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MODERN METHODS OF DIAGNOSIS AND TREATMENT OF CHRONIC ENDOMETRITIS, IN PREPARING PATIENTS FOR ASSISTED REPRODUCTIVE TREATMENT TECHNOLOGIES (LITERATURE REVIEW)

Abstract. Since the chronic endometritis often leads to impaired reproductive function causing infertility, failed IVF attempts, miscarriage, and complicated pregnancy and childbirth, it has become not only medically relevant but also socially significant. For successful embryo implantation, the thickness of the endometrium should be at least 7 cm. Even though there is always a chance for embryo implantation, despite the endometrial hypoplasia, the attachment may be fragile, and such pregnancy may cease its development further on. Recently, in connection with an increase in the rate of developing allergic reactions, dysbacteriosis, and the emergence of drug-resistant strains of microorganisms, a search for new treatment methods to avoid these complications has begun. One of such methods in treating chronic endometritis, satisfying several requirements (efficiency, comfort, accessibility, safety), is the ultrasonic cavitation of the uterine cavity.

Key words: ART, infertility, chronic endometritis, hypoplasia of endometrium, failed IVF attempts, ultrasonic cavitation.

Despite tremendous successes achieved in recent decades in the field of reproductive medicine, embryology, and genetics, the problem of infertile marriage is still far from being solved. According to world statistics, the effectiveness of Assisted Reproductive Technologies (ART) in overcoming infertility per transfer of one embryo does not exceed 25-40 %.

Infertility is the inability of a sexually active couple, who do not use contraception, to achieve pregnancy within one year. According to the World Health Organization (WHO), the infertility rate fluctuates between 15 and 18 % and does not tend to decrease [1].

The beginning of the age of reproductive medicine has revealed new possibilities for preservation of fertility in both women and men. Today, the world uses such technologies as IVF, ICSI, epididymis and testis biopsy, gamete donation, surrogacy, preservation of fertility in cancer patients by cryopreservation of gametes - sperm and egg cells, cryopreservation of ovarian tissue for the future autotransplantation, preimplantation genetic testing of the embryo, and recently, experimental modification of human embryo genome [2, 3, 4]. Nevertheless, the development of new methods that can improve the effectiveness of ART is still ongoing.

In Kazakhstan, according to various sources, infertility rates reach 20 %. Thus, this has led to increased use of ART as the most effective way to overcome infertility, as well as the implementation of ART into the state program [4].

Disruption of proper implantation during the transfer of good quality embryos due to non-receptive endometrium is the most significant cause of reproductive failure in ART, taking up to 70 % of their structure. Successful implantation requires a receptive endometrium, a functional embryo at the stage of

blastocyst, and a synchronized “dialogue” between maternal and embryonic tissues [5, 6]. The problem of repeated implantation failure is considered to be one of the most difficult to overcome in the practice of reproductive medicine and infertility specialists.

The processes required for conception, such as trophoblast invasion and further fetus development, occur in the endometrium during certain days [7]. Due to the formation of connective tissue, as a result of prolonged inflammation in the endometrium, blood circulation is disturbed, and sensitivity to hormones decreases; thus, changes in normal functioning cause chronic endometritis [8].

Chronic endometritis (CE) is a clinicopathologic syndrome where as a result of prolonged damage to the endometrium by an infectious agent, morphofunctional changes take place, disrupting the cyclic transformation and receptor apparatus of the uterine mucosa [5]. This pathology occurrence rate varies from 3 to 73 %, giving rise to primary infertility in 24.8 %, secondary infertility in 35.6 %, unsuccessful IVF attempts and embryo transfers in past medical history in 30 % of cases, as well as miscarriage, complicated pregnancy, and childbirth [9, 10, 11].

Risk factors for the development of CE in patients of reproductive age with menstrual dysfunction are age group of women older than 30 years, the presence of urinary system diseases, history of abortion and premature birth, chronic salpingo-oophoritis and endometrial polyps, history of uterine fibroids, surgical interventions on the reproductive system organs, prolonged use of intrauterine contraceptives [8, 12, 13].

