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Medical Center "Professor Stefan Khmil Clinic"**MODERN APPROACHES TO THE TREATMENT OF ENDOMETRIOID CYSTS BEFORE CONTROLLED OVARIAN STIMULATION PROTOCOLS**

The article is devoted to the current problem of endometriosis-associated infertility. In recent years, a great deal of information has been accumulated on the etiology, diagnosis and treatment of genital endometriosis and endometriosis-associated infertility. According to world studies, endometriosis remains one of the most pressing problems in modern gynecology. This is evidenced by statistics showing that the disease occurs in every 10 women of fertile age, and a total of 176 million women worldwide. Approximately 20–50 % of women included in this number have a problem of infertility. Hence, the problem of this disease is not only a medical but also a social problem.

**Conclusions.** The tactics of treatment of patients with endometriosis who are planning a pregnancy and are included in the ART protocols are significantly different from the tactics of treatment of patients who believe that they have performed reproductive function.

**Key words:** endometriosis; infertility; in vitro fertilization; sclerotherapy.

**СОВРЕМЕННЫЕ ПОДХОДЫ К ЛЕЧЕНИЮ ЭНДОМЕТРИОИДНЫХ КИСТ ПЕРЕД ПРОТОКОЛАМИ КОНТРОЛИРУЕМОЙ ОВАРИАЛЬНОЙ СТИМУЛЯЦИИ (КОС)**

Статья посвящена актуальной проблеме современности – эндометриоз-ассоциированному бесплодию. В последние годы накопилось много информации по этиологии, диагностике и лечению генитального эндометриоза и эндометриоз-ассоциированного бесплодия. По данным мировых исследований, эндометриоз остается одной из наиболее актуальных проблем в современной гинекологии. Об этом свидетельствуют статистические данные, согласно которым это заболевание встречается у каждой 10-й женщины репродуктивного возраста, и в целом в 176 млн женщин во всем мире. Примерно в 20–50 % женщин, которые входят в это число, возникает проблема бесплодия. Исходя из этого, проблематика данного заболевания является не только медицинской, но и социальной проблемой.

**Выводы.** Тактика лечения пациенток с эндометриозом, которые планируют беременность и включены в протоколы ВРТ, существенно отличается от тактики лечения пациенток, которые считают, что репродуктивную функцию выполнили.

**Ключевые слова:** эндометриоз; бесплодие; экстракорпоральное оплодотворение; склеротерапия.

**СУЧАСНІ ПІДХОДИ ДО ЛІКУВАННЯ ЕНДОМЕТРІОЇДНИХ КИСТ ПЕРЕД ПРОТОКОЛАМИ КОНТРОЛЬОВАНОЇ ОВАРІАЛЬНОЇ СТИМУЛЯЦІЇ (КОС)**

Стаття присвячена актуальній проблемі сьогодення – ендометриоз-асоційованому безпліддю. Протягом останніх років накопичилось багато інформації щодо етіології, діагностики та лікування генітального ендометриозу та ендометриоз-асоційованого безпліддя. За даними світових досліджень, ендометриоз залишається однією з найбільш актуальних проблем у сучасній гінекології. Про це свідчать статистичні дані, згідно з якими це захворювання зустрічається у кожній 10-ї жінки репродуктивного віку й загалом у 176 млн жінок у всьому світі. Приблизно у 20–50 % жінок, які входять у це число, виникає проблема безпліддя. З огляду на це, проблематика даного захворювання постає не лише медичною, а й соціальною проблемою.

**Висновки.** Тактика лікування пацієнток із ендометріозом, які планують вагітність та включені в протоколи ДРТ, суттєво відрізняється від тактики лікування пацієнток, які вважають, що репродуктивну функцію виконали.

**Ключові слова:** ендометриоз; безпліддя; екстракорпоральне запліднення; склеротерапія.

Endometriosis is a widespread, polyetiological disease in women of child-bearing age, which, despite the large amount of research and information, remains insufficiently studied. However, all literature sources indicate that genital endometriosis adversely affects the reproductive function of women [1]. According to various authors, the frequency of this disease ranges from 7 to 59 %. More accurate statistics indicate that endometriosis occurs in every 10 woman of reproductive age, and a total of 176 million women worldwide [1–3]. Approximately 20–50 % of women included in this number have a problem of infertility. Hence, the problem of this disease is not only a medical but also a social problem [3].

Over the last decade, there has been an increasing trend in the incidence of genital endometriosis, although it is difficult to draw accurate conclusions about the spread of the disease because there are no clear epidemiological studies.

Adverse ecological situation, pollution of the environment with harmful products of industrial production, in particular dioxins, contribute to the development and progression of endometriosis. In industrialized countries, the percentage of sick women is higher than in countries with poorly developed industry. There is also a clear gradation between the development of this disease in different races, in particular in Asian women, mostly Japanese, the percentage of this disease is higher than in European women, who in turn have endometriosis more often than the Negroid race women [4].

