similar for all treatment options, which suggests a small difference in their ability to relieve the pain. There is a group of extremely inexpensive hormonal medications and a group of highly expensive treatments, including dienogest and GnRH antagonists. Inexpensive agents should be regarded as first-line medications, while expensive options should only be used in women tolerant of the first-line treatment.[8]

Progestogens Use in Treatment of Endometriosis

Neoangiogenesis plays an undeniable role in the growth and development of endometriotic heterotopias by affecting the connective tissue matrix metalloproteinases (MMPs). In the study comparing MMP-1 and MMP-9 levels in the eutopic and ectopic endometrium from women with endometrial cysts and in the normal endometrium of women without endometriosis by immunohistochemistry,[31] increased concentrations of MMP-1 and MMP-9 were observed in the uterine gland and the stroma of the ectopic and eutopic endometrium in women with endometriotic ovarian cysts compared to normal endometrium. The reported changes are indicative of a greater proliferative activity both in the eutopic and ectopic endometrium as compared to normal, which pathogenetically substantiates the therapeutic use of proliferation inhibitors. Evaluation of the effects of progestogens (specifically progesterone and dydrogesterone) on the expression of matrix MMPs and angiogenesis factors using models of human ectopic heterotopy[32] revealed their inhibitory effect on the onset and maintenance of ectopic endometrial lesions by suppressing the proliferative activity of stromal cells.

The best-known progestogens used in women with endometriosis are levonorgestrel, medroxyprogesterone acetate, norethisterone, dienogest, and dydrogesterone; all these agents were investigated in a wide variety of studies and have proven their clinical efficacy.[17,26] However, only two progestins—norethisterone acetate and medroxyprogesterone acetate—are approved by the Food and Drug Administration, while dienogest is approved in Japan, Europe, Australia, and Singapore. Generally, these substances are used in more than 100 countries. Progestogens can be administered via an oral, intramuscular/subcutaneous, or intrauterine route.

In 2018, data from the comparative study of therapeutic and side effects including molecular mechanisms of action of dydrogesterone and dienogest in endometriosis on mice were published.[33] Following the assessment of the size and volume of lesions, histological parameters, and biochemical markers of proliferation and apoptosis during and after treatment, it was concluded that dydrogesterone and dienogest are effective treatments for endometriosis due to their selective effects on proliferation, apoptosis, and molecular mechanisms of endometriosis. Both dydrogesterone and dienogest significantly reduce the size of the lesions and prevent the development of cells in endometriotic foci. Their primary therapeutic effects are related to progesterone receptors—suppression of cell proliferation and activation of apoptosis in endometriotic foci. However, less-pronounced antiproliferative and apoptosis effects were observed in dienogest compared to dydrogesterone.[33]

It is worth noting that, despite the absence of differences in efficacy, their safety profiles are different. Norethisterone and dienogest have more potentially dangerous side effects, such as abnormal lipoprotein and cholesterol levels, decreased bone density, etc.[34–36] It is currently unknown whether this may lead to any cardiovascular complications in the long term, but this information will be available in the near future, given the young age of women using dienogest.[8] Norethisterone belongs to the largest group of synthetic progestogen and testosterone

derivatives.[35] Apart from its progestogenic and antigonadotropic activity, it exerts additional androgenic activity that may cause such adverse effects as acne, hirsutism, and fluid retention. If administered in high doses, this progestin may lead to an increase in the atherogenic index and entail the risk of cardiovascular complications.[36]

In a 52-week multicenter study in adolescent patients, dienogest 2 mg once daily was effective in relieving the symptoms (pelvic pain, dysmenorrhea, and dyspareunia) and signs (tenderness during bimanual exam and induration) of endometriosis, but was associated with a mean decrease in bone mineral density (BMD) by 1.2% in the end of treatment. Follow-up assessment in 60 of 73 patients with decreased lumbar spine BMD showed a partial recovery 6 months later.[37]

In addition to lipid spectrum disorders and decrease in BMD associated with dienogest administration, other common adverse effects include metrorrhagia, headache, constipation, nausea, hot flushes, weight gain,[38] breast discomfort, irritability,[39] and fatigue.[40] Amenorrhea, weight gain (57%), hair loss (22%), acne (18%), and backache are common in patients on dienogest treatment for over 52 weeks.[41] Such symptoms as weight gain, hair loss, and acne are primarily associated with androgenic effects. Dienogest has an antagonistic activity on androgen receptors, resulting in limited androgen-like adverse effects.[42] In addition, dienogest causes significant hypoestrogenic side effects.[43] Depressive states were observed in 28% of patients.[41] All of these complications lead to discontinuation of dienogest and switching to another treatment (11%).[41] Particular attention should be given to the need for and possibility of switching from one medication to another in the treatment of pain syndrome.

