

Chronic Autoimmune Endometritis as the Main Cause of Reproductive Disorder

Zhumaeva D. R.

Asian International University

Abstract: The main role of inflammatory diseases of the internal genital organs in the structure of the reproductive function of women, as well as chronic endometritis, as a cause of infertility of uterine genesis, which tends to steadily increase. Etiological risk factors for the development and trigger mechanism of chronic inflammatory processes in the endometrium, features of the pathogenesis and clinical picture of endometritis are identified. Criteria for morphological diagnostics of endometritis, morphological signs of endometritis with an autoimmune nature of the inflammatory process, various extranosological structural and functional disorders in the endometrium are determined. The significance of diagnostics of autoimmune chronic endometritis by the immunohistochemical method, the expediency of immunohistochemical study for assessment of receptor expression and severity of local immunity in the endometrium, the necessity of determination of the fertility protein alpha-2-microglobulin, the presence of pathogenic bacterial and viral microflora in the vagina, cervical canal and in the uterine cavity in the aspect of prevention of reproductive losses and treatment of infertility of uterine genesis are shown. The necessity of synchronization of processes of differentiation of endometrial cells and embryogenesis, the influence of sex steroids on the endometrium are specified.

Keywords: autoimmune chronic endometritis, infertility of uterine genesis, immunocompetent cells, receptor expression, glycodelin, gravid transformation.

Introduction

Inflammation of the endometrium is one of the main causes of the "uterine factor" of infertility. Infertility is a serious problem in reproductive medicine, in which there is a combination of social, mental distress and almost always physical ill health in the family (WHO, 1979). Women's reproductive health is one of the most acute medical and social problems. One of the leading places in the structure of reproductive dysfunction in women is occupied by inflammatory diseases of the internal genital organs, causing significant medical, social and economic problems throughout the world [17].

Inflammation is a "...complex vascular- mesenchymal response to damage, aimed not only at eliminating the damaging agent, but also at restoring damaged tissue...". The main role of the inflammatory response is to eliminate the damaging agent and repair the damage. Restoration of damaged tissues largely depends on the state of the immune system, which determines the further outcome of the pathological process. Inflammatory diseases of the pelvic organs include inflammation of the uterus, ovaries, fallopian tubes, parametrium and pelvic peritoneum. Isolated lesions of the listed parts of the genital tract are rare in clinical practice, since they are all connected into a single functional whole. The main cause of inflammatory diseases in the uterus and appendages are mixed polymicrobial infections [9].

Mixed infection is a serious problem, as the pathogenicity of each pathogen increases. The scale of this problem can be illustrated by WHO materials, according to which the risk at the age of 15-19 years is 1 in 8. Inflammatory diseases can be a consequence of untreated acute conditions, and in 80% of women the disease initially has a latent course and is immediately verified as primary chronic. Chronic inflammation of the pelvic organs in 80-82% of cases leads to infertility, in 40-43% of patients it causes menstrual dysfunction. Diseases of the uterus and endometrium, the so-called "uterine factor" of infertility, occur in more than half of women of reproductive age [19,20].

Their frequency, according to domestic authors, ranges from 46% to 68% [6,16], and foreign authors – from 25% to 42%.

The cause of infertility of uterine genesis is mainly chronic endometritis, which is characterized by a tendency to a low-symptom and asymptomatic course. It has been scientifically proven that the functional and basal layers of the endometrium are involved in the inflammatory process in CE, and the presence of morphological changes in the endometrium has been established, which are similar to changes in chronic inflammation in other organs and tissues [13].

The prevalence of chronic endometritis varies from 10% to 98%, which is due to certain difficulties in diagnosis, clinical and morphological verification of this disease, which develops mainly in women of reproductive age and has a tendency to steadily increase. The highest prevalence rates of CE are noted in women suffering from infertility, especially with tubal-peritoneal factor - 68%, a history of unsuccessful attempts at in vitro fertilization and embryo transfer - 60%, and habitual miscarriage - more than 73.1%, as well as in women with non-developing pregnancy (56%) and complicated course of the gestational process and childbirth in the anamnesis [22,25].

