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Chronic endometritis and reproductive disorders: versions and contraversions (review)

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ABSTRACT

Among married couples of childbearing age, the frequency of infertility in different regions of Russia and the world ranges from 10 to 21%. The effectiveness of the results of in vitro fertilization (IVF) and embryo transfer is determined by two factors: the functional completeness of the embryo at the blastocyst stage and the absence of intrauterine pathology. One of the main causes of imperfect or unsuccessful implantation is an impaired function and damaged endometrial structure, which is often caused by a chronic inflammatory process in the endometrium.

Chronic endometritis (CE) is a condition associated with a violation of the coexistence between microorganisms and the immune system of a macroorganism in the endometrium. A majority of CE cases produce no noticeable clinical signs or mild symptoms and the CE prevalence rate is approximately 10% based on the histological findings of an endometrial biopsy.

The interconnection between CE and reproductive dysfunctions, such as implant damage and repeated miscarriage, has been studied by many researchers at the present stage. Chronic endometritis is common among patients with unexplained infertility. Diagnosis and treatment of chronic endometritis increase the frequency of spontaneous pregnancies and live births in such patients. The diagnosis of chronic endometritis is not simple, often contradictory, and, thus, requires close cooperation between the fertility specialist and the pathologist. In this study, we reviewed the literature on the pathophysiology of chronic endometritis and how it may be associated with infertility, as well as the literature regarding the diagnosis and treatment of CE, published at PubMed as on May 2019 in a version and contra-version format.

Key words: ART, chronic endometritis, endometrium, female infertility, hysteroscopy, IVF, repeated implantation failure, recurrent pregnancy loss.

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Хронический эндометрит и репродуктивные нарушения: версии и контраверсии

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РЕЗЮМЕ

Частота бесплодия в разных регионах России и в мире среди супружеских пар репродуктивного возраста колеблется от 10 до 21%. Существует два основных фактора, определяющих эффективность результатов экстракорпорального оплодотворения (ЭКО) и переноса эмбрионов: функциональная полноценность эмбриона на стадии бластоцисты и отсутствие внутриматочной патологии. Одной из главных причин неполноценной или неудачной имплантации являются нарушенная функция и поврежденная структура эндометрия, часто обусловленная хроническим воспалительным процессом в эндометрии. Хронический эндометрит (ХЭ) – это состояние, связанное с нарушением сосуществования между микроорганизмами и иммунной системой макроорганизма в эндометрии. В большинстве случаев ХЭ не имеет заметных клинических признаков, а его распространенность на основании гистологического заключения биопсии эндометрия составляет около 10%. Связь между ХЭ и репродуктивными нарушениями, такими как имплантационная недостаточность и повторный выкидыш, стала предметом пристального внимания многих современных исследований. Обращает на себя внимание распространенность хронического эндометрита у пациенток с необъяснимым бесплодием, а диагностика и лечение хронического эндометрита повышают частоту спонтанных беременностей и живорождений у таких пациенток. Диагноз хронического эндометрита является не простым, а зачастую противоречивым и требует тесного сотрудничества специалистов – репродуктологов и патоморфологов.

В этом обзоре мы рассмотрели литературу по вопросам патофизиологии ХЭ, возможных причин, ассоциированных с бесплодием, а также привели результаты научных исследований, касающихся диагностики и лечения ХЭ, которые были опубликованы в коллекции PubMed по состоянию на май 2019 г. в формате изложения версий и контраверсий.

Ключевые слова: хронический эндометрит, эндометрий, оплодотворение, ВРТ, ЭКО, гистероскопия, повторная имплантационная недостаточность, периодическая потеря беременности.

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INTRODUCTION

Among married couples of childbearing age, the frequency of infertility in different regions of Russia and the world ranges from 10 to 21% [1–3]. The effectiveness of in vitro fertilization (IVF) and embryo transfer (ET) is determined by two factors: the functional completeness of the embryo at the blastocyst stage and the absence of intrauterine pathology. One of the decisive and main reasons for imperfect or unsuccessful implantation is an impaired function and damaged endometrial structure, often caused by a chronic inflammatory process in the endometrium. Chronic endometritis is a clinico-morphological syndrome, in which multiple secondary morphofunctional changes, disrupting cyclic biotransformation and uterine mucosa receptivity, occur as a result of persisting endometrial damage by an infectious factor [1].