Regardless of the location, genital endometriosis is not a local but a common disease. For its development in the body under the influence of a number of factors (hereditary, neuropsychiatric, somatic pathologies, chronic inflammatory processes in the genitals, changes in the function of the hypothalamic-pituitary-ovarian system, adrenal glands,

immune system, surgery on the genitals and other organs) should form a certain neuro-endocrine background. To date, no single trigger mechanism of the disease has been described, which leads to conclusions about the multifactorial nature of the process [5].

Typical and common symptoms of the disease are: dysmenorrhea and menstrual disorders (occurs in 70 % and 15 % of patients, respectively), pelvic pain (in 40 % of women), 33 % of women suffer from dyspareunia, 25–60 % have endometriosis-associated infertility [4]. Other clinical symptoms include: pain during ovulation; profuse bleeding during menstruation; effects on pregnancy (miscarriage, premature birth); dark bloody discharge from the vagina before and after menstruation; pain in the sacrum; bloody discharge from the genital tract in the middle of the menstrual cycle; fatigue. In general, endometriosis is characterized by a variety of symptoms – from asymptomatic to the clinic of “acute abdomen”. Although the main triad of symptoms identified by the World Endometriosis Society is dysmenorrhea, dyspareunia and dyschesis. It is logical that the clinical picture of the disease depends on the location and prevalence of the process. However, modern studies show that there is no connection between the degree of the disease and its symptoms, the severity of the pain syndrome does not always correspond to the prevalence and size of endometrioid heterotopias detected by clinical and endoscopic examination [6].

For women of reproductive age, in whom endometriosis is much more common, infertility caused by endometriosis is an important problem [7]. It is caused by dysfunction of the fallopian tubes due to occlusion and germination of heterotopias in the lumen, their uncoordinated activities; disorders in the system hypothalamus – pituitary – ovaries (anovulation, luteinization of follicles, luteal phase insufficiency); imbalance in the immune system, which contributes to the violation of the functional activity of sperm or embryo implantation; peritoneal adhesions; common sexual dysfunction due to pain (dyspareunia) [8].

The main mechanisms that explain infertility in endometriosis are: violation of folliculogenesis, inferiority of the secretory phase, impaired fertilization, reduced likelihood of implantation, changes in the properties of peritoneal fluid, the development of the adhesive process. These pathophysiological causes that contribute to the development of infertility occur as a consequence of chronic inflammatory processes and violations of the mechanisms of oxidative defense [9–11]. Inflammatory processes in turn lead to changes in the composition of peritoneal and follicular fluid. It is proved that peritoneal fluid is significantly higher in women with endometriosis-associated infertility than in women with other forms of infertility [12]. The composition of peritoneal fluid includes: steroid hormones of the ovary (estrogens and progesterones), cellular components, including endometrial cells, electrolytes, erythrocytes, lymphocytes, macrophages; each of these components produces active substances that provoke oxidative stress [10, 12], which in turn affects the quality of eggs and the process of implantation [13]. In total, due to the action of the cascade of all these biochemical and pathophysiological processes, the anatomy of the pelvic organs, ovarian function, embryo implantation and fertility are impaired [14].

Despite the fact that today all pathogenetic mechanisms and theories of endometriosis development have been

deeply described, statistical data show an increase in the number of cases, which is the reason for continuing scientific research to solve this medical and social problem.

Recently, the **diagnosis** of the disease remains an important focus in practice, as endometriosis is often referred to as “missed disease”, and the average time between the onset of pain and diagnosis, for example, in the United Kingdom of Great Britain is 8 years and 12 years in the United States of America [15].

The “gold” standard for the diagnosis of endometriosis is still a direct visualization of lesions during surgery, mainly in combination with histological confirmation of endometrioid tissue [6, 16]. This method is the most accurate, although it has its drawbacks: the average delay in diagnosis (from the onset of symptoms to the final diagnosis) grows, and the risks inherent in all surgical procedures with possible general anesthesia complications increase.

Definitely, “office”, minimally invasive diagnostics is considered theoretically simpler, although it is not perfect and remains a subject of scientific interest and a promising direction in the practice of specialists. Because endometriosis is considered a dyshormonal, immune-dependent disease, scientists have already proposed a sufficient number of predictors with which to diagnose endometriosis faster, in the early stages and without much technical difficulty [10]. But today such methods are qualitatively inferior to instrumental (colposcopy, hysteroscopy, ultrasound, CT, MRI), which not only confirm the existence of the process, but also with which you can assess the degree of tissue damage. Despite many studies, no biomarker or biomarker panel for a non-invasive diagnostic test with sufficient sensitivity and specificity has been confirmed so far [10, 17]. Further research is needed to develop a clinically useful test.