1. Risk factors for the development of endometritis are all invasive interventions in the uterine cavity: hysteroscopy with curettage of the uterine cavity, endometrial biopsy, hysterosalpingography, unsuccessful attempts at in vitro fertilization, artificial insemination with the husband's or donor's sperm. A huge role is played by infectious and inflammatory complications after childbirth and abortions, diseases of the urinary system, a history of salpingo-oophoritis, the use of an intrauterine device for contraception, vaginal and cervical infections, bacterial vaginosis, deformation of the uterine cavity with impaired cyclic desquamation of the endometrium, as well as previous operations on the pelvic organs [28].
2. Etiology of chronic endometritis. In 95% of cases, CE is primary, developing directly in the endometrium due to the introduction of exogenous strains of sexually transmitted microorganisms or the proliferation of opportunistic microflora in the endometrium after intrauterine therapeutic and diagnostic manipulations. Only in 5% of cases is endometritis secondary, developing when infection enters the endometrium from extragenital foci via hematogenous, lymphogenous or descending routes [28].

Methodology

By etiologic factor, endometritis is divided into: non-specific (without detection of specific microflora) developed against the background of IUD, radiation therapy of the pelvic organs, bacterial vaginosis of infected patients and specific - with detection of monoinfection and / or polymicrobial association. Specific CE can be chlamydial, viral: herpes simplex virus, cytomegalovirus, enteroviruses; bacterial (pathogens of tuberculosis, gonorrhea, meningitis, syphilis), mycoplasma, fungal, protozoal (toxoplasma, schistosome) and parasitic etiology, and also develop against the background of sarcoidosis. The trigger for the development of chronic processes in the endometrium is viral and / or bacterial invasion. Almost all microorganisms present in the vagina, with the exception of lacto- and bifidobacteria, can participate in the development of inflammation [17].

The vaginal microbiocenosis is under the control of the nervous, immune and endocrine systems. The normal vaginal microflora is divided into obligatory, facultative and transient. Obligatory microflora includes microorganisms that are constantly part of the normal vaginal microflora (non-pathogenic, opportunistic). Participating in the metabolism of the host organism, they prevent pathogenic bacteria from penetrating the vagina. Transient microflora includes non-pathogenic, opportunistic and pathogenic microorganisms accidentally introduced into the genital tract from the environment. In the normal state of the vaginal tract microecology, these microorganisms, as a rule, are incapable of long-term presence in it and do not cause the development of a pathological process. The frequency of seeding and the number of strictly anaerobic and most aerobic representatives of the normal microflora are higher in the proliferative phase than in the secretory phase. The most reliable information about the quantitative and qualitative composition of vaginal microflora is in the first phase of the menstrual cycle. During menstruation, the maximum number of microorganisms in the vagina is determined, but the level of lactoflora does not change. Dysbiotic conditions (bacterial vaginosis and vaginal candidiasis) are favorable conditions for the occurrence and development of inflammation and persistence of microorganisms in the endometrium [49].

