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REVIEW PAPER

Progestins and combined oral contraceptives in the hormonal treatment of endometriosis – a review

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ABSTRACT

Introduction and aim. Endometriosis is a common inflammatory disease affecting 6-10% of women of reproductive age. It is defined as the growth of endometrial-like tissue outside the uterine cavity. Dysmenorrhea, pelvic pain, dyspareunia and infertility are the main symptoms of endometriosis patients. Endometriosis treatment methods can be broadly divided into surgical and pharmacological. Currently, hormonal drugs are often used for women with endometriosis to relieve bothersome symptoms. The aim of this article is to review new publications presenting the effectiveness as well as side effects of the use of progestins and combined oral contraceptives in the hormonal treatment of endometriosis.

Material and methods. A review of the literature regarding progestins and combined oral contraceptives in the treatment of endometriosis was performed using the PubMed database. In the end, 67 articles were included in this review.

Analysis of the literature. Progestins and combined oral contraceptives significantly reduce dysmenorrhea, dyspareunia and pelvic pain in women with endometriosis. However, there is a risk of potential side effects, which should be taken into account when choosing a therapy for each patient individually.

Conclusion. Endometriosis is a chronic disease that has a significant impact on the health-related quality of life of patients. When choosing a treatment, many aspects should be considered, primarily the patient's preferences, drug tolerance and safety. Further drug research is needed to determine the most effective treatment for endometriosis.

Keywords. combined oral contraceptives, endometriosis, health-related quality of life, infertility, pelvic pain, progestins

Introduction

Endometriosis is a chronic inflammatory disease, that affects about 6-10% of women of reproductive age and is characterized by endometrial tissue outside the uterus. It is a common cause of infertility, pelvic pain and dyspareunia. The clinical picture is often non-specific, which leads to diagnostic difficulties and delayed diagnosis.[1,2] Currently, three subtypes of endometriosis are presented: superficial peritoneal, deep and ovarian.[3] Laparoscopy is the preferred method in diagnosing endometriosis.[4] Although causal treatment is not possible, clinical trials have provided many strategies for managing the symptoms of this disease - combating pain, improving fertility and treating complications. They can be divided into surgical removal of lesions and drug treatment.[1] Currently, the role of hormone therapy in endometriosis is emphasized, which effectively relieves the symptoms of the disease and improves the health-related quality of life (HRQoL).[5]

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Aim

The aim of this article is to review the latest publications mostly from 2015-2022, which present the medical approach with progestins and combined oral contraceptives in the hormonal treatment of endometriosis, the advantages and potential side effects of this pharmacological treatment.

Material and methods

Using the PubMed database, a literature review on progestins and combined oral contraceptives in the hormonal treatment of endometriosis was performed; search terms "*endometriosis, endometriosis treatment, progestins, dienogest, dydrogesterone, norethindrone acetate, medroxyprogesterone acetate, levonorgestrel intrauterine device, etonogestrel-releasing subdermal implant, combined oral contraceptives, ethinylestradiol, drospirenone, levonorgestrel, desogestrel*" were applied. Ultimately, 67 articles were used for this review.

Analysis of the literature

Estrogens stimulate the proliferation of the endometrial mucosa and increase the number of receptors for progesterone. In turn, progesterone induces cyclical secretory changes in the endometrium in preparation for implantation.[6] Ectopic endometrial lesions respond to the cyclical secretion of ovarian steroids, mainly estrogen and show significant resistance to progesterone.[7] The aim of hormonal therapy is to block menstruation by inducing a state of iatrogenic menopause or pseudopregnancy. Medical hormone therapy can control pain symptoms to prevent or postpone surgery.[5] Commonly used drugs are Progestins, Combined Oral Contraceptives Pills, Gonadotropin Releasing Hormones (GnRH) agonists, Gonadotropin Releasing Hormones (GnRH) antagonists, Aromatase inhibitors, Danazol, Gestrinone, Selective estrogen receptor modulators (SERM), Selective progesterone receptor modulators (SPRM). In addition, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are used in the symptomatic treatment of pelvic pain and dysmenorrhea.[8] Surgical interventions are aimed at removing endometriosis lesions. Resection of endometriosis helps in restoring fertility and reduces pelvic pain symptoms.[9,10]

