THE LATEST VIEWS ON THE TREATMENT OF ENDOMETRIOS

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Summary. Regardless of the localization and severity of clinical manifestations, E affects the functions of not only damaged and adjacent, but also distant organs: liver, pancreas and thyroid glands, adrenal glands, cardiovascular and nervous systems. The true mechanisms that regulate the processes of implantation and development of endometrioid heterotopias are complex and insufficiently studied, which does not allow us to assume the possibility of a complete cure, and in a number of patients, even achieving long-term remission or stopping the progression of the disease. Certain successes have been achieved in the treatment of E in recent years, especially in connection with the use of modern hormonal drugs. The treatment of clinically inactive E, which is more often observed in lesions of the peritoneum of the small pelvis, ectocervical and extracervical localizations, should be approached carefully and differentiated, since sometimes hormone therapy can contribute to the activation of the process.

Key words: endometriosis, hormonal drugs, nanoparticles, metformin, iron oxide

Introduction. Endometriosis (E) is a common gynecological disease that affects women starting from the period of menarche and does not end with the onset of menopause. E is accompanied by a number of painful symptoms and infertility, which largely determines the quality of life of women, affecting their career, daily activities, sexual and social relationships and fertility. Regardless of the localization
and degree of severity of clinical manifestations, E affects the functions of not only damaged and adjacent, but also distant organs: liver, pancreas and thyroid glands, adrenal glands, cardiovascular and nervous systems.

Modern ideas about the etiology of the disease are so ambiguous, sometimes contradictory, that E is interpreted as a "disease of theories" or as a "new disease of civilization."

The true mechanisms that regulate the processes of implantation and development of endometrioid heterotopias are complex and insufficiently studied, which does not allow us to assume the possibility of a complete cure, and in a number of patients even achieving long-term remission or stopping the progression of the disease [1].

Certain successes have been achieved in the treatment of E in recent years, especially in connection with the use of modern hormonal drugs [2]. However, the issue of treatment of patients with E depending on age, individual characteristics, localization of foci, clinic of the disease, assessment of quality of life by patients is still far from being resolved. Taking into account the multifaceted potential danger of E, all patients need careful dynamic monitoring. Patients with clinically active E, which disrupts the functions of the genital and adjacent organs, causes deterioration of somatic pathology and leads to a decrease in work capacity and the development of neurological disorders, are subject to treatment. The treatment of clinically inactive E, which is more often observed in lesions of the peritoneum of the small pelvis, ectocervical and extracervical localizations, should be approached carefully and differentiated, since sometimes hormone therapy can contribute to the activation of the process[3].

For those reasons, the search for the latest methods of treatment of E in the scientific medical community is unceasing and well-founded.

**The purpose of the work:** to conduct an analysis of the latest methods of treatment of endometriosis according to the data of modern medical literature.

**Materials and methods.** Foreign works on the treatment of E, which were freely available, were subject to processing.

**Research results and their discussion.**

Elevated transgelin protein (TAGLN) was found in the search for new treatment methods for patients with E. This is natural, since the protein is associated with processes that are important for the development of E. Transforming growth factor beta (TGF-β) induces TAGLN activation. Since TGF-β is released by macrophages, the body's natural anti-inflammatory response and immune regulatory cells, it leads to the conclusion that these macrophages are activated in response to Fusobacterium. A group led by Professor Yutaka Kondo and Associate Professor Ayako Muraoka from Nagoya University Graduate School of Medicine [4] in collaboration with the National Cancer Center found that the uterus of mice infected with Fusobacterium contained more severe lesions. However, mice treated with an antibiotic to kill Fusobacterium showed improvement in lesion formation. These data may have a strong and new rationale for prescribing Fusobacterium antibiotic therapy as a non-hormonal agent for the treatment of E [4].

Researchers at Oregon Health & Science University and Oregon State University have found that nanotechnology (iron oxide nanoparticles) can help treat
E by identifying and removing painful, dangerous lesions in the ovaries, fallopian tubes and pelvis without invasive surgery. Iron oxide nanoparticles — tiny particles about 1/1000 the size of a powder — were injected into mice intravenously to determine the site of the lesion. Nanoparticles accumulated in damaged tissues, allowing them to be identified by imaging. Once inside the lesions, the nanoparticles were exposed to an alternating magnetic field, causing the nanoparticles to reach temperatures of more than 120 degrees Fahrenheit—hot enough to remove the lesions with heat rather than surgery.

To reach temperatures high enough to remove the damage, the researchers designed the nanoparticles to be hexagonal rather than spherical; the hexagonal shape has more than six times greater heating efficiency when exposed to an alternating magnetic field [5].

In May 2021, the journal Frontiers in Medicine published a review of medical studies on the use of metformin for the treatment of E [6]. Metformin is an insulin sensitizer used in the treatment of type 2 diabetes. The pleiotropic effect of metformin is mainly through the activation of AMP-activated protein kinase, which is a key regulator of cellular energy homeostasis, which inhibits mTOR, the master suppressor of autophagy. Metformin regresses endometrioid implants by increasing superoxide dismutase activity. Metformin is also a metalloproteinase-2 inhibitor, reducing vascular endothelial growth factor and matrix metalloproteinase-9 in animal studies. Due to its unique therapeutic mechanisms and lack of serious side effects, metformin may be a useful anti-inflammatory and anti-proliferative agent in the treatment of E. This may be the missing link in the successful treatment of this chronic disease.

