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CHRONIC ENDOMETRITIS - MODERN CONCEPTS, PRINCIPLES OF MAINTENANCE. LITERATURE REVIEW

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ABSTRACT

In our review article, we assessed the etiological factors of chronic endometritis, the most frequent manifestations of clinical and endoscopic data, the effectiveness of various diagnostic procedures and existing treatment methods. However, until now, many questions of the optimal algorithm for the diagnosis and treatment of this pathology remain open and require further study. In connection with the above, a certain practical and scientific interest may be of prospective studies assessing modern diagnostic and treatment methods for ChE, their impact on the number of unsuccessful reproductive outcomes of ART programs, taking into account the personal characteristics of the reproductive system of patients.

Key words: *Chronic endometritis, CD138, infertility, endometrial receptivity, implantation, reproductive failure, pregnancy failure.*

Chronic endometritis is a persistent inflammation of endometrium which caused by infectious agents, leading to disruption of cyclic biotransformation and endometrial receptivity [1]. CE, as a separate nosological form, was first identified in the International Statistical Classification of Diseases, Injuries and Causes of Death, Revision 9, 1975. The disease occurs mainly in women of reproductive age. The number of patients with chronic endometritis and infertility are increasing. According to Japanese researchers, chronic endometritis occurs in 22 per cent of IVF patients, in 14 per cent of unexplained infertility and in 23.6 per cent of women with miscarriages in the first trimester [1.2]. Among women with verified CE, 60 per cent are diagnosed with infertility (22.1 per cent with primary fertility, 36.5 per cent with secondary fertility), and 40 per cent of women are diagnosed with IVF failure. In patients with several failed attempts of IVF, the prevalence of CE is as high as 80 per cent, with the average number of failures in ART programmes being approximately 3 per woman. According to various studies, CE is the only diagnosed cause of pregnancy failure in 47.4-52.1 per cent. [3,4,5,6].

The endometrial factor occupies a significant place in the genesis of reproductive failure. Optimal conditions for the embryo implantation may occur only during a regulated days which is called "implantation window". The period when the uterus is receptive for the embryo implantation, occurs around 6 days after the peak of luteinizing hormone level [7], or 20-24 days of 28-day menstrual cycle (m. c.) [7,8]. Implantation is a multi-stage process of intermolecular and intercellular interactions, which are determined by the synchronicity of embryo development and endometrium [7]. Successful implantation defines a complex of structural-functional characteristics of endometrium (genetic, proteomic and morphological), united by the term of «endometrial receptivity» [8]. Expression of genes encoding specific proteins reflects the essence of the genetic level of endometrial receptivity. The protein level includes receptors for sexual steroid hormones, various adhesion molecules, cytokines, and growth factors that play a crucial role in the blastocyst implantation process. [9] The morphological characteristics are the state of stroma and endometrial glands and the quantity and quality of endometrial pinopodium. [10] Integrin molecules are the transmembrane glycoprotein family consisting of non-covalently bound α- and β-subunits which play a significant role in the processes of implantation and progression of pregnancy. [11]

ETIOLOGY

For almost a century, the cavity of the uterus was considered sterile under normal conditions [12, 13]. This sterility was thought to be supported by the mucous membrane of the cervix, which provided an impenetrable barrier against the penetration of bacteria from the vagina [14]. However, this hypothesis has been disproved, and recent studies have shown that microorganisms have been detected even in the endometrium of healthy women. [15-17]. In addition, it has been shown that cervical mucus does not completely block the penetration of vaginal bacteria into the uterine cavity [17, 18]. In addition, microbial particles can be moved from the vagina to the uterus through the cervical canal for several minutes due to the function of the uterine peristaltic pump [19.20]. The existence of microorganisms in the uterus are thought to be a main cause of CE, since antibiotic treatment has been reported to be an effective therapy for CE. The prolonged and often asymptomatic persistence of infectious agents in endometrium at CE leads to pronounced changes in

tissue structure and function, caused disruption of proliferation and normal cyclic transformation, impeding normal implantation and placentation, forming a pathological response to pregnancy [21, 22]. The most frequent infectious agents are common bacteria frequently found in the uro¬genital area such as Streptococcus (27%), E. coli (11%), Enterococcus faecalis (14%) and Ureaplasma urealyticum (11%) (19). The presence of Chlamydia trachomatis is only 2.7%, and Neisseria gonorrhoeae is practically un¬detectable as causative in CE (20). These findings are in line with the results of the PEACH study (21), showing that 60% of women with PID present non-gonococcal or Chlamydia infection. [17,21,22].

