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ТИББИЁТДА ЯНГИ КУН НОВЫЙ ДЕНЬ В МЕДИЦИНЕ NEW DAY IN MEDICINE

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THE ROLE OF IMMUNOLOGICAL MARKERS IN EARLY PREDICTION OF ENDOMETRITIS RECURRENCE

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✓ Resume

The data on the diagnosis of postpartum infections in women with chronic endometritis, which occurs against the background of the use of intrauterine devices and without the use of intrauterine devices, are presented. High levels of cytokines were found in women in both groups, and an immunomodulator was used for modern treatment

Key words: chronic endometritis, inflammatory diseases of the pelvic organs, intrauterine adhesions, inflammation, fibrosis, antibiotic therapy, immunomodulation, bovyaluronidase azoximer

РОЛЬ ИММУНОЛОГИЧЕСКИХ МАРКЕРОВ В РАННЕМ ПРОГНОЗИРОВАНИИ РЕЦИДИВА ЭНДОМЕТРИТА

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✓ Резюме

Представлены данные по диагностике послеродовых инфекций у женщин с хроническим эндометритом, который возникает на фоне применения внутриматочных средств и без применения внутриматочных средств. У женщин в обеих группах был обнаружен высокий уровень цитокинов, и в целях современного лечения был использован иммуномодулятор

Ключевые слова: хронический эндометрит, воспалительные заболевания органов малого таза, внутриматочные сращения, воспаление, фиброз, антибиотикотерапия, иммуномодуляция, бовгиалуронидаза азоксимер

ЭНДОМЕТРИТНИНГ ҚАЙТАЛАНИШИНИ ЕРТА БАШОРАТ ҚИЛИШДА ИММУНОЛОГИК МАРКЕРЛАРНИНГ РОЛИ

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✓ Резюме

Бачадон ичи воситасиз ва бачадон ичи воситаси фонида пайдо бўлган сурункали эндометрити бор аёлларда тузрукдан кейинги юқумли касалликлар диагностикаси тўғрисидаги маълумотларни тақдим этишдир. Иккала гуруҳдаги аёлларда ҳам цитокинларнинг юқори даражаси аниқланди ва замонавий даво мақсадида иммуномодулятордан фойдаланилди

Калит сўзлари: сурункали эндометрит, тос аъзоларининг яллигланиш касалликлари, фиброз, антибиотик терапияси, иммуномодуляция, бовгиалуронидаза азоксимер

Relevance

Chronic endometritis (CE), despite the apparent simplicity of the definition, remains a disease that causes a large number of disputes and controversies. Subclinical endometrial inflammation in clinical practice is significant not in itself, but in connection with impaired fertility: among women with a histologically confirmed diagnosis of CE, infertility occurs in 60%, unsuccessful attempts at extracorporeal fertilization (IVF) – in 40-50% of cases [1]. At the same time, CE does not determine reproductive disorders and can become a random finding when examining a woman with normal fertility for any reason. The modern definition of CE presents it as a clinical and morphological syndrome, in which, as a result of persistent damage to the endometrium by an infectious agent, many secondary morphofunctional changes occur that disrupt the cyclic bio-transformation and mobility of the uterine mucosa [2]. But if the leading role of the infectious factor in the development of endometritis is not questioned, then the question of the significance of the persistence of the infectious agent in the mucosa in the pathogenesis of its chronic inflammation remains open. The pathophysiology of inflammation allows its preservation during the elimination of the primary pathogen against the background of disturbances in the balance of pro-inflammatory and anti-inflammatory components, which interfere with the normal completion of the inflammatory reaction. It is this inflammatory and immune abnormality (CE) that causes endometrial dysfunction and leads to negative clinical outcomes in the form of infertility and/or miscarriage. Thus, the concept of endometritis, which denotes one of the forms of inflammatory diseases of the pelvic organs (PID) of infectious origin, and the concept of CE, which refers more to endometrial dysfunction than to its damage, should be separated. Inflammatory endometrial dysfunction is able to exist outside of a persistent lesion, develop in response to an external event that is not associated with infection, despite the fact that its transition to a stable pathological state.