In 95 % of cases, endometritis is exogenous (primary), caused by sexually transmitted infections, or occurred as a result of intrauterine diagnostic and treatment procedures. In the other 5 % of cases, endometritis is endogenous (secondary) and develops when infection from extragenital sources gets through hematogenous, lymphogenous, or descending pathways [5, 8, 12].

CE has typical characteristic features such as a change in the etiological structure, drug-resistant bacterial flora growth, long periods of therapy, changes in clinical symptoms towards weakened or barely perceptible forms and atypical course of a disease. CE clinical presentation includes disruption of menstrual and reproductive functions. A persistent inflammation area existing in the small pelvis results in disruption of the menstrual cycle in 45-55% of patients, manifesting in the form of meno- and metrorrhagia, oligo- and opsomenorrhea, algodismenorrhea, and amenorrhea. 21% of patients experience chronic pain [14, 15]. 80-90 % of patients suffering from CE present with symptoms as intermenstrual bleeding, menorrhagia, and contact-spotting [5, 12].

In 60 % of cases of typical miscarriages, there is a close link to CE. Endometrial stromal fibrosis takes the main part in the pathogenesis of this problem, resulting in a significant decrease in blood flow due to the reduction of the capillary bed. This, in turn, leads to inadequate secretory transformation of the endometrium and disrupts pregravid restructuring of the mucosa of the uterine body [5, 12, 13].

The CE diagnosis is based on a comprehensive assessment of a number of clinical, morphological, and instrumental data.

A comprehensive method for the diagnosis of CE allowed to improve verification of this pathology by 64.6 % compared to histological confirmation of CE only after a biopsy of the endometrial tissue [16].

Ultrasound examination of pelvic organs is a screening method for chronic endometritis. Sonographic signs of CE include the following: irregular form areas and reduced echogenicity of the endometrium; changes in the endometrium structure; identification of gas bubbles, sometimes with the typical “comet tail” acoustic effect; clear hyperechoic formations 0,1-0,2 cm in diameter, visualized in the basal endometrium layer and being sources of fibrosis, calcinosis; expansion of the uterine cavity up to 0,3-0,7 cm due to fluid contents. Dopplerometric studies show hemodynamic disturbances in the vessels of the uterus and the vascular basin of the pelvis and asymmetry of the myometrium vascularization [8, 12, 13, 17].

During hysteroscopy, the uneven color and hyperemia of the endometrium are observed. Morphological examination of the endometrium on the 7-10th day of the menstrual cycle is the "golden standard" for the CE diagnosis [13, 5]. Diagnostic signs of CE detected during hysteroscopy are revealed only in 82,6 % of patients, which is verified by the morphological method and immunohistochemical CD138 studies [8, 18, 19, 20, 21]. These data coincide with the results of studies accomplished by other authors, demonstrating that only 30% of female patients have the most informative CE signs, such as uneven thickness of the endometrium, polypoid growths, uneven color and hyperemia of the mucous membrane. At the same time, the sensitivity of this method is only 40 % and specificity is 80 %

(for comparison, the corresponding morphological indexes of endometrial aspirates are 93 and 100 %) [22]. Therefore, in cases of suspected CE, hysteroscopy is an important step to exclude the entire spectrum of intrauterine pathology, but not to verify the diagnosis.

Comprehensive treatment of chronic endometritis should include antibacterial, metabolic, antioxidant, immunomodulating and physiotherapy. The therapy effectiveness criteria present as relief of clinical symptoms, restoration of the endometrium echographic picture, elimination or reduction of the infectious agent activity, restoration of the morphological structure of the tissue, as well as restoration of fertility.

Despite the recent innovations in stimulation protocol schemes, reproductive immunology, culture medium, technical equipment, and application of preimplantation genetic testing, implantation and genetic health of embryos remain the leading cause behind the effective implementation of IVF programs [15, 23, 24].

The issues of pregravid preparation of married couples, taking into account microflora status and dysbiosis of the vagina and uterus, are being discussed [19].