There is a question about the origin of bacteria in the uterine cavity. Cicinelli and et al. [17] examined bacterial cultures of endometrial tissues in 438 CE patients and found pathogens in only 73% of their cohort. Moreover, in patients positive for pathogenic bacteria in both vaginal secretions and endometrial tissue, only 32.6% cultured the same bacterial species. These data suggest that the results of bacterial cultures in the vaginal cavity cannot predict the microbiome of endometrium in patients with CE. In addition, the cause of CE may not necessarily be a rising infection from the intravaginal bacterial flora, or the progression of intrauterine bacterial colonization is not depend on the vaginal bacterial flora after its formation. [18] According to the recent research the peritoneal microorganisms from the gastrointestinal tract can reach the uterus via the fallopian tube and could be one of the cause of CE. Future investigation is needed to determine the origin and pathway of colonized microorganisms causing CE. The herpes simplex virus and cytomegalovirus may also cause CE, but the link between the viral infection and the occurrence of CE remains undetermined. [24]

The results of these studies indicate that the role of microorganisms in the occurrence of CE and the mechanism of their progression require further study.

CLINIC

Chronic endometritis (CE) is generally asymptomatic or has vague symptoms, such as abnormal uterine bleeding, pelvic pain, and leu¬korrhea. Clinically CE presents with very subtle symptoms or remains asymptomatic, like dysfunctional uterine bleeding(DUB), pelvic discomfort, leukorrhea and hence the reduced rate of getting diagnosed in usual population. [25]. According to FIGO 2009, abnormal uterine haemorrhage is characterized by intermittent uterine haemorrhage (which was previously treated as metrorragia, peri- and postmenstrual secretions) and heavy menstrual haemorrhage. Some authors believe that the leading clinical symptom of CE is extensive intermenstrual uterine haemorrhaging, diagnosed in 52-94% of cases [26, 27]. Several authors report a high incidence of persistent pain syndrome - 50-56% of cases [28]. 60.4% of cases are diagnosed with infertility (more often secondary), as well as failed attempts of IVF and ET in 37% [30]. E.Johnston-Macananny et al. showed that in IVF cycles, the frequency of implantation in patients with CE was lower than in the control group without CE, 12% and 33% respectively. The key to the success of the restoration of reproductive function is the rapid and accurate determination of the cause of infertility, which is possible by only in rational finding the methods of diagnostics and the connections between the different stages of examination and treatment. [29, 30]

DIAGNOSTICS

The gold standard for diagnosis of CE is a hysteroscopy with endometrial morphology, which is carried out by aspiration biopsy by vacuum Pipelle curettes. Difficulties of the hysteroscopy interpretation are the lack of typical macroscopic characteristics of the CE, the hotspot nature of the inflammatory process and the erased forms of the disease. The sensitivity of hysteroscopy diagnostic is 55%, and the specificity is 92-99%[30]. The endometrial pipelle biopsy is painless and practically does not cause complications, therefore it does not require anesthesia. Early morphological examination of the endomerium can be crucial in determining the mechanisms of the endometrial receptivity violation and for restoration of possible reproductive health disorders [31, 32]. Usual hysteroscopic findings for characteristic CE in¬clude presence of local or diffuse hyperemia, edema of the stroma and presence of micropolyps (less than 1 mm in size, Fig.1) [33].