Discussion and Results

In case of frequently recurring candidiasis vulvovaginitis, the reservoir of fungi and the source of vaginal reinfection is the gastrointestinal tract. Candidiasis usually occurs endogenously as a consequence of dysmetabolic disorders and dysfunction of the immune system. In the vast majority of cases, the cause of the inflammatory process in the endometrium are polymicrobial associations, which include parasitic protozoa (*Trichomonas vaginalis*), pathogenic (*Chlamydia trachomatis* , *Neisseria gonorrhoeae* , herpes simplex virus , *mycoplasma genitalium*), as well as opportunistic microorganisms (*Staphylococcus* spp ., *Escherichia coli* , *streptococcus* spp .), anaerobic bacteria (*Bacteroides* , *Peptostreptococcus*), (*Escherichia coli* , *Gardnerella vaginalis* , *Haemophilus influenza*), as well as the growth of microflora resistance to pharmacotherapy [24]. Among persistent viruses, the most important are: herpes virus infections, cytomegalovirus, human papillomavirus. Herpetic lesion of the endometrium, as a rule, occurs in women suffering from atypical or asymptomatic forms of genital herpes caused by long-term persistence of HSV in the endometrium. In most cases, the infection is mixed, and in women with CE, the infection is detected in the uterine cavity 1.5 times more often than in the cervical canal. The diagnosis of "chronic endometritis" is histologically verified in 86.7% of patients with persistence of opportunistic microorganisms in the endometrium. Social factors (early onset and promiscuous sexual activity, high frequency of sexual intercourse, sexual intercourse during menstruation, smoking, alcohol consumption) play a major role in the genesis of the development of CE [11].

3. Pathogenesis of chronic endometritis. The inflammatory reaction is a universal protective reaction of the body to the action of various pathogenic factors, with the neutralization and destruction of the factors that caused the damage. The mechanism of development of CE corresponds to chronic productive interstitial inflammation, which is characterized by the predominance of proliferation of cellular elements. The main sign of productive inflammation is infiltration by mononuclear cells , especially macrophages, lymphocytes and plasma cells, proliferation of fibroblasts, in many cases - increasing fibrosis and mild destruction (alteration) of tissue. Exudation processes occur, but they are not expressed. Among the types of productive inflammation, the following are distinguished: interstitial (intermediate) inflammation, granulomatous inflammation, inflammation with the formation of polyps and genital warts. Interstitial inflammation is characterized by the formation of focal or diffuse inflammatory cellular infiltrate in the stroma of organs. The infiltrate is represented by lymphocytes, histiocytes, plasma cells, neutrophils, eosinophils and mast cells. Interstitial inflammation tends to be chronic, resulting in connective tissue proliferation. The epithelium of the mucous membranes undergoes hyperplasia, proliferation in the form of polyps, the base of which is diffusely infiltrated by lymphocytes, plasma cells , macrophages and other cellular elements.

Long-term and often asymptomatic persistence of microorganisms in the glands and stroma of the endometrium leads to activation of cytokines - mediators of inflammation, and as a result of mediator reactions, microcirculation is disrupted, leukocytes chemotaxis to the damage zone, neutrophils and macrophages are activated. Inflammation in the endometrium causes a pronounced tissue reaction, destruction accompanied by damage to the epithelium with a change in the structure and function of the endometrium, disruption of proliferation and normal cyclic transformation of the tissue [5,16]. The pathogenesis of CE is characterized by a wave-like, progressive nature of the pathological process with proliferation of cells of hematogenous and histiogenic origin, their differentiation and cellular transformations. The criteria for morphological diagnosis of CE are: inflammatory infiltrates consisting mainly of lymphoid elements, located more often around glands and blood vessels, less often diffusely. Focal infiltrates have the appearance of "lymphoid follicles" and are located not only in the basal, but also in all parts of the functional layer, they also include leukocytes and histiocytes; plasma cells; focal fibrosis of the stroma, arising with a long-term course of chronic inflammation, sometimes capturing large areas; sclerotic changes in the walls of the spiral arteries of the endometrium, appearing with the longest and most persistent course of the disease and pronounced clinical symptoms [19].