The problem of relatively ineffective results in ART programs leads one to consider various aspects of increasing the frequency of implantation and childbirth.

The effectiveness of IVF programs directly correlates with the age of female patients; according to various authors, embryo implantation takes place more often in patients of a younger age [25].

During the initial implantation stages, the endometrium is invaded by trophoblast cells; thus, cytoplasmic characteristics of invading cells play a significant role. Probable genetic abnormalities during further embryo growth might lead to a developmental arrest. Perhaps, this sequence of events leads to a high incidence of clinical pregnancy, along with a high frequency of pregnancy interruption in female patients of young age. The low rate of progressive pregnancy after embryo transfer (ET) within a group of women over 40 years old allows doctors to recommend these patients the use of donor oocytes [25, 26].

Among the variety of causes for failed embryo implantation, endometrial thickness remains one of the most important factors affecting pregnancy rate in ART. Good quality embryo and receptive endometrium are the main factors for achieving a successful pregnancy. That is why thin endometrium significantly reduces the pregnancy rate. Endometrium thickness of less than 7 mm is believed to give minimal chances for successful conception [27].

The study of American scientists regarding the effects of endometrial thickness on pregnancy rate in 897 female patients with embryo transfer in IVF programs revealed that high pregnancy rate is observed in women with an endometrial thickness of 9 mm or more, making it 39 % of females tested, whereas in patients with an endometrial thickness of less than 9 mm it was 16 % [27, 28].

The use of technologies, such as hyperbaric oxygenation therapy (HOT), in patients preparing for IVF programs in both men and women, leads to oxygen deficiency elimination, regional hemodynamics improvement, biosynthesis activation; moreover, it has an anti-inflammatory and immunomodulating effect [28] for embryo transfer and treatment of “thin endometrium” [30, 31, 32]. The procedure can be performed not only during ovarian stimulation but also before and after embryo transfer.

On a 20-21st day of the cycle, endometrial scratching by pipelle-biopsy carried out using a special catheter, and a sample is sent for histological and immunohistochemical studies if necessary. According to modern data, there are conflicting opinions about the effectiveness of endometrial scratching. Some studies provide information that confirms an increase in implantation rate, pregnancy, and childbirth [33, 34]. At the same time, other studies have not shown a significant increase in the positive outcome of embryo transfer programs [30, 31, 32, 35, 36].

To improve the receptivity and thickness of the endometrium, in 2011, researchers proposed the use of granulocyte colony-stimulating growth factor (G-CSGF) for the first time. The mechanism of action consists of colony-stimulating factors taking part in the repeated modeling of endometrial vessels, local immune modulation, and cell pathways of adhesion [30, 37].

Studies regarding the use of peripheral blood mononuclear cells show that, within the implantation site, maternal blood containing peripheral blood mononuclear cells (PBMC) surrounds the embryo. The number of maternal immune cells dramatically increases during the decidualization process. PBMCs directly interact with trophoblast and then return to the mother’s bloodstream. There is a suggestion that PBMCs, along with human chorionic gonadotropin (HCG), contribute to the interaction between the embryo and the endometrium. Therefore, intrauterine administration of mononuclear cells from

autologous blood cells suggests an increase in endometrial receptivity of female patients with repeated embryo transfer failure [21, 30, 38].

As of today, there are several studies on the use of platelet-rich plasma; the first studies were published in 2015 by Y. Chang et al. [29, 38]. With intrauterine administration of plasma, the release of biologically active substances, cytokines, and growth factors takes place. Among those growth factors are fibroblast growth factor, platelet growth factor, vascular endothelial growth factor, transforming growth factor, IGF-1, IGF-2, connective tissue growth factor, and interleukin-8. S. Zadehmodarres et al., and A. Molina et al. in their studies noted the positive impact of this technique on outcome results in female patients with thin endometrium and RIF [27, 40, 41].