Progestins

Progestins are synthetic compounds that have a similar effect to progesterone. They differ in potency and profile in the hypothalamic-pituitary axis, genitals and breast tissue. Progestins reduce the frequency and increase the amplitude of the pulsatile release of gonadotropin-releasing hormone (GnRH), which causes a decrease in the secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Administration of progestins in continuous therapy leads to inhibition of ovarian steroidogenesis and anovulation.[11] Progestins binding to progesterone receptors (PRs) may induce anti-estrogenic, anti-inflammatory and pro-apoptotic effects. They help to relieve pain and suppress endometriosis.[12] Side effects of progestins are included in Table 1. According to the guidelines, progestins are the first-line therapy for the treatment of pain in endometriosis.[13] There are various forms of progestins available to treat endometriosis. They can be administered by an oral, intramuscular, subcutaneous, patch or intrauterine route.[14] Below is a description of a few selected representatives from this group.

Table 1. Major side effects and complications of endometriosis treatment with progestins and COCs

Medical treatment	Side effects and complications
Progestins	unscheduled bleeding, breast tenderness, bloating, mood changes, weight gain,[15] hot flushes, acne, loss of libido, headache, fatigue,[14] possible reduction in bone density (long-term use of depot medroxyprogesterone acetate and dienogest)[16]
Combined Oral Contraceptives (COCs)	weight gain, water retention, leg swelling, cellulite, breast tenderness, nausea, headaches, spotting, negative impact on carbohydrate metabolism, lipid profile and liver function, risk of venous thromboembolism[17]

Dienogest

Dienogest is a derivative of 19-nortestosterone with a high specificity towards PR.[8] Dienogest inhibits the systemic secretion of gonadotropins and exerts local anti-inflammatory and anti-proliferative effects.[18] This progestin is administered orally, mainly at a dose of 2 mg per day.[19] Dienogest has been shown to improve endometriosis-related symptoms such as chronic pelvic pain, dysmenorrhea, dyspareunia and thereby improve HRQoL.[20] Randomized controlled trials showed dienogest efficacy comparable to GnRH analogues but with better tolerability.[21,22] Dienogest has also been shown to be superior to NSAIDs in improving pain relief and quality of life in long-term therapy.[23] The study proved that long-term dienogest treatment (24 months at a dose of 2 mg once a day) in women with endometriosis has a positive effect on the quality of life and sexual function. A slight improvement in dysmenorrhea, chronic pelvic pain and dyspareunia was observed in the study group after 3 months of treatment with dienogest, and a greater improvement from 6 to 24 months. The Female Sexual Function Index and the Female Sexual Distress Scale did not change after 3 months but improved from 6 to 24 months. Quality of life from 6 to 24 months improved in all categories. No changes were observed in the control group receiving NSAIDs.[24] Another study showed a delay in regaining fertility during the first three cycles after discontinuation of dienogest. Subsequently, the cumulative conception rate was no different from that observed in fertile women who were not using contraception.[25] The most common side effects of dienogest are abnormal uterine bleeding, weight gain, headache, acne and

depressed mood.[26,27] There is a possibility of bone loss in some women, therefore bone mineral density (BMD) should be checked in patients on long-term treatment.[28]