NOSOLOGICAL FORM OF CHRONIC ENDOMETRITIS AND ITS PREVALENCE

The question of the necessity of distinguishing CE in a separate nosological definition has been discussed at length in the scientific society; the reason for this discussion is the existence of two divergent views on the importance of the infectious factor in CE genesis. Some researchers adhered to the point of view that the uterine cavity is sterile and in cases of penetration of conditionally pathogenic microflora (CPM) into the endometrium, a pathological process occurs in about 60% of cases [4]. Other researchers [5] argued that the uterine mucosa cannot be sterile due to permanent microbial colonization from the lower genital tract.

Currently, CE is identified in the International Classification of Diseases and Causes of Death (CDC) of the 10th revision: Class XIV (N071.1.) as an independent nosological unit [1].

The prevalence of CE varies from 10 to 85%, due to the difficulties of clinical and morphological verification of the disease [6, 7]. According to various sources, among women with infertility, the number of CE cases is on average 10% (from 7.8 to 15.4%). 80–90% of CE is detected in women of reproductive age. It eventually causes menstrual and reproductive function disorders, leading to the development of infertility, failures in IVF programs and embryo transfer, miscarriage and complications in the course of the gestational process and childbirth [6, 7]. Infertility is diagnosed in 60% of women with CE (in primary 22.1%, in secondary 36.5%), unsuccessful attempts of IVF and embryo transfer were noted in 40% of women with CE. Some unsuccessful IVF attempts reach 80% in women with CE in the medical history, and the average number of failures in assisted reproductive technologies (ART) programs is approximately 3 per woman. According to other studies [8], CE is the only diagnosed cause of miscarriage in 47–52% of cases.

Foreign studies declare a CE prevalence rate of 10–11% based on the histological conclusion of an endometrial biopsy of patients who underwent hysterectomy due to benign gynecological conditions [9]. CE was diagnosed in 15% of infertile women who underwent IVF cycles, and the prevalence of CE was 42% in women with recurrent implantation failure (RIF) [10]. The prevalence of CE was 14% and 27% in the group of recurrent pregnancy loss (RPL) and women with RIF in a modern prospective study [11]. Thus, CE should be considered as a gynecological disease that cannot be ignored in the context of infertility treatment and assisted reproductive technologies.

Another point of view of J.C. Kasius et al. [12] is that the clinical signs of CE are minimal as they diagnosed this condition in only 2.8% of asymptomatic infertile women without abnormalities during transvaginal ultrasound examination (TUE). The opinion of these authors is that chronic endometritis does not adversely affect the reproductive outcome during normal cycles of in vitro fertilization or intracytoplasmic sperm injection (ICSI). At the same time, they emphasize that low detection and unknown clinical significance of chronic endometritis require further research [12].

Nevertheless, many researchers believe that CE usually occurs without clinical manifestations or has non-specific clinical signs, such as abnormal uterine bleeding, chronic pelvic pain and leukorrhea [13]. Chronic endometritis is associated with RPL, defined as three or more pregnancy losses before 20 weeks of pregnancy, which occurs in 3% of all couples [14].

It was observed that women with repeated abortions have chronic endometritis (68.3%) and women who received adequate antibiotic treatment had a significantly higher frequency of successful pregnancies compared to women who were not treated. The authors report that in this population the most common infectious agents were disruptive pathogenic bacteria and mycoplasmas [14]. Other symptoms that are associated with chronic endometritis were noted [13]. One of them is abnormal uterine bleeding (such symptoms may appear as intermenstrual discharge or metrorrhagia), however, to date, the relationship between abnormal uterine bleeding and chronic endometritis is not completely clear. Another symptom is dysmenorrhea. The current hypothesis defines prostaglandins, released through the endometrial cell membranes damaged by the inflammatory process, as the main cause of dysmenorrhea. Symptoms also include dyspareunia (pain during intercourse), genitourinary symptoms and leukorrhea. Sometimes there is unpleasant, purulent vaginal discharge with an increased frequency of urination and/or symptoms similar to the symptoms of cystitis, as well as concomitant irritation of the bladder. Fever usually occurs in the acute phase and

in some cases mild fever can be noted in the chronic form of CE.