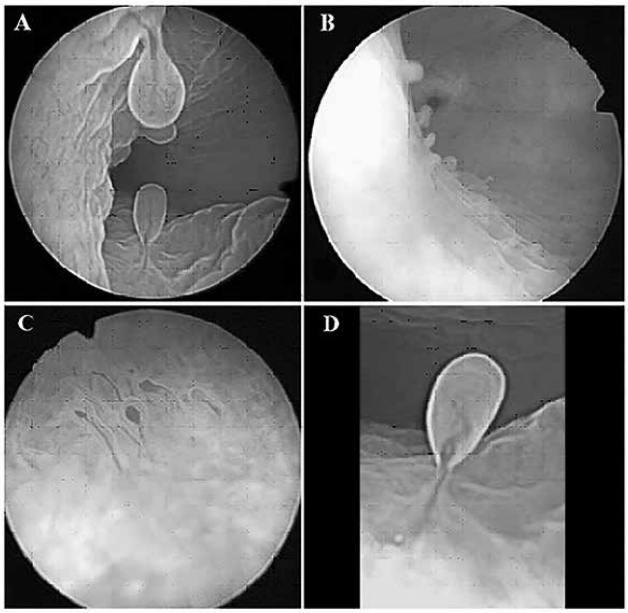

Figure 1 -

A)The surface of the endometrium is completely covered with micropolyps. B) Isolated micropolyps on the laterall wall of the cavity. C) The mucosa appears thick, edematous, diffuse hyperemic, with presence of micropolyps. D). Detailed image of the appearance of the endometrium micropolyp.

According to Cicinelli et al. [34,35] the presence of endometrial mycropolips at hysteroscopy suggests the existence CE. The presence of micropolyp in fluid hysteroscopy was reported to have high positive predictive values (93.7%). 85 micropolyps were recorded in 96 cases (11.7% of all hysteroscopy results), 90 (93.7%) of which had histologically confirmed CE. Women without micropolyps had a significantly lower incidence of CE (78 cases, prognostic value 10.8%).

In recent years, the commonly accepted criteria for the morphological diagnosis of chronic endometritis are [36]: inflammatory infiltrates, the presence of plasma cells, focal fibrosis of stroma, sclerotic changes in the wall of the endometrial spiral arteries.

Differences in the interpretation of histological characteristics of CE are due to the existence of variants, which are determined by the peculiarities of the general and tissue reactivity, the etiological factor, the duration of the disease, the presence of aggravations and the degree of their expression. (Savelyeva G.M., Breusenko V.G., Kapushova L.M., Hysteroscopy, Atlas and Management, 2013)

In addition to plasma cells, there may be a high proliferation of stromal cells, dissociated maturation between epithelium and stroma, and a pronounced inflammatory reaction. [37, 38] If the role of plasma cells (secretes large concentrations of antibodies) is taken into account, CE can describe a condition in which immune cells control some aberrant pathogens that have been present in the uterine cavity for long periods, and regulate their location until intense inflammation [39,40]. There is no single diagnostic criterion for CE worldwide.

According to Bayer-Garner IB and et al. [41] the accepted gold standard for diagnosis of CE is a pres¬ence of the plasma cells in endometrial tissue. However, their histological identification is sometimes hampered by the presence of mononuclear cell infiltration, mitosis and proliferation of stromal cells, plasmacytoid appear¬ance of stromal cells (fibroblasts and mononuclear cells) or decidual transformation of the endometrium during late secretory phase. Also, the plasma cell membrane demonstrates a strong positive immunohistochemical staining of the CD138, while the cytoplasm demonstrates a mild positive staining, which makes it easy to distinguish cells in fields of 200x and 400x. Therefore, in samples of endometrium suspected of chronic endometritis, plasma cells have not been identified using hematoxyline and eosine staning in preparations where CD138 plasma cells have been easily identified, thereby increasing the frequency of detection of chronic endometritis. Hence, the immunohistochemical staining of CD138 can improve the frequency and accuracy of diagnosis of chronic endometritis [Bayer-Garner IB, Nickell JA, Korourian S. Routine syndecan-1