Dydrogesterone

Dydrogesterone (6-dehydro-retroprogesterone) is a retroprogesterone that is similar in structure and pharmacology to endogenous progesterone. It is a selective progesterone receptor agonist and has good oral bioavailability.[29] Dydrogesterone is used as a postmenopausal replacement hormone, in endometriosis and the treatment of menstrual disorders. It has been shown to improve endometriosis symptoms and reverse lesions. Meta-analysis showed the advantage of dydrogesterone over gestrinone in relieving dysmenorrhea and increasing pregnancy rates. Compared to GnRH-a, dydrogesterone reduced the risk of endometriosis recurrence.[30] In a 6-month cohort study, it was proven that prolonged cyclical and continuous regimens of dydrogesterone treatment (dydrogesterone 10 mg 2 or 3 times a day, between days 5 and 25 of the menstrual cycle as an extended cyclic regimen or continuously as a continuous regimen) showed a significant reduction in chronic pelvic pain, dysmenorrhea, improved HRQoL and sexual well-being.[31] Dydrogesterone is preferred in cases where the patient is planning a pregnancy because when taken in a cyclical regimen, it does not inhibit ovulation. Abnormal bleeding from the uterus is the most common side effect.[32]

Norethindrone acetate

Norethindrone acetate is effective in the long-term treatment of endometriosis. By inhibiting gonadotropins, it causes hypoestrogenism, inhibition of ovulation, development of amenorrhea and endometrial tissue atrophy.[33] Norethindrone acetate has progestogenic and androgenic effects. It can cause weight gain, seborrhea and acne.[34] There was a study that looked at the percentage of patients who were satisfied with their treatment of norethindrone acetate (2.5 mg/day) and dienogest (2 mg/day). The percentage of women satisfied with the treatment with norethindrone acetate was 71% and with dienogest 72%. Switching from norethindrone acetate to dienogest was not associated with significant improvements in pain relief and HRQoL. Dienogest should be suggested in women intolerant to norethindrone acetate.[35]

Medroxyprogesterone acetate

Medroxyprogesterone acetate is a 17-OH derivative of progesterone. It is available as an oral or depot preparation (DMPA) that can be administered intramuscularly or subcutaneously every 3 months. The standard dose of DMPA is 150 mg/ml intramuscularly.[36,37] In a clinical trial, DMPA-SC (104 mg/0.65 ml given by subcutaneous injection) was shown to be as effective as leuprolide (11.25 mg by intramuscular injection). However, DMPA-SC has fewer hypoestrogenic side effects and less impact on BMD, but more bleeding.[38] This therapy should not be used in women who want to get pregnant in the near future, due to long-term inhibition of ovulation and its delayed return. In a clinical study evaluating the pharmacokinetics and pharmacodynamics of medroxyprogesterone acetate, none of the women ovulated before 7.5 months.[39]

Levonorgestrel intrauterine device (LNG-IUS)

LNG-IUS can be used as an alternative therapy in women with endometriosis. The LNG-IUS is a small device that is placed in the uterus. LNG progestin is a 19-nortestosterone derivative. The LNG-IUS delivers LNG directly to the endometrium at a rate of 20 μg per day and can stay in place for five years or more.[40] The main mechanisms of LNG-IUS in the treatment of endometriosis are an intensification of apoptotic activity, induction of endometrial gland atrophy and stroma transformation.[8] LNG-IUS is also used for contraception, treatment of heavy menstrual bleeding, and protection of the endometrium in women with breast cancer receiving tamoxifen.[41-44] This method of treatment also comes with some potential side effects. The risks associated with the device, such as expulsion, pelvic inflammatory disease and perforation, are suggested to be low. Breakthrough bleeding and spotting may occur during the first few months of use. Other side effects include pelvic pain, ovarian cysts, breast tenderness, acne and weight gain.[40]

Etonogestrel-releasing subdermal implant (ENG-implant)

ENG is a subcutaneous implant that systematically releases a synthetic substance similar to progesterone.[45] In a study evaluating the effectiveness of the ENG-implant compared to the 52-mg LNG-IUS in the control of endometriosis-related pelvic pain, both contraceptives were shown to significantly improve dysmenorrhea, pelvic pain and HRQoL.[46] Subdermal implants (ENG-implant 68 mg with a life span of 3 years) have been found to be as effective in pain relief over 12 months of use as DMPA. ENG-implant is safe, well tolerated and achieving contraception.[11]