PATHOGENETIC ASPECTS OF CHRONIC ENDOMETRITIS

The traditional idea that the uterine cavity is sterile underwent reanalysis when microorganisms were detected in the uterine cavity of non-pregnant women [15]. Ascending from the lower parts of the genital tract, microorganisms can colonize the uterine cavity, in which case the host's protective mechanisms must limit both the invasion and reproduction of bacteria [15, 16]. Protective factors include the cervical mucosa [17, 18], endometrial epithelium and its immune cellular components (neutrophils, macrophages and natural killer cells), as well as elements of the innate immune system, including the natural antimicrobial peptides present in the endometrium [18]. In 95% of cases, CE is primary, developing in the endometrium as a result of the introduction of sexually transmitted microorganisms, either exogenous strains or the multiplication of CPM in the endometrium after intrauterine treatment and diagnostic procedures. Only 5% of endometritis is secondary, developing when infection enters the endometrium from extragenital foci by hematogenic, lymphogenic or descending pathways [19, 20].

The study of the microbial landscape of the endometrium has a relatively short history. For the first time, the persistence of mycoplasma in the endometrium is mentioned in the work of Z. Koren in 1978 [21]. The persistence of more than 20 types of microorganisms of the opportunistic group was found in the endometrium. A total of 129 strains was identified, including obligate anaerobes – 64% (bacteroids, eubacteria, peptostreptococci, clostridia), microaerophiles – 31.8% (genital mycoplasmas and diphteroids), and facultative anaerobes – 12%. Monocultures were identified in only 14% of women; in the rest, associations of 2–6 types of microorganisms were found.

The vaginal microbiome is characterized by a deficiency of lactobacilli (52.5%), a low concentration of lactobacilli (44.3%), a high frequency of excretion of enterococci (59%), coagulase-negative staphylococci (57.4%) and multicomponent associations (67.2%) in women with chronic endometritis. The microbiota of the intestinal biotope was characterized by a high frequency of detection of enterococci (62.2 %) and dysbiosis of the 1st and 2nd degree (89.2%); the microbiota of the nasopharyngeal biotope was characterized by a deficit of indigenous flora and a high frequency of S. pneumoniae (25.5%) [22, 23].

It has been hypothesized that in women with chronic endometritis, normobiota representatives have a symbiotic relationship with CPM in all open biotopes, which confirms the decrease in normobiotic colonization resistance and its inability to suppress pathogenic biota [22, 23].

At the present stage, it is known that microorganisms form biofilms (dense shells of polymer compounds) to counteract the immunological mechanisms of the host; the effect of biofilms counteracting natural and synthetic antibiotics is known [24]. It was found and proved that chronic infections, such as valvular endocarditis, otitis media, chronic bacterial prostatitis and periodontitis, are associated with the presence of bacterial biofilms that contribute to subclinical colonization of the uterine cavity [25, 26].

One of the main and complex problems in the treatment of infertility, miscarriage and premature birth is the persistent effect of the microbial factor on the quality of the endometrium [6, 27]. Microorganisms are only a part of the problem; septic conditions are also associated with problems of inflammation control and/or anti-inflammatory response of the host [28]. There are studies of the mechanisms of preterm delivery, which showed that microorganisms on the surface of the endometrium do not cause a pro-inflammatory reaction and support peaceful coexistence with the host during normal pregnancy [24, 29, 30]. However, if the host organism (in this context, the mother, embryo/fetus or both) "learned" about microbial carriage through recognition receptors and initiated a pro-inflammatory response, peaceful coexistence will no longer be possible. Changes in virulence patterns, such as planktonic bacteria released from biofilms, have also caused a change in the balance between microorganisms and the host, leading to preterm delivery caused by inflammation.

The result of successful implantation and prolongation of pregnancy is a delicate balancing mechanism between the embryo and endometrium, which is expressed in the predominance of the TH2 profile compared to the profile of TH1 cytokines in the endometrium. Thus, all the reasons that upset this balance can affect endometrial susceptibility.

It was found that immunocompetent cells in the endometrium secrete chemokines, attracting natural killers and macrophages from the circulating peripheral blood into the endometrium [31, 32]. In turn, trophoblasts organize the production of pro-inflammatory cytokines from monocytes and macrophages, which are also of great importance in implantation and formation of the placenta [32].

An increase in the number of NK cells in the peripheral blood, leading to an increase in TH1 cytokines, has a negative effect on the invasion and implantation of trophoblast, which increases the likelihood of premature pregnancy loss [33].