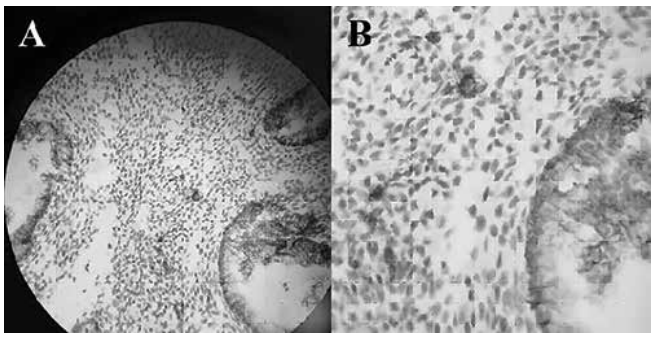

Figure 2 - Immunochemistry of chronic endometritis.

A. Fragment of endome¬trial biopsy specimen showing glandular cell surface syndecan 1 immuno¬reactivity. Plasma cells are highlighted by syndecan 1 staining in the center of the picture (original magnification: ×400) and B. More detailed picture of plasma cell syndecan 1 immunoreactivity.

Syndecan 1 is a proteoglycan of the transmembrane heparan sulfate type presenting on the surface of plasma cells and keratinocytes, while it is not expressed in mono¬nuclear cells, lymphocytes or endometrial stromal cells. It is also known as CD138, facilitating detection of plasma cells and presence of CE, not affected by intra- and inter-observer variability (42).

Yu-qing Chen1 and et al. compared the frequency of chronic endometritis with the presence of CD138 and the traditional histological method with hematoxyline eosine staining, and proved the diagnostic value of the CD 138 marker. It is recommended to carried out clinical immunohistochem¬istry and histological examination at the same time to increase the accuracy of the CE diagnosis [43,44]. Furthermore, it is im¬portant to obtain standardization of the current diagnostic techniques.

The most important factor in the diagnosis of chronic endometritis and especially find out the prediction of Repeated Implantation failure (RIF) is the determination of levels of estradiol (E2) and progesterone (P) receptors in endometrium. In women with reproductive impairment against the background of CE, there is a tendency to decrease the expression of progesterone and estrogenic receptors both at the stage of their formation in the proliferative phase and during the period of «window of implantation », which should be considered as one of the pathogenetic stages in the development pregnancy failure. The inflammatory process in endometrium, manifested by clear morphological changes on the 6th to 9th day of the menstrual cycle, alters the formation of estrogen and progesterone receptors, and this trend increases in the secretory phase of the menstrual cycle. This confirms that the main mechanism for the formation and development of proliferative processes in the uterus is the violation of the expression of steroid hormone receptors [45,46].

Multiple proteins are essential for the endometrial receptivity. The member of the family interleukin-6 - leukemia-inhibiting factor (LIF) - is synthesized in different tissues and organs, plays a significant role in regulating the female reproductive system [47,48]. The expression of receptors to LIF (LIF-R and glycoprotein gp130) is observed on the surface of the blastocyte and placenta, as well as on the surface of the iron and epithelium [49]. The interaction of LIF with its LIF-R receptor triggers signaling pathways, activating the synthetic function of endometrium, thus ensuring its receptivity [47]. It is assumed that LIF plays a significant role in the implantation processes and pregnancy progression [50]. LIF is currently the most studied proteins. The implantation process is directly influenced by integrins, molecules of a family of transmembrane glycoproteins consisting of non-covalently bound α- and β-subunits. The binding of integrins by their ligands leads to the rearrangement of cell cytoskeleton proteins and the activation of intracellular signaling pathways involved in the regulation of adhesion, migration, and invasion. Several integrin subclasses [51] are expressed on the surface of endometrial cells. The role of the integrins β1 and β3 in the implantation process has been proven [52]. Some researchers believe that the determination of the level of integrin αvβ3 in endometrium during the «window of implantation» period is a reliable diagnostic marker in the evaluation of the endometrial receptivity. [53].