Combined oral contraceptives

COCs inhibit LH and FSH, resulting in the inhibition of ovulation. They significantly reduce pelvic pain, dysmenorrhea, profound dyspareunia and dyschezia in women with endometriosis.[47] A clinical study was conducted in women with recurrent dysmenorrhea after conservative surgery for endometriosis, which demonstrated that continuous and long-term use of COCs reduces the frequency and severity of pain symptoms of patients.[48] Studies have shown that treatment with

COCs, compared to placebo, relieves dysmenorrhea, dyschezia, dyspareunia and reduces the size of endometriosis.[49,50] Another study evaluating the effects of oral contraceptives and dienogest on endometriosis-related chronic pelvic pain, sexual function, and quality of life found comparable efficacy for both treatments.[51] A systematic review reported that the effectiveness of COCs in reducing pain was similar to or less than that of GnRH agonists and oral progestogens.[52] There is evidence that COCs taken for six months reduce heavy menstrual bleeding (HMB) in women. However, compared to LNG-IUS, combined oral contraceptives were less effective.[41] The use of COCs causes a 4 to 7-fold increase in the risk of thromboembolic disease.[53] The risk factors for thromboembolic events are mainly age, positive family history, genetic thrombophilias, smoking, obesity, hypertension, atrial fibrillation, prolonged immobilization, major surgery or trauma.[54] The most common side effects of COCs are listed in Table 1.

Ethinylestradiol/Drospirenone

Ethinylestradiol(EE)/drospirenone is a new generation COC that has antimineralocorticoid and antiandrogenic effects. This combined formulation contains 3 mg of drospirenone and 20 μg of EE. The 24/4 regimen causes less fluctuation in hormone levels compared to the conventional 21/7 regimen. This COC provides good cycle control and reduces estrogen-related side effects. EE/drospirenone has a good safety profile and good tolerability. There is a low risk of thrombosis, water retention and weight gain. Side effects are mainly headache, nausea and chest pain.[55] An observational study has shown that HRQoL is significantly improved after treatment with EE 20 μg/drospirenone 3mg in a 24/4 cycle in patients with dysmenorrhea.[56] Menstrual pain can be severe during withdrawal bleeding, which is why an extended EE 20 μg/drospirenone 3mg regimen has been developed. It is taken for a maximum of 120 days, followed by a 4-day tablet-free period. This COC has been used successfully in the treatment of dysmenorrhea and pelvic pain associated with endometriosis.[57] Another study showed that a flexible extended regimen of EE 20 μg/drospirenone 3mg (one tablet daily for 24–120 days followed by a 4-day rest period) compared with a 28-day cyclical regimen (one tablet daily for 24 days followed by 4 days of a placebo tablet for six cycles) reduced the number of days with dysmenorrhea in women and was well tolerated.[58]

Ethinylestradiol/Levonorgestrel

LNG is a second-generation synthetic progestin that, in combination with estrogen, is a long-term contraceptive.[59] A study was conducted to evaluate the 28-day cyclic and 84-day extended regimen of EE 0,02 mg/levonorgestrel 0,09 mg in patients with dysmenorrhea. Extended and cyclic regimens significantly reduced the severity of dysmenorrhea compared to placebo. However, the extended regimen was superior to the cyclic regimen in reducing these symptoms. The use of this COC carries the risk of side effects. Cyclic regimens are associated with symptoms such as headache, bloating, nausea, and breast tenderness. Prolonged and continuous regimens may cause breakthrough bleeding.[60] The use of low dose (<50 μg ethinylestradiol) COCs containing cyproterone acetate, desogestrel, dienogest, drospirenone or gestodene was associated with an increased risk of venous thromboembolism compared to COCs containing levonorgestrel.[61]