A study of 438 cases of hysteroscopically diagnosed CE confirms the theory that the infectious factor is crucial in the pathogenesis of CE [34]. The researchers reported that 73.1% of women with CE showed ≥1 positive detection of pathogens. The structure of endometrial infections was as follows: 58% of common bacterial infections, including gram-negative bacteria, 10% of Ureaplasma urealyticum, and 2.7% of Chlamydia trachomatis. It has been established that gram-negative bacterial colonization of the endometrium can reduce the rate of implantation of embryos, leading to an increase in the frequency of miscarriages. Gram-negative bacteria endotoxins elicit a predominant TH1 response to decidual tissue to stimulate the production of pro-inflammatory cytokines. Thus, a paracrine medium is formed, which can cause damage to the embryo, impaired implantation, or spontaneous miscarriage [35].

Thus, chronic inflammation of the inner lining of the uterus disrupts the production of endometrial cytokines and, accordingly, endometrial function [36], leading to the formation of pathological lymphocytes and a change in the secretion of paracrine factors. As a result of this, the susceptibility of embryos to the endometrium decreases [33] and, in fact, in cases of CE, delayed differentiation of the endometrium in the middle secretory phase was observed [37]. Endometrial proliferation was detected in the secretory phase due to an increase in estrogen receptors and nuclear expression of the Ki-67 marker in patients with CE [38].

E. Cicinelli et al. [39] demonstrated that CE was a condition often associated with RIF (66.0%), which was 2 times greater than 30.3% in a study by E.B. Johnston-MacAnanny et al. [40]. The most common infectious agents were common bacteria and mycoplasmas in this population-based study. In addition, antibiotic treatment was associated with the normalization of the endometrial pattern on hysteroscopy and a significant improvement in the reproductive results of IVF.

DIAGNOSIS OF CHRONIC ENDOMETRITIS

The generally accepted histological diagnostic criterion for CE is the presence of plasma cells in the stroma of the endometrium during endometrial biopsy [9, 12]. However, the frequency of an erroneous diagnosis may be higher than ideal [12, 13]. The accuracy of morphological conclusions can be called into question due to the following conditions: proliferation of stromal cells, infiltration of mononuclear inflammatory cells, plasmacytoid cells of the stroma, or a pronounced pre-relapse reaction in the late secretory endometrium. In addition, histological examination is a very time-consuming and invasive method.

The method of staining with hematoxylin and eosin (H & E) had a low level of CE verification (<10%) in women with infertility and repeated spontaneous miscarriages in the medical history [41]. Immunohistochemical (IHC) studies can detect specific antigens for CD38 and CD138 plasma cells inside the endometrium [42]. IHC showed a significantly higher sensitivity for the diagnosis of CE (56% versus 13% for H & E strain) [43]. Plasma endometritis showed no correlation with bacterial colonization of the endometrium or the clinical picture of pelvic inflammatory diseases [44]. Plasma endometritis was histologically diagnosed in 39% of women who underwent endometrial biopsy, but 82% of women had positive results in microbial cultures of CE biopsy samples. Haggerty et al. [45] reported that histological endometritis revealed no association between reproductive diseases and antibiotic treatment in randomized controlled trials (RCTs). These experts believe that the histological diagnosis of CE cannot determine which patients can benefit from further antibiotic treatment and which cannot do this in terms of fertility outcomes.

An effective diagnostic method for the verification of CE is liquid hysteroscopy [46, 47]. Signs of CE in liquid hysteroscopy are endometrial polyps, stromal edema, focal or diffuse hyperemia. The diagnostic value of liquid hysteroscopy concerning CE is manifested in the great sensitivity of the method for diagnosing CE, in comparison with the microbio-

logical culture method for studying the endometrium [48]. Studies comparing the accuracy of the histological diagnosis of CE and fluid hysteroscopy showed a very high diagnostic accuracy of the latter (93.4%) [46, 47, 49]. Apparently, the discrepancies between hysteroscopic observations and histological studies can be associated with many limitations characteristic of the CE histological diagnosis [50].

Modern research studies the changes in the qualitative and quantitative composition of the vaginal and other biotopes of the body's open cavities and the presence of pathogenicity genes in microorganisms, as well as clarification of their relationship with inflammatory markers and factors contributing to the chronic process in the uterus. Researchers note an increased level of pathogenicity in the dominant E. faecalis and E. faecium species in different biotopes (vaginal, intestinal and nasopharyngeal) in women with CE, which is manifested in an increase in the number of enterococcal autostrains with nucleotide sequences of the pathogenicity gene synthesizing serine proteinase (sprE) (penetration, colonization, tissue damage). The presence of morphological signs of CE (inflammatory infiltrates, endometrial stromal fibrosis, sclerotic changes in the walls of arteries and plasma cells) is associated with the presence of genaserin proteinase (sprE) in the prevailing enterococci in the vaginal, intestinal, and nasopharyngeal biotopes [22, 23, 51].