Unequivocally, to date there is no single unified tactic for the treatment of endometriosis. The best is an individual approach with a comprehensive solution to the problem of a woman's age, location and prevalence, severity of symptoms, fertility and the need to restore reproductive function, the presence of concomitant gynecological and somatic pathology, the effectiveness of previous treatment [18, 19].

Of course, the tactics of treating patients with endometriosis who are planning a pregnancy and are included in ART protocols are different from those who believe that they have performed reproductive function. To date, the issue of treating endometriosis associated with infertility before ART programs remains controversial, but most are inclined to believe that:

- in the case of newly diagnosed endometriosis, drug therapy is recommended before in vitro fertilization (IVF);
- when recurrent endometriosis and cyst sizes of 30–40 mm, IVF is possible without prior surgery;
- for recurrent cysts and cysts larger than 40 mm, surgical treatment with subsequent assessment of the ovarian reserve is recommended;
- postoperative drug therapy is not effective and does not improve the incidence of pregnancy.

Drug therapy is to suppress the hypothalamic-pituitary system and induce the development of atrophic changes in the tissue of endometrioid heterotopias. For this purpose, use: GnRH agonists, aromatase inhibitors, COCs, progestogens, IUD with levonorgestrel. Also for the correction of immune disorders, suppression of pain, analgesics, antispasmodics, nonsteroidal anti-inflammatory drugs are used for

antioxidant effect and desensitizing therapy. Unfortunately, conservative treatment only reduces the symptoms of the disease and improves the functions of the reproductive system for some time [20].

At present, it is technically impossible to remove the anatomical substrate of endometriosis by any method other than surgery. Therefore, it is considered the "gold standard" of treatment. However, even surgical treatment is not always appropriate, as it leaves a fairly high risk of disease recurrence and in most cases adversely affects the state of the ovarian reserve, deteriorating the quality of oogenesis, which is critical for patients who want to become pregnant [21].

It is also proven that the use of IVF as a first-line therapy increases the pregnancy rate to 56.1 % compared with a significantly reduced frequency of pregnancies – 37.4 % during IVF after surgery [22].

The issue of endometriosis-associated infertility therapy has been and remains relevant. Treatment of this disease should be comprehensive and gradual. The modern and optimal approach to treatment is the use of surgical and conservative treatment, searching new and improving existing treatments, monitoring the effectiveness of infertility therapy and preventing the progression of genital endometriosis. The use of assisted reproductive technologies is considered to be a progressive direction in the treatment of endometriosis-associated infertility.

Intrauterine insemination (IUI) is recommended for young women with uterine tubes and a regular ovulatory cycle, in the absence of significant abnormalities in the man's spermogram. To restore reproductive function in women with genital endometriosis in unsuccessful attempts at IUI, impaired fallopian tubal patency and, or in the presence of male infertility, superovulation stimulation is used to obtain a large number of follicles, remove eggs from them, and use them in assisted reproductive technology programs. The use of ART methods is also effective in women over 35 years. IVF is a first-line therapy in women with endometriosis-associated infertility [23, 24]. Pregnancy after IVF in women with genital endometriosis occurs much less frequently than in women with other factors of female infertility, which in turn is associated with a reduced percentage of fertilized cells, implantation, a small number of oocytes [25]. The probability of pregnancy depends on the extent of the process, in particular in women with severe endometriosis, pregnancy occurs less frequently than in women with mild disease [24].

Retrospective meta-analyses showed that the presence of endometrium on the ovary during the stimulation protocol in infertility women on the background of inguinal endometriosis with severity degree I–II of the disease, do not affect the number of eggs obtained, fertilization factors and quality of embryos, but women with severity degrees III–IV the disease have lower rates of pregnancy and live birth [26].

Surgical treatment of endometrioid cysts as a "gold standard" is used to remove endometrioid heterotopias and diagnose the stage of endometriosis. After therapy, access during transvaginal puncture is improved and the toxic effect of endometrioid content on the oocyte is reduced, but the disadvantage of this method is the reduction of ovulatory reserve, because along with endometrioid cyst the doctor removes healthy ovarian tissue, also possible postoperative complications, economic costs and low level of evidence of a positive impact on the outcome of IVF may occur [27].