Ethinylestradiol/ Desogestrel

Long-term continuous use of a COC containing EE 0.02 mg and desogestrel 0.15 mg is effective in relieving menstrual pain in women with endometriosis. Side effects include intermenstrual bleeding, bloating, weight gain, headache, breast tightness, and decreased libido.[48] COCs containing 0.03 mg of EE and 0.15 mg of desogestrel have been proven to influence the immune mechanisms in endometriosis. They cause an increase in the level of NK cells and Tregs, as well as a significant decrease in the number of macrophages.[62] In a randomized controlled trial, cyproterone acetate 12.5 mg and a monophasic COC with continuous action containing EE 0.02 mg and desogestrel 0.15 mg have been shown to be an effective and safe option in the treatment of recurrent pelvic pain associated with endometriosis.[63]

Risks and benefits for both types of treatment

Endometriosis is an estrogen-dependent disease, which means that estrogen is the key hormone that is responsible for the growth and development of ectopic endometriosis lesions. In a clinical study, the effects of COCs (combination of EE 0.03 mg and desogestrel 0.15 mg) and desogestrel alone on cell proliferation and apoptosis in ectopic endometrial tissue were evaluated. Patients treated daily with desogestrel alone or COC (EE/desogestrel) for 28-35 days were compared with patients not receiving treatment. This study proved that desogestrel alone increased cell apoptosis in the ectopic endometrium. In turn, COCs increased proliferation and caused a greater apoptotic effect in endometriosis lesions.[64] Progestins do not cause endometrial proliferation, but they also have side effects, which are included in *Table 1*. There is a potential for bone loss in some patients with long-term use. Therefore, it suggests that the addition of a small amount of estrogen may be beneficial for patients requiring long-term use of dienogest.[65] There are concerns about BMD with ultra-low-dose oral contraceptives (<20 μg EE), while COCs containing 20 to 30 μg EE may protect against bone loss.[66] Low-estrogen COCs cause more frequent spotting and breakthrough bleeding.[67] There is an increased risk of venous

thromboembolism with the use of COCs. To reduce the risk of thrombosis, COCs with the lowest possible dose of estrogen should be chosen. Both COCs and progestins have been shown to be effective in the treatment of symptomatic endometriosis. However, progestins do not increase the risk of thrombosis and can be used in women with contraindications to estrogens, as well as in those who do not tolerate estrogens.[34] Pre-operative hormonal treatment is not recommended in patients scheduled for surgery. However, in the postoperative period, in women who do not have procreative plans, hormonal treatment can be introduced in order to reduce the risk of recurrence of pain and endometriosis.[13]

Conclusion

Endometriosis is a chronic disease and treatment should focus on drugs that can be used long-term with minimal side effects. The nature of this disease makes progestins and COCs often the first-line treatment. These drugs relieve troublesome symptoms and improve the HRQoL of patients suffering from endometriosis. When choosing a specific treatment regimen, the type of ailment, the patient's preferences regarding the method of drug administration, drug tolerance and safety, procreation plans and treatment costs should be considered. Endometriosis is still an under-researched disease that is often underdiagnosed. Due to the high prevalence in society, actions should be taken to raise awareness and educate in this regard. This disease requires a holistic therapeutic approach as it can affect many different organ systems. Patients should be educated about the multitude of therapeutic methods in the treatment of endometriosis, their effectiveness and potential side effects. Despite the widespread use of COCs and progestins in clinical practice, there is still little current literature on the treatment of endometriosis with them. Further research is needed to determine the length of treatment, choice of preferred drugs and their dose, intermittent therapy and combinations with other drugs that are most effective in the treatment of endometriosis.

Declarations

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Author contributions

Conceptualization, K.R., A.J., An. S., W.S., M.Z. and Ag. S.; Validation, M.Z., Ag. S.; Resources, M.K., Ad. S.; Data Curation, M.K., Ad. S.; Writing – Original Draft Preparation, A.J., W.S., M.K. and Ad. S.; Writing – Review & Editing, K.R., An. S.; Supervision, K.R.; Project Administration, K.R.

Conflict of interest

The authors declare no conflict of interest.

Data availability

Data supporting the results of this study shall, upon appropriate request, be available from the corresponding author.

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