TREATMENT OF A CHRONIC ENDOMETRITIS

All the studies of foreign colleagues that we have discovered come down to the fact that chronic endometritis therapy is based on the use of broad-spectrum antibiotics [52, 53]. Typically, the drug of choice is doxycycline in doses of 100 mg every 12 hours for 14 days or, alternatively, the introduction of cephalosporins, macrolides or quinolones is possible. It is also preferable for the partner to undergo the same antibiotic treatment. In case of failure of antibiotic therapy and/or preservation of endometritis at the same, an endometrial culture with a relative antibiogram should be considered and appropriate antibiotic treatment should be prescribed.

The Centers for Disease Control (CDC) recommend the following treatment options [39]: with a positive result for gram-negative bacteria: ciprofloxacin 500 mg 2 times a day 10 days as first-line therapy; for gram-positive bacteria: amoxicillin + clavulanate 1g two times a day for 8 days; infections of Mycoplasma and U. Urealyticum: Josamycin 1 g two times a day for 12 days; in case of persistence: minocycline 100 mg two times a day for 12 days; gram-negative cultures: ceftriaxone 250 mg IM in a single dose plus doxycycline 100 mg orally two times a day for 14 days with metronidazole 500 mg orally two times a day for 14 days.

If the signs of chronic endometritis remain in the following hysteroscopy, the protocol can be repeated up to three times. If there is confirmed tuberculosis endometritis, the patient should be given special antibacterial therapy for tuberculosis (isoniazide, ethambutol, rifampicin and pyrazinamide for 2 months, then isoniazid and rifampicin for another 4 months) [54, 55].

Cicinelli et al. [14] reported in their study of patients with unexplained recurrent implantation failure and chronic endometritis diagnosed by hysteroscopy that the incidence of clinical pregnancy in the group where hysteroscopic values were normalized 1 year after antibiotic treatment was significantly higher than in the comparison group: 74.8% (88 out of 118) versus 24.4% (22 out of 90). A study by McQueen et al. [41] showed that in patients with RPL and chronic endometritis, the frequency of live births per pregnancy increased significantly to 56% after antibiotic treatment compared with 7% before treatment.

According to a retrospective study by R. Yang et al. [56], in patients with RIN and CE undergoing in vitro fertilization cycles – embryo transfer (IVF-Cryo transfer) the implantation success rate increased up to 18.6% (18 out of 97) versus 4.9% (3 out of 61]) and the pregnancy rate 29.3% (12 out of 41) versus 7.4% (2/27). IVF cycles increased significantly after antibiotics treatment compared to the results before treatment. Cicinelli et al. [56] conducted a retrospective study of patients with RIN who underwent new IVF cycles with Cryo-transfer. They found that the frequency of clinical pregnancies and the rate of live births in the group with normal hysteroscopic indices after antibiotic treatment was significantly higher than in the group with sequential results of CE 65 % versus 33% and 60.8% versus 13.3%, respectively. The above values indicate that CE has an important role in infertility.

Diagnostic hysteroscopy is actively discussed in the treatment of chronic endometritis. Many studies have suggested that endometrial damage associated

with diagnostic hysteroscopy can increase the frequency of implantation and the frequency of clinical pregnancies in women with previous failed IVF-Cryo transfer attempts [57–59]. The hypothetical biological basis for this assumption is as follows [60]: first, local trauma in the endometrium can increase the implantation speed, which will lead to decay; secondly, cytokines and growth hormone released during the restoration after artificial damage to the endometrium, may have a beneficial effect on the implantation of embryos. Third, artificial endometrial damage may delay earlier endometrial maturation associated with hyperstimulated ovaries in the next IVF-Cryo transfer cycle.

Meta-analyzes [61, 62] regarding artificial endometrial injuries during ART or hysteroscopy reported a significant improvement in the clinical pregnancy rate. However, this possibility has not yet been confirmed by well-developed RCTs, so this assumption should remain hypothetical.