In the foci of inflammation, there is a pronounced proliferation of monocytes, which, having reached extravascular tissues, are transformed into macrophages. The formation of macrophages is ensured by three mechanisms: from circulating blood, local proliferation, prolonged survival and immobilization of macrophages in the inflammation zone. Macrophages affect the increase in the viability of endothelial cells through the secretion of vascular endothelial growth factor (VEGF), the main regulator of angiogenesis in the endometrium, which in turn increases the proliferative activity of endothelial cells and vascular permeability. Maximum expression of VEGF is detected in the secretory phase, which corresponds to the period of the greatest proliferative activity of endometrial cells and increased angiogenic properties of the endometrium. VEGF production is regulated by steroid hormones, and therefore it can be one of the mediators of sex steroids in the endometrium. Activated macrophages in the inflammation focus are the source of cytokine synthesis stimulating cellular proliferation of T- and B-lymphocytes, endothelial cells, platelets, and promote the appearance of active forms of oxygen and hydrogen peroxide. They control capillary growth and regulation of granulation tissue formation in chronic inflammations, initiate angiogenesis processes, secreting proangiogenic factors that affect the proliferation, migration, and differentiation of endothelial cells. Macrophages also secrete enzymes (acid phosphatases – hydrolases, lipases, esterases ; neutral proteases – elastases , collagenases , etc.) that destroy and change the structure of the extracellular matrix, thereby stimulating the growth and development of the vascular network and causing apoptosis of endothelial cells through the secretion of antiangiogenic factors thrombospondin – 1 (TSP-1) and tumor necrosis factor – α (TNF- α), ensuring the termination of angiogenesis [26].

TNF- α is a polypeptide mediator of inflammation and cellular immunity: activates granulocytes, macrophages, endothelial cells; stimulates proliferation and differentiation of neutrophils, fibroblasts, endothelial cells, hematopoietic cells, T- and B-lymphocytes, hepatocytes ; is the most important regulator of inflammatory processes as a modulator of activation, proliferation and differentiation of inflammatory cells; stimulates the production of IL-1, IL-6; is a representative of the " effector " cytokines that can directly affect the target cell, causing its death. A key role in the pathogenesis of endometritis is played by endogenous intoxication with bacterial endotoxin of gram-negative microorganisms - a classic stimulator of macrophage function, which in the inflammation zone activates the generation of active oxygen forms and contributes to the development of oxidative stress, leading to hyperproduction of free radicals and destruction of membranes, with a violation of the antioxidant defense function. In conditions of progression of the pathological process, the inadequacy of its activity is accompanied by an increase in endotoxicosis and secondary damage to cell membranes with an aggravation of

disturbances of biophysical processes [24]. Damage to the vascular epithelial surface (due to persistence of infection) is one of the main reasons for the disturbance of the production and ratio of prostacyclin and thromboxane, resulting in thrombosis [8].

3. Receptor function of the endometrium. The endometrium is a target organ for sex hormones due to the presence of specific receptors in it. Functional completeness and adequate maturation of the endometrium is achieved through endometrial cell receptors and is an important condition for the onset of pregnancy. Successful implantation requires the presence of a receptive endometrium and normal interaction between it and the embryo [20].

The expression of steroid hormone receptors in endometrial glandular and stromal cells varies during different stages of proliferation and secretion during a normal menstrual cycle. The early phase of glandular epithelium proliferation is characterized by moderate expression of estrogen and progesterone receptors. In the middle and late phases of proliferation, pronounced maximum expression of these receptors is observed. The early and middle stages of secretion are characterized by a sharp decrease in the expression of estrogen receptors and a more prolonged decrease in the expression of progesterone. In the late phase of secretion, the expression of estrogen and progesterone receptors decreases. A different picture is observed in the stroma. In the early and middle phases of proliferation, the expression of estrogen receptors increases and then gradually decreases until the late phase of secretion. Progesterone expression has two types of maximum values: in the late phase of proliferation and the middle phase of secretion [12].

Conclusion

Thus, early diagnostics by immunohistochemistry of local immune disorders in autoimmune endometritis, as well as damage to the receptor apparatus of the endometrium and disorders of the secretory function of the endometrioid glands due to the inflammatory process, helps in individual selection of treatment and restoration of normal gravid transformation of the endometrium. Adequate treatment and properly performed pregravid preparation for uterine infertility associated with chronic endometritis of autoimmune genesis will provide greater efficiency compared to standard methods.

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