Although progestogens may inhibit ovulation and induce amenorrhea, their use does not result in thinning of the endometrium. On the contrary, long-term use of COCs leads to a decrease in the concentration of estrogen receptors in the normal endometrium and a reduction of the thickness of its functional layer, which is an unfavorable factor in pregnancy planning. In addition, according to studies conducted in 2010,[44] some endometriotic implants demonstrate resistance to progesterone and are sensitive to estrogens. Therefore, estrogens used in COCs can play an unexpected role and contribute to the progression of endometrioid heterotopias.

According to Vercellini, treatment of endometriosis requires therapeutic methods that would effectively treat or manage the disease without inhibiting ovulation, thereby allowing pregnancy for those who wish to become pregnant during the treatment.[45]

The use of dydrogesterone allows the patient to choose a treatment regimen. A multicenter, open-label, observational program aiming to describe the effects of dydrogesterone therapy in women with diagnosed endometriosis is currently ongoing in Russia. The primary objective of the research is the effectiveness of reducing pain syndrome in various regimens of pharmacologic therapy.[46] The long-term use of dydrogesterone 10 mg 2–3 times/day from day 5–25 of the menstrual cycle appeared to be the most effective regimen to reduce pelvic pain. If used for ≥6 months, this scheme results not only in pain reduction but also a significant decrease of endometriotic lesions as confirmed by repeated laparoscopy. At the same time, dydrogesterone can be used to relieve pelvic pain at 20 mg per day from day 5–25 and from day 16–25 of the menstrual cycle, which also significantly improves the quality of life in patients. Dydrogesterone is recommended to be prescribed at up to 30 mg per day for ≥3–6 months without interruption for those women who are not planning a pregnancy in the near future.

In different studies, dydrogesterone has been used in doses ranging from 10–60 mg/day for a varying number of days in a cycle for 3–9 months. For most women, the number of symptoms and their severity decreased. In several studies, these results were also confirmed by laparoscopic examinations. The cyclic use of dydrogesterone caused regular menstruation and decreased blood loss and relieved symptoms in women with dysmenorrhea. However, it should be noted that all of these studies are relatively old and there is a need to conduct new high-quality trials.[47]

Moreover, dydrogesterone does not inhibit ovulation in therapeutic doses and does not affect estrogen levels; it is therefore indicated to be used in preparation for pregnancy (with no need for treatment discontinuation) and can be continued after pregnancy is confirmed.[46] One of the trials concluded that the medicinal product is effective in preconception preparation at 10 mg 3 times/day from day 5–25 of the menstrual cycle before pregnancy followed by continued use in pregnancy at 20 mg per day until week 20 of pregnancy and gradual discontinuation. It is worth noting that dydrogesterone is associated with at least a 50% pregnancy rate and a ≥2-fold decrease in the risk of pregnancy loss with threatened sporadic miscarriage.[26]

In another study,[48] patients who underwent laparoscopy received dydrogesterone at doses of 10–20 mg/day depending on the severity of the case from day 5–25 of the menstrual cycle for 3–6 months. The results of the study indicated a reduction in symptoms after the first treatment cycle. By the end of the 6th month, there was a decrease in pelvic pain (95%), dysmenorrhea (87%), and dyspareunia (85%). The amount of menstrual bleedings also fell by 12% after 2 months and this trend continued until the end of the study. Every fifth patient was recognized as cured and an improvement was observed in two-thirds of the patients. The treatment was rated excellent or good by 74% of patients and 70% of physicians.

In case of postsurgical use of GnRH agonists and antagonists, the duration of their administration should not exceed 6 months followed by a switch to dydrogesterone. Considering the antiproliferative effect of dydrogesterone, it will contribute to the restoration of reproductive function if given at the earliest possible time interval after surgery.

It should be noted that, in 2012, Cochrane published the results of a systematic review and meta-analysis of the available data on progestogens and anti-progestogens in the treatment of endometriosis-associated pain.[49] The authors concluded that there is only limited evidence to support the use of these drugs. However, there is no update of the review available since then. This review is only based on two studies when it comes to progestogens versus no treatment or placebo which were published in 1994 and 1987: one of them compared dydrogesterone to placebo while another one compared medroxyprogesterone acetate to placebo. Following well-conducted randomized trials, an update to the meta-analysis is needed to arrive at a consensus.

Thus, at the moment dydrogesterone appears to be potentially effective in endometriosis; however, further large-scale high-quality studies are needed which will finally answer the question of its efficacy. The advantage of dydrogesterone is the possibility to use it for treatment personalization in most cases both for women who are not planning a pregnancy and for those who have not yet reached their reproductive potential and do not exclude pregnancy during treatment.

Conclusion

Endometriosis is a typical chronic disease which should be treated to achieve long-term remission. Patients often need a personalized long-term pharmacological treatment which is defined by age, reproductive motivations, and clinical manifestations. Currently, it is not possible to use medications that would selectively target the ectopic endometrium. Only this type of agent could provide long-term treatment for pelvic endometriosis without concurrent uterine infertility due to suppression of the eutopic endometrium. Such agents do not currently exist and the best available treatment options are hormonal drugs. Russian guidelines mention progestogens as the first-line treatment for endometriosis and, in case of treatment failure, GnRH agonists and antagonists as the second-line treatment.

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