The analysis of Russian literature and studies on the principles and methods of treatment of chronic endometritis is characterized by the presence of the second stage of treatment (after antibiotic therapy) and the variety of methods used. A large number of authors point to the high effectiveness of physiotherapy: they use electro-pulse therapy, interference currents, infrared laser irradiation, magnetotherapy, and hirudotherapy. Physiotherapeutic methods help stimulate receptor function, improve the pelvic hemodynamics, accelerate endometrial regeneration processes, and increase the immune status [63]. An advisability of hormone therapy is under discussion. Some authors consider hormone therapy ineffective in this pathology, except in cases of patients having ovarian hypofiction or anovulation [64]. Others claim that in case of chronic inflammation, in the presence of pathological tissue regeneration, hormone replacement therapy has a positive anti-inflammatory effect [6, 65]. Correction of immune status occupies a special place in the treatment of chronic endometritis in the domestic literature. In the case of infection persistence in the body, the use of inducers of interferongenesis is important. Based on the data of studying the immune and interferon status of patients with chronic endometritis, the correction of immune disorders is carried out using a number of drugs: glavit, immunomax, and polyoxidonium [65, 66]. Sessions of intrauterine ozone laser therapy and intrauterine endometrial laser therapy using the He-Ne laser were effective in women with infertility and miscarriage [66, 67]. There are observational studies of bacteriophage therapy, which had a good therapeutic effect in 78.3–93.6% of cases; there is evidence of intrauterine irrigation with a liquid bacteriophage at a dose of 20 ml daily for 5 days with a pronounced clinical effect [68]. The therapeutic effect of bacteriophages is associated with lytic activity, immunomodulating the antigenic property of components of destroyed microbial cells located in the phage lysates, especially with repeated administration of the drug [69]. Several observational studies indicate the effectiveness of metabolic therapy, including the use of riboxin, wonbenzyme, vitamin therapy, glutamic acid, systemic enzyme therapy and actovegin [65]. Some researchers consider taking probiotics the second stage after antibiotic treatment, explaining that the risk of developing gastrointestinal disorders caused by antibiotic therapy is reduced and the restoration of intestinal microbiocenosis and other disturbed physiological processes in the body is initiated [69]. However, most authors agree on the opinion that the use of bacteriophage therapy does not mean a complete rejection of antibiotics, however, it will assist their strict prescription according to indications [65, 66]. Monitoring the effectiveness of complex therapeutic measures is recommended not earlier than 2 months after the end of the entire course of treatment, taking into account physiotherapy. At the same time, the dynamics of clinical symptoms, echographic and dopplerometric indicators, the elimination of microbial agents, and the restoration of the morphological structure of the tissue according to the control aspiration biopsy are evaluated.

Criteria of the clinical effectiveness of chronic endometritis are reduction of clinical manifestations combined with elimination of pathogenic microflora from uterine cavity against the background of normalization of immunocompetent cell and pro-inflammatory cytokine levels in the endometrium, restoration of endometrial microcirculation, improvement of blood rheological properties, and reduction of the intensity of fibrosation and sclerosis processes. The final criterion of successful treatment is the restoration of the reproductive function followed by pregnancy and consecutive live births [70].

CONCLUSION

Currently, limited evidence confirms that hysteroscopy can be a powerful tool for the physical

removal of entrometrial bacterial biofilms, which contribute to the pathogenetic development of CE. After hysteroscopy, reproductive results in subsequent IVF cycles may improve in patients with RIFs and latent CE. Recent meta-analyses regarding hysteroscopy or artificial endometrial injuries in ART (hatching) have reported a significant improvement in the clinical pregnancy rate. However, this possibility has not yet been confirmed by well-developed RCTs, so this proposal should remain hypothetical.

To date, CE remains a rather difficult problem from the point of view of nosology, pathogenetic mechanisms, diagnosis and treatment in terms of reproductive disorders. This was associated among other things with poor reproductive results in the context of ART. In cases of CE, the peaceful coexistence between host immunity and microorganisms is impaired, the distribution of lymphocytes involved in embryo implantation, and, ultimately, endometrial susceptibility is reduced due to inadequate secretion of various cytokines. Recent clinical trials of patients with RPL have shown that antibiotic treatment for CE can lead to significant changes in future pregnancy outcomes. The use and effectiveness of various treatment methods as the second stage of treatment of CE requires well-developed RCTs. Due to the lack of qualitative data in the published literature, such treatment methods are still hypothetical and empirical. Well-planned prospective studies or RCTs should be conducted to clarify the possible correlations between CE and poor reproductive outcomes, as well as the effectiveness of endometrial interventions. CE is a clinically significant nosological unit from the perspective of reproductive medicine, further study of the features of its etiology and pathogenesis is required in order to improve understanding of the course of the inflammatory process and improve treatment and prevention methods.

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