The authors included six studies; two in rats, three in laboratory conditions and one in humans with E. The study found that metformin inhibited the production of IL-8 (interleukin-8), a cytokine that signals the recruitment of neutrophils to the site and induces inflammation. The result is reduced activity of aromatase, the enzyme that converts androgens into estrogens in the ovaries, as well as in fat cells, reducing the growth and proliferation of endometrial cells. The researchers believe that these results indicate that metformin is a promising treatment option for E and recommend further studies [7].

Studies have confirmed that metformin affects the pathophysiology of E by reducing the expression of matrix MMPs, although this is not the main mechanism of its action [8].

There is a study that studied the mechanism of action of clotrimazole (CTZ) and its side effects on the E model [9]. After autologous endometrial implantation, 18 rats were randomized to two treatment groups: 200 mg/kg CTZ or vehicle for 15 consecutive days. Lesion growth, implant size, glandular atrophy, serum nitric oxide (NO) levels, macrophage cell numbers, and inducible nitric oxide synthase (iNOS) immunoreactivity were significantly reduced in the CTZ group compared with controls. CTZ (p < 0.05) reduced the levels of lipid peroxidation and protein carbonylation in the liver, but did not alter the levels of superoxide dismutase (SOD), glutathione (GSH), or glutathione S-transferase (GST) in the brain; however, the drug significantly reduced the activity of SOD and increased the activity of GST in the liver. These results suggest that CTZ inhibits the production of active forms of nitrogen by
reducing the expression of iNOS and thus enhances the antioxidant system, promoting atrophy and regression of endometrial lesions without adversely affecting the brain and/or liver.

Pelvic wall cells in women with E produce more lactate, a potentially harmful byproduct that is normally produced by muscles and red blood cells when the body is deprived of oxygen during exercise. With E, laboratory experiments have shown that lactate creates an environment that stimulates the development and growth of endometrial tissue. When cells were treated with dichloroacetate in the laboratory and in experiments on mice, lactate production decreased to normal levels and the size of endometrial lesions decreased. The drug is already licensed as a medicine to treat rare childhood metabolic disorders and various cancers, meaning it has an established safety profile. In a pilot study involving 30 women, the main side effects were mild stomach upset at the start of medication and a tingling sensation in the fingers [10].

Linzagolix is an oral GnRH receptor antagonist with low pharmacokinetic/pharmacodynamic variability. It works by binding to and blocking the GnRH receptor in the pituitary gland, causing a dose-dependent decrease in LH and FSH production/

It works by binding to and blocking the GnRH receptor in the pituitary gland, causing a dose-dependent decrease in LH and FSH production. This drop in LH and FSH levels results in a dose-dependent decrease in estrogen concentrations.

At appropriate doses, linsagolix has been found to maintain estradiol levels in the target range of 20–60 pg/ml, which is ideal for alleviating symptoms associated with E while mitigating bone mineral density loss and other adverse effects associated with a decrease in estradiol[11].

The use of metformin in combination with letrozole in the treatment of E is beneficial in guaranteeing a better quality of life with improved physical and mental health of patients and deserves further investigation for reference purposes in practical cases in the future[12].

In a number of works [13, 14] it was noted that hyperproduction of prostaglandin F2 (PGF2) is the cause of severe pain associated with the phenomenon of dysmenorrhea. By following the correct daily diet, patients will be able to provide their body with a large amount of fats rich in omega-3 acids, which are the source of PGE1 synthesis, and reduce the consumption of stimulating fatty acids that produce PGF2, i.e. saturated fats: butter, meat, offal, lard and bacon/ The recommended diet for women with E is an antioxidant diet because they are deficient in vitamins, especially vitamins C and E. A diet rich in antioxidants consists of vegetables and fruits: legumes, red and orange vegetables and fruits such as cauliflower, broccoli, Brussels sprouts, spinach, grapes, black rowan, black elderberry, strawberries, apples, oranges, blueberries, tomatoes, beets, green tea, vegetable oils, milk and milk products, fatty fish, spices and herbs (cinnamon, oregano, curry), whole grains, nuts and seeds. A proper diet can increase the activity of antioxidant enzymes and reduce the concentration of markers of oxidative stress. Antioxidant intake has been shown to reduce chronic pelvic pain in women with E and markers of inflammation in peritoneal fluid.
Physiotherapy measures aimed at restoring the functions of soft tissues and organs in the area of the pelvic floor, as well as increasing the elasticity of scars and adjacent structures are considered for the treatment of E.[14]. Patients with E suffer from severe pain, muscle contractions, growths, and movement disorders. One of the most popular methods is manual therapy aimed at the lumbopelvic area, where the therapist works on the mobility of individual motor segments, symmetry and correct positioning of the pelvis in relation to the spine [15]. Pelvic floor muscle training with E is aimed at reducing muscle tone and muscle relaxation, as E increases tension and contracture. The training performed is known as reverse pelvic floor muscle training and involves relaxation exercises performed in conjunction with deep breathing and high concentration.

CONCLUSIONS

Taking into account the problematic nature of endometriosis, the lack of possibility of complete cure even thanks to the expansion of the arsenal of hormonal drugs, the use of drugs of non-hormonal origin, metformin, diet therapy, physiotherapeutic methods and their combination should take place in the modern approach to endometriosis therapy.

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