The individual implantation window is a short period, corresponding to the 7-8th day after the luteinizing hormone peak, during which adhesion and invasion of the blastocyst into the endometrium becomes possible. In 2011, a group of researchers developed a transcription ERA signature, which makes it feasible to determine the susceptibility of the endometrium to embryo implantation based on an integrated algorithm for assessing the expression levels of matrix RNA-238 genes [41, 42]. In the natural cycle before ET, on the 7th day after ovulation or on the 5th day of taking progesterone, in cycles with cyclic hormonal therapy, endometrial pipelle-biopsy is performed. After receiving the results that the endometrial receptivity status corresponds to the stage of the implantation window, preparations for the ET procedure begin, performing it on the same day of the cycle with the established endometrial receptivity. In the case of detecting a non-receptive status of the endometrium, the procedure is repeated, changing the day of material sampling, sometimes repeating the study in several cycles, until a positive result is obtained. Thus, the authors proposed an individual approach to choosing the day for ET [41, 42, 43].

Treatment of the uterine cavity with a mixture of CO₂ and N₂ gases improves blood circulation in the endometrium and increases the thickness of basal and functional endometrial layers [44, 45].

Gynecological massage is a scientifically proved therapeutic method that is widely used in gynecological practice in Russia but has not yet found proper application in preparing women for IVF [27].

Physiotherapeutic procedures are important methods for treating female reproductive system disorders, as well as acute and chronic pathologies. Modern, technologically advanced techniques of physiotherapeutic treatments include ultrasonic (US) cavitation of the uterine cavity. This method can be used in both complex treatments, in combination with drug therapy, and also as monotherapy. There are two possible ways to perform this procedure: contact (through a liquid medium) and non-contact. The finely-dispersed cavitated solution is used as a liquid medium to irrigate the tissue.

Ultrasonic irrigation methods are based on the effect of low-frequency ultrasonic vibrations (up to 50 kHz) on a solution, passing through a 2 mm diameter hole in the working part of the waveguide. In this case, the process of cavity formation, called cavitation, takes place in the areas of rarefaction of the medium. The resulting cavity is filled with vapors of liquid and gas, soluble in the mentioned fluid. During the formation of cavitation bubbles, the medium is compressed, and the previously formed cavities burst, accompanied by sharp hydraulic impacts [12, 13, 46].

Treatment of the uterine cavity with antiseptic solutions, cavitated by low-frequency ultrasound, is characterized by the following therapeutic effects: antibacterial, immunological, potentiating, trophic, microcirculatory, and antioxidant [8].

Antibacterial and immune therapeutic effects manifest in a direct antimicrobial action due to the disintegration of the microbial wall, the destruction of bacterial biofilms, and the activation of local immune reactions; while inactivation of viruses occurs due to their oxidation by free radicals and peroxidation compounds that briefly form in the intercellular space. The potentiating effect can be seen in increasing sensitivity of microorganisms to the action of antibiotics and antiseptics, which leads to their rapid elimination with small doses of drugs. Microcirculatory and antioxidant effects are achieved by improving local blood flow due to myometrium micro-massage, resulting in an increase in endometrium thickness during its hypoplasia (thin endometrium), prevention of scarring tissue changes, and development of adhesions [47, 48, 49, 50, 51]. In preparation for ART and treatment during pregnancy, combined use of uterine cavity irrigation with medicinal solutions, cavitated by low-frequency ultrasound, as well as mud therapy in women after termination of non-developing pregnancy, results in a significant

decrease in the level of pro-inflammatory cytokines and normalization of the genital tract microbiocenosis and anaerobic vaginal dysbiosis [50, 51, 53, 54, 55, 56]. The scope of possible usage for ultrasound cavitation varies; some of the cases are endometritis, myometritis, purulent wounds, postpartum ulcers, vaginitis, cervical insufficiency, preparation for intrauterine interventions. The technique shows good clinical results and may come to be a real alternative to multistage antibiotic therapy [57, 58, 59].

Timely diagnosis and modern principles of treatment of CE with a personalized approach can increase the effectiveness of IVF programs and reduce the frequency of miscarriage.

