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Non-surgical methods of pain treatment improving the quality of life of patients with endometriosis

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Abstract

Introduction : Endometriosis is a disease that currently affects 10-15% of women of reproductive age worldwide. The main problem of female patients, in addition to infertility, is pain, which varies greatly, significantly reduces the quality of life and affects family, social, sexual and professional life. Pharmacological treatment, which is applied both after the excision of the lesions and in patients who were not eligible for surgery, is an important element of pain therapy. There are also other methods, such as appropriate diet change, supplementation, acupuncture, electrotherapy, which are partially effective.

Method : review of the recent literature based on PubMed ,Google scholar research based on the following keywords : endometriosis treatment, hormonal treatment of endometriosis, quality of life of patients with endometriosis

Purpose of work : Comparison of the mode of action and effectiveness of individual non-surgical methods of treating pain in patients with endometriosis.

Key words: endometriosis, hormonal treatment, pain treatment

Introduction:

Endometriosis poses a social and economic problem. The disease is still poorly understood, as the intermediate time from the first symptoms to diagnosis is 8-10 years.(1) The symptomatology of the disease is complex. The most common symptom occurring in 90% of patients is dysmenorrhea. Pelvic pain is the next, accounting for 77% and having the greatest

impact on quality of life. (2) Patients also suffer from dyschezia, hematochezia, gradually increasing acute premenstrual pain, pain in the sacral region of the spine, painful ovulation, pain when defecating or urinating, pain radiating to the back, blood in the stool, gastrointestinal symptoms like diarrhea or constipation, and chronic fatigue. Other symptoms that have a negative impact on quality of life include dyspareunia, sexual dysfunctions, dissatisfaction, and distress. They cause difficulties in the sexual life of the patient and her partner, which negatively affects the relationship. (4) It is worth adding that many studies show the relationship between the occurrence of endometriosis and the patient's mental health. It is estimated that as many as 87% of patients with endometriosis develop some type of psychiatric disorder. (5) Infertility is also a huge problem, which affects up to 50% of patients (3).

State of knowledge:

The pathophysiology of pain is associated with chronic inflammation that is dependent on hormonal changes following the ectopic progression of the endometrium during the menstrual cycle. Increased levels of pro-inflammatory cytokines such as IL-6, TNF-, IL-1 β and IL-8 is a factor of great importance here. (6) Peritoneal macrophages of patients with endometriosis show increased expression of cyclooxygenase-2 (COX-2) mRNA, which results in increased secretion of prostaglandins, which are responsible for the contractions of the myometrium and intrauterine vessels. The initiation, development and progression of endometriosis is associated with too intensive production of pro-inflammatory cytokines and a reduced concentration of anti-inflammatory factors by several types of cells: stromal, epithelial, smooth and immune. (7)

Treatment methods are varied and rely mainly on pharmacotherapy and surgery. However, surgery is not a necessity in every patient. The gold standard that allows for an unambiguous diagnosis of endometriosis is undoubtedly obtaining a positive histopathological examination of the material collected during laparoscopy, however pain relief after empirical hormone treatment is an indirect evidence of the disease, and it is often allowed to implement such a procedure in patients for whom there are no additional indications for surgery. Currently, it is believed that in the case of young women and patients without lesions requiring surgery (large endometrial cysts > 7-8 cm, suspected malignant lesion, deeply infiltrating endometriosis of the rectovaginal septum or the urinary bladder, ureteral structure, adnexal masses of uncertain appearance at diagnostic imaging procedures, ureteral stenosis causing hydronephrosis, bowel stenosis associated with sub-occlusive symptoms) the therapy should certainly be started with an attempt at conservative treatment. (8)

In the case of ovarian cysts, it is important not to degrade the level of follicles, which may one day become an ovum, because each operation on the ovary reduces the pool of the ovarian reserve which is disadvantageous for patients who want to become pregnant in the future.

Pharmacological treatment is used in women of reproductive age to reduce or eliminate pain, and to inhibit the development of endometriosis. Pharmacotherapy can be part of preparation for surgery, as well as complementary to surgery. Empirical therapy, which is used in patients who do not qualify for laparoscopic surgery, involves the introduction of drugs only on the basis of a physical examination and imaging tests. (3) Hormonal contraceptives, progestins, anti-progestogens, GnRH agonists, and GnRH antagonists should be used in the treatment of pain associated with endometriosis. All drugs show similar efficacy in reducing the intensity of pain associated with endometriosis and the duration of improvement after the end of treatment. When selecting drugs, the occurrence of side effects, safety profile and costs should be taken into account, due to the fact that the therapy may last for years. This type of treatment is not recommended for women who wish to become pregnant or have clear indications for surgery. Also, the treatment will not have positive consequences in case of infertility. (9)

Combined oral contraceptives (COCs) are used in empirical therapy in women with histopathologically unconfirmed endometriosis as the method of choice. These drugs are well tolerated and low cost, however the estrogen content may be a drawback. While this treatment is widely used, recent studies show that pain rates with oral contraceptives were higher than with GnRH or progestin. There is currently no evidence that this treatment is effective, despite the fact that this therapeutic pattern has been used for decades. About 50% of patients have only partial or no improvement in their endometriosis symptoms with oral contraceptives. These drugs have also been shown to result in a higher risk of developing endometriosis in the future (10). COCs reduce menstrual flow, decidualize endometrial implants, and reduce cell proliferation. (11) The advantage is that there is no hypoestrogenism that can lead to osteoporosis. It has also been shown to reduce the intensity of menstruation and relapse of endometriosis in patients who had previously undergone surgery. (12) Treatment can be carried out in two ways: cyclical with the onset of menstruation and continuous, which is more beneficial in relieving the symptoms of endometriosis. The risk of side effects is the same as when using hormonal contraception.(13)