Therefore, persisting microbial agents in endometrium alter the expression level of immunomodulator molecules responsible for the functional integrity of the immune system, and the hyperexpression of sindechen-1 (CD138) contributes to the modification of the endometrial receptivity. [54]

TREATMENT OF CE

Treatment of chronic endometritis is a complex but important task, especially in women with infertility and repeated implantation failure. The majority of scientists agree on the advisability of carrying out integrated treatment of CE in two stages [55,56]. The essence of the first stage is eliminating the microbial factor and/or reducing the activity of the viral invasion by means of ethitotropic therapy [57]. The aim of the latter is to restore the morphofunctional potential of endometrium by eliminating secondary tissue damage - the correction of fibrous and sclerotic processes, regeneration of hemodynamics and activity of endometrial receptivity. [58,59]. The complex therapy of chronic endometritis makes it possible to restore the damaged tissue, homeostasis and the endometrial receptivity, which leads to the restoration of reproductive function.

Doxycycline, a broad-spectrum antibiotic, is a standard treatment to prevent intrauterine infection after abortion and has long been used worldwide and has been listed for treatment of CE. Johnston-Mckinney et al. reported that 66.7 per cent of patients with CE were included in the study and were cured by the administration of doxycycline (200 mg / day for 14 days); The scheme of the second treatment, including ciprofloxacin and metronydazole (500 mg each day for 14 days), cured the remaining patients [60]. Kitaya et al., also reported that 92.3% of CE and RIF patients were treated in the same way [62]. Additional treatment using a combination of ophloxacin (400 mg / day for 14 days) and metronidazole (500 mg / day for 14 days) cured the remaining patients. Overall, the recovery rate was 99 %.

According to the results of the endometrial microbial examinations, Cicinelli et al. classified the antibiotic regimens for the treatment of CE women with a history of RIF (63). Ciprofloxacin (1,000 mg per day for 10 days) was used for most patients who were positive for Gram-negative bacteria, whereas a combination of amoxicillin/clavulanate (2 g per day for 8 days) was given to those with Gram-positive bacteria. The patients with mycoplasm and/or ureaplasm species were treated with josamycin (2 g per day for 12 days) along with minocycline (200 mg per day for 12 days) as the second-line regimen. The patients with negative endometrial microbial examinations were administered a combination of ceftriaxone (250 mg, single dose, IM injection), doxycycline (200 mg per day for 14 days), and metronidazole (1,000 mg per day for 14 days). In this retrospective study, 28 of the patients overcame CE with a single course of antibiotic regimen, whereas 23% (14/61) and 25% (15/61) required the second course and the third course of antibiotic treatment, respectively. The remaining 25% (15/61) were resistant to three-time repetition of the same regimen.

According to a retrospective study by Cicinelli et al, the results of ART programmes in women after oral antibiotic therapy (AB) were significantly higher than in untreated patients (65 per cent versus 33 per cent and 60.8 per cent versus 13.3 per cent, respectively) [64].

Konstantinos Sfakianoudis et al described a series of cases, where patients were offered the option of intrauterine antibiotic infusion, in order to to provide a more efficiency approach in treating the persistent nature of CE. The treatment cycle was set for a period of one month, including 10 infusions during this period. With regard to the volume used for intrauterine infusions, each infusion included 3-4 ml, a volume corresponding to the cavity's maximum capacity. Regarding to the antibiotic regime in use, their protocol included a solution for intravenous injection of ciprofloxacin at a concentration of 200 mg / 100 ml. The antibiotic infusions were carried out using a 23 cm soft Embryo Replacement Catheter. After treatment, patients were sent for reassessment during the subsequent follicular phase of the menstrual cycle with a biopsy of endometrium, for histological and microbiological studies. The reassessment provided encouraging evidence that intrauterine infusion therapy with antibiotics was not only well tolerated by patients without adverse or unexpected events, but was also largely able to mitigate the signs of endometritis.[65]

The hormonal therapy in the comprehensive treatment of CE remains a matter of debate. Currently, only differential hormonal therapy is considered warranted in the case of ovarian hypofunction or anovulation. However, according to the randomized studies, hormonal therapy has been justified to improve the endometrium thickness and its microcirculation - combined oral contraceptives from the 1st to 5th day of the menstrual cycle of at least 3 months or progestins from 16 to 25 monthsDay of menstrual cycle at least 3 months (didrogestron at 10 mg twice a day or micronized progesterone at 100 mg twice a day). In addition, when infection is generalized, the excess of inflammatory response is reduced the systemic anti-inflammatory and immunomodulating action of the COC's component [66].