Despite the high achievements in scientific and clinical practice, the search continues for various ways to increase the effectiveness of IVF programs.

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СОЗЫЛМАЛЫ ЭНДОМЕТРИТ ДИАГНОСТИКАСЫ МЕН ЕМІНІҢ ЗАМАНАУИ ӘДІСТЕРІ, ПАЦИЕНТТЕРДІ ҚОЛДАУ БАГДАРЛАМАЛАРЫНА ДАЙЫНДАУДА ҚОЛДАНЫЛАТЫН РЕПРОДУКТИВТІ ТЕХНОЛОГИЯЛАР (ӘДЕБИЕТКЕ ШОЛУ)

Аннотация. Қазіргі уақытта созылмалы эндометрит проблемасының өзектілігі тек медициналық тұрғыдан ғана емес, сонымен қатар әлеуметтік тұрғыдан да маңызға ие болып отыр, Өйткені бұл ауру көбінесе репродуктивті функцияның бұзылуына, бедеулікке, ЭҚҰ-ның сәтсіздігіне, жүктілікке және жүктілік пен босануға әкеледі. Жатырдың шырышты қабатында эмбрионды сәтті бекіту үшін эндометрияның қалыңдығы кем дегенде 7 см болуы керек. Эндометриялық гипоплазия кезінде имплантация жасалуы мүмкін, бірақ тіркеме нәзік болып, мұндай жүктілік оның дамуын одан ары тоқтатуы мүмкін. Соңғы уақытта, аллергиялық реакциялардың, дисбактериоздың даму жиілігінің жоғарылауына және антибиотикалық терапия кезінде микроорганизмдердің төзімді штамдарының пайда болуына байланысты осы асқинулардың алдын алу үшін емдеудің жаңа әдістерін іздеу жүргізіліп келеді. Бірқатар талаптарды қанағаттандыратын созылмалы эндометритті емдеудегі осындай әдістердің бірі (тиімділік, қолайлылық, қолжетімділік, қауіпсіздік) – жатыр қуысына ультрадыбыстық кавитация енгізу әдісі.

Түйін сөздер: КРТ, бедеулік, созылмалы эндометрит, эндометриялық гипоплазия, ЭҚО сәтсіз әрекеттері, ультрадыбыстық кавитация.

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СОВРЕМЕННЫЕ МЕТОДЫ ДИАГНОСТИКИ И ЛЕЧЕНИЯ ХРОНИЧЕСКИХ ЭНДОМЕТРИТОВ В ПОДГОТОВКЕ ПАЦИЕНТОК К ПРОГРАММАМ ВСПОМОГАТЕЛЬНЫХ РЕПРОДУКТИВНЫХ ТЕХНОЛОГИЙ (ОБЗОР ЛИТЕРАТУРЫ)

Аннотация. В настоящее время актуальность проблемы хронического эндометрита приобретает не только медицинское, но и социальное значение, поскольку данное заболевание часто приводит к нарушению репродуктивной функции, являясь причиной бесплодия, неудачных попыток ЭКО, невынашивания беременности, осложненного течения беременности и родов. Для успешного закрепления эмбриона в слизистой оболочке матки, толщина эндометрия должна составлять не менее 7 см. При гипоплазии эндометрия есть вероятность того, что имплантация произойдет, но прикрепление может оказаться непрочным и такая беременность может в дальнейшем прекратить свое развитие. В последнее время в связи с ростом частоты развития аллергических реакций, дисбактериоза и возникновением резистентных штаммов микроорганизмов при антибактериальной терапии ведётся поиск новых методов лечения, позволяющих

избежать этих осложнений. Одним из таких методов в терапии хронического эндометрита, удовлетворяющих ряду требований (эффективность, комфортность, доступность, безопасность), является метод ультразвуковой кавитации полости матки.

Ключевые слова: ВРТ, бесплодие, хронический эндометрит, гипоплазия эндометрия, неудачные попытки ЭКО, ультразвуковая кавитация.

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