The drugs of first choice in the treatment of endometriosis are progestogens. (14) The most commonly used are dienogest (DNG), norethindrone acetate (NETA) and medroxyprogesterone acetate (MPA). The route of administration can be oral, intramuscular and intrauterine hormone releasing system (IUS). The action of progestins is comprehensive and has a beneficial effect by reducing pain, inhibiting the development of endometrial foci and their atrophy. The mechanism of action is a reduction in FSH and LH secretion resulting in suppression of ovulation and amenorrhea. Like combined oral contraceptives, they have anti-inflammatory effects, induce apoptosis, reduce oxidative stress and inhibit angiogenesis, but unlike COCs, they also cause hypoestrogenism due to their anti-estrogenic effects. Side effects from progestins are common and include weight gain, fluid retention, depressed mood, and acyclic bleeding. Bone loss occurs with long term MPA depot. (16)

Gonadotropin releasing hormone agonists (GnRH-a) bind to GnRH receptors and stimulate the pituitary gland to produce LH and FSH for 10 days, then these receptors are down-regulated, which reduces the secretion of LH and FSH and, subsequently, inhibits the production of estrogens in the ovaries. (17) As a result, hypoestrogenism reduces endometrial foci. Treatment is as effective in relieving pain as it is with progestins. It is worth mentioning that there are side effects such as amenorrhea, vasomotor symptoms, atrophy of the genitourinary system, sleep disturbances and accelerated bone loss. Therefore, caution should be exercised when using this medicine in adolescent patients who have not yet achieved maximum bone mineral density. To reduce side effects, it is common to add so-called add-back therapy in the form of low dose COCs, estrogens or progestins, bisphosphonates, tibolone or raloxifene. Therapy usually lasts up to 6 months. Unfortunately, the high price of these drugs is a major limitation. (18)

GnRH antagonists inhibit gonadotrophin hormone production by competing with endogenous GnRH for pituitary receptors. The effect of the action takes place quickly. These drugs do not induce the initial phase of relapse as in the case of GnRH-a.

Drugs that are currently under development and not used in clinical practice include Selective progesterone receptor modulators (SPRM), Selective estrogen receptor modulators (SERMs), and Aromatase inhibitors. SPRMs act as a tissue selective agonist, antagonist or partial agonist / antagonist for a variety of progesterone-sensitive tissues. These drugs inhibit ovulation, but do not cause hypostrogenism, as they maintain the physiological levels of estradiol. Although good efficacy of SPRM has been suggested due to the fact that they inhibit endometrial proliferation, inhibit bleeding, affect endometrial blood vessels and reduce prostaglandin production, they are not used in clinical practice. Numerous side effects and an

increase in liver function tests were reported in 3.4% of patients. Currently, there are insufficient data on the effectiveness and safety of SPRM.

Selective estrogen receptor modulators (SERMs) bind to estrogen receptors and act as an antagonist or agonist depending on the tissue. An example of a drug in this group is raloxifene, which induces the regression of endometriotic lesions, but has failed in the studies and performed worse in pain relief compared to placebo. Bazedoxifene, which reduces the expression of the nuclear antigen of proliferating cells and the expression of the estrogen receptor in the endometrium in combination with estrogens, is a potential new treatment for endometriosis. This combination is called the tissue selective estrogen complex (TSEC) and shows high efficiency with low side effects.

Aromatase inhibitors also have a high potential for efficacy, but exhibit quite intense side effects such as bone and muscle pain and fatigue, which is why ESHRE guidelines prescribe the use of aromatase inhibitors in combination with COC, progestins or GnH-a. (16)

Summary

Introduction and purpose: Endometriosis is a disease that significantly reduces the quality of life of patients and affects various spheres of life. The aim of the study is to highlight non-operative methods of treatment and to draw attention to drugs that are not yet used routinely in the treatment of endometriosis, but have potential.

State of knowledge: Treatment of endometriosis is based on surgical procedures and pharmacotherapy, which is symptomatic treatment aimed at relieving pain and other unpleasant ailments. However, surgery is not the most appropriate course of action in all patients. In women for whom surgery is not necessary or contraindicated for internal medicine reasons, it is worth using the so-called empirical therapy that relies on drug administration and observation. In the case of complete or partial pain relief under the influence of drugs, the diagnosis of endometriosis should be made. Commonly used drugs are Combined Oral Contraceptives, Progestogens, Gonadotropin Releasing Hormone Agonists, GnRH Antagonists, and drugs under development include Selective Estrogen Receptor Modulators, Selective Progesterone Receptor Modulators and Aromatase Inhibitors. The tissue selective estrogen complex (TSEC), the main component of which is Bazedoxifene, is characterized by a high potential for efficacy and a low percentage of side effects.

Conclusions: Drug treatment of endometriosis is a constantly evolving topic. When selecting pharmacotherapy, attention should also be paid to the patient's lifestyle, the cost of the drug as well as its safety and tolerance. More research is required on drugs under development. Patients with endometriosis treated pharmacologically should be regularly monitored for pain reduction and reduction of endometriotic foci.

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