CONCLUSION

Therefore, the chronic inflammatory process in endometrium is realized at the cellular level in the form of the following disorders: disorders of metabolism, disorders of the immunocompetent chain and development of autoimmune processes, deterioration of microcirculation, increasing hypoxia, imbalance of pro-oxidant and antioxidant systems. CE is a clinically significant nosological unit from the point of view of reproduction, and further study of its etiology and pathogenesis is needed to improve understanding of the inflammatory process and to improve the treatment and prevention methods. Recent clinical studies of RPL and RIF patients have shown that antibiotic treatment of CE can significantly alter reproductive outcomes. The curing of CE should be monitored.

The issue of hyperdiagnosis of CE and the risk of hyperpolyprogrammasy also deserves attention. The diagnosis of CE should be based on a combination of histeroscopy, routine histology, immunogistics and clinical data.

In our review, we have evaluated the effectiveness of various diagnostic procedures and treatment of CE. We have evaluated the efficiency of the various diagnostic procedures. However, the questions of optimal algorithm of diagnosis and peculiarities of treatment of this pathology remain open and require further study. Therefore, in order to clarify the assessment of the effectiveness of diagnosis and treatment, as well as possible correlations between CE and poor reproductive outcomes, well-designed predictive studies or Rcts should be conducted.

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РЕЗЮМЕ

ХРОНИЧЕСКИЙ ЭНДОМЕТРИТ – СОВРЕМЕННЫЕ ПРЕДСТАВЛЕНИЯ, ПРИНЦИПЫ ВЕДЕНИЯ. ОБЗОР ЛИТЕРАТУРЫ

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В нашей обзорной статье мы провели оценку этиологических факторов хронического эндометрита, наиболее частых проявлений клинических и эндоскопических данных, эффективности различных диагностических процедур и существующих методов лечении. Однако до настоящего времени многие вопросы оптимального алгоритма диагностики и лечения данной патологии, остаются открытыми и требуют дальнейшего изучения. В связи с вышеизложенным определенный практический и научный интерес могут представлять проспективные исследования оценки современных методик диагностики и лечения ХЭ, их влияние на число неудачных репродуктивных исходов программ ВРТ с учетом персональных особенностей репродуктивной системы пациентов.

Ключевые слова: *хронический эндометрит, репродуктивные неудачи, рецептивность эндометрия, имплантация, СД 138,*

ТҮЙІНДЕМЕ

СОЗЫЛМАЛЫ ЭНДОМЕТРИТ- ЗАМАНАУЙ КӨЗҚАРАСТАР, ЖҮРГІЗУ ПРИНЦИПТЕРІ. ӘДЕБИ ШОЛУ

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Бұл мақалада біз созылмалы эндометриттің пайда болу себебінің этиологиялық факторларын,жиі кездесетін клиникалық және эндоскопиялық белгілерін, сонымен қатар әртүрлі диагностикалық және емдеу әдістерінің тиімділігін бағаладық. Бірақ, осы уақытқа дейін диагностиканың оңтайлы алгоритмі және бұл патологияны емдеу ерекшеліктері туралы сұрақтар ашық күйінде қалып, әрі қарай зерттеуді қажет етеді. Сондықтан да жоғарыда көрсетілген мәліметтер бойынша диагностика мен емдеудің тиімділігін бағалау үшін белгілі бір практикалық және ғылыми қызығушылықтарды, сондай-ақ созылмалы эндометрит және сәтсіз репродуктивті нәтижелер арасындағы ықтимал корреляцияны нақтылау үшін пациенттердің репродуктивті жүйесінің жеке ерекшеліктерін негізге ала отырып мұқият әзірленген проспективті зерттеулер немесе РКИ жүргізу керек.

Түйін сөздер: *созылмалы эндометрит, репродуктивті сәтсіздіктер, эндометрий рецептивтілігі, имплантация, СД 138*