Objective of the study: To study the role of immunological markers in early prediction of relapse of endometritis

Materials and methods

(CE) is more often associated with infectious damage. According to modern concepts, all microorganisms found in the vaginal-cervical ecosystem, with the exception of lactobacilli and bifidobacteria, can initiate the development of endometritis [3]. The obligate urogenital pathogens *Neisseria gonorrhoeae* and *Chlamydia trachomatis* are the undisputed cause of endometritis and other ODMTs, but other microorganisms such as *Mycoplasma genitalium*, anaerobes, streptococci, syphilococci, *Escherichia coli* and *Haemophilus influenzae* are increasingly involved in the development of acute *Escherichia coli* и *Haemophilus influenzae* inflammatory disease. Combinations of different bacilli are detected with high frequency, and a number of researchers believe that mono infections, even such as *N. gonorrhoeae* and *C. trachomatis*, lose their leading role in the pathogenesis of PID [4]. The etiological role of *M. hominis* and *Ureaplasma urealyticum* in the genesis of CE is also questioned, since these compounds are detected in the vagina in 30-50% of sexually active healthy women, and some authors consider them only as markers of the presence of other pathogenic microflora in the endometrium [5]. The opinion about the prevalence of microbial associations in the genesis of endometritis, especially conditionally pathogenic aerobic and anaerobic bacteria [6], when the virulence of microorganisms composing the biofilm and their resistance to antibiotics increases, is the most popular today [7]. Polymicrobial etiology is most significant in CE associated with habitual miscarriage. On the other hand, over the past decade, the view of CE has evolved as a condition that is not necessarily associated with infection. This position is justified by the role of inflammatory endometrial dysfunction in the outcome of a frozen pregnancy, regardless of the infectious lesion. Indeed, it can be agreed that an abnormal inflammatory response does not necessarily accompany pregnancy loss, and, on the other hand, it itself triggers cascade of disorders leading to reproductive loss and infertility. Consequently, in contrast to endometritis as a form of PID, in the formation of CE, the emphasis shifts from the infectious factor to the factor of perverted inflammatory / immune (local or systemic) response of the macroorganism to any external, rather than only infectious, impact. At the same time, infectious diseases contribute to the perversion of the inflammatory response, causing serious changes in immunity, which are expressed in an increase in the number of T-lymphocytes, NK cells, macrophages, the predominance of the T1-cell link of immunity over the T2-link, a decrease in the levels of immunoglobulin (Ig) M, IgA, IgG. Infection is a source of persistent antigenic irritation, a trigger and maintenance mechanism of an inflammatory reaction against the background of the failure of local anti-infective protection factors

[8]. Some microorganisms have the property of interfering with the functions of the local immune system. Thus, mycoplasmas secrete adhesins, exo- and endotoxins, hemolysins, violating the barrier of local protection and promoting colonization of the lower and upper parts of the genitourinary tract by other bacteria [9-13]. Various properties of taxonomic groups of microorganisms are important not only because of the development of pathological inflammation, but also from the standpoint of violations of the homeostasis of reproductive organs. Currently, the study of the human microbiome in the context of the development of certain diseases, including reproductive health disorders, passes only the stage of knowledge accumulation [14].

Both microorganisms and the endometrium itself carry an equal burden in the pathogenesis of CE. Whether the penetration of microbial agents into the uterine mucosa occurs, whether an inflammatory reaction develops, whether it ends or becomes abnormally chronic determines not only the virulence of the microorganism, but also the state of the host immune system, which, in turn, is associated with genetic determinants and the totality of the host's immune system. previously rescheduled a number of events [15]. Of course, the formation of CE, a postinfectious inflammatory syndrome that is histologically associated with the formation of special protein complexes (inflammasomes) in macrophages and neutrophils of the endometrium and is accompanied by hyper production of proinflammatory cytokines that support the inflammatory process after the agent is eliminated, also depends on the immune system. Inflammasomes play an important role in the innate immune system; they are formed in macrophages and neutrophils and trigger an inflammatory response when the cell comes into contact with microorganisms [16]. It is shown that inflammasomes are not always destroyed after pathogen elimination and can support aseptic inflammation by stimulating the production of caspase and inflammatory cytokines-tumor necrosis factor (TNF)