In order to preserve the ovarian reserve of the ovaries and remove the endometrioid content before the IVF protocol, a relatively new method of treatment has been proposed – sclerotherapy of endometrioid cysts [28]. This procedure is performed by transvaginal puncture of the cyst and aspiration of its content under the control of transvaginal ultrasound, introduction into the capsule of the cyst (without violating its integrity) sclerosing solution, followed by aspiration. Due to the action of sclerosant in the endometrium, inflammatory and fibrosis processes are triggered, which leads to obliteration of the cyst [29]. This procedure is performed for several minutes and is performed without general anesthesia. The advantages of the method are: minimally invasive, accessible, safe, low frequency of postoperative complications, reduction of pain, preservation of ovarian ovulation and improved access to the ovary during the oocyte aspiration. Data from retrospective studies indicate that patients who underwent sclerotherapy before the controlled ovarian stimulation protocol had more follicles and eggs than patients who underwent laparoscopic cystectomy, but there is no difference in the rates of pregnancy [15].

The choice of sclerosant and its effectiveness remain a debatable and important issue today in the method of sclerotherapy. A considerable number of sclerosing substances has been proposed, the potential of which is being studied. The main requirements for these agents are: reduction in the number of recurrences of endometrioid cysts and safety, ie the necessary minimal impact on the surrounding ovarian tissues to maintain ovulatory reserve. Among the solutions used as a sclerosant, ethyl alcohol is most often used, and an alcohol extract of the Antiflazide, Solcovagin, methotrexate is also used [30].

The ethanol solution (after pre-aspiration of the endometrioid content of the cyst) is installed in a volume of 50–100 % of the size of the cyst under ultrasound control. Ethanol has a cytotoxic effect, causes dehydration of cells and the production of mediators of inflammation and fibrosis. According to various studies, the average recurrence rate after the use of this sclerosant is 14.9 %, and varies depending on the method of procedures. With partial aspiration of the solution, recurrences were observed in 13.3 % of women, with complete aspiration of ethanol – in 32.1 % of women [31].

When sclerotherapy with methotrexate using 30 mg of methotrexate diluted in saline 100:1 and sclerotherapy with tetracycline, a low recurrence rate is observed, but these drugs adversely affect the quality of eggs [32].

When using as sclerosant drug Antiflazide endometrioma content is aspirated and washed with saline, administer 50 % of the volume of the cyst Solcovagin drug, which is diluted with 96 % ethanol in a ratio of 1:20, after exposure to 10 minutes the contents are aspirated again and administer 15–20 % of the volume of the alcohol extract of the Antiflazide drug. In the postoperative period for 3 months prescribe hormone therapy with antiandrogenic effect and oral administration of alcohol extract of the Proteflazide drug three times a day for 1 month. After sclerotherapy there is a decrease in serum levels of CA-125 and 100 % of patients show a decrease in pain. Thus, sclerotherapy is an alternative method of choice for the treatment of endometrioid cysts, especially recurrent before IVF protocols [30].

Given the negative impact of endometriosis on a woman's reproductive function, folliculogenesis and egg quality in

particular, pregravid preparation before the ART protocol is extremely important. The use of inositol-containing drugs ("FT500 Plus") is considered one of the newer approaches in the pregravid preparation of patients with endometriosis-associated infertility [33]. The mechanism of action of inositol is aimed at improving the antioxidant defense system, and reducing the effects of oxidative stress, which improves the quality of eggs, and in the future increases the chances of positive attempts in ART.

**CONCLUSIONS.** Clearly, the tactics of treatment of patients with endometriosis who are planning a pregnancy and included in ART protocols are different from those who believe that they have performed reproductive function. Surgical treatment leaves a fairly high risk of recurrence of the disease and in most cases adversely affects the state of the ovarian reserve, deteriorating the quality of ovogenesis, which is critical for patients wishing to become pregnant. A new technique and a good alternative to open surgical tactics for the treatment of ovarian endometriosis is the method of sclerotherapy of endometrioid cysts, which has a number of advantages: minimally invasive, accessible, eliminating the risk of postoperative complications, reducing the risk

of recurrence of endometrioid cysts and most importantly – the preservation of a woman's ovarian reserve. It has been shown that the use of aspiration sclerotherapy in women with endometriosis before IVF increases the effectiveness of ART compared with the use of surgical treatment, and high-quality pre-pregnancy training ("FT500 Plus") improves the quality of eggs.

**PROSPECTS FOR FURTHER RESEARCH.** Despite the large amount of existing scientific research and proposed theories on the development and impact of endometriosis on the reproductive system and its functionality in this disease, it is still necessary to study in more detail the qualitative impact of endometrioid cysts on the quality of folliculogenesis and eggs in infertile women in IVF protocols. Since the method of sclerotherapy of endometrioid cysts is a relatively new method of treatment, it remains necessary to investigate the morphological features of the wall of endometrioid cysts depending on the selected method of sclerotherapy with further evaluation of its effectiveness and to study the quality of sclerosing properties (degree of sclerosis of the epithelial lining and subepithelial stroma, the percentage of recurrences, restoration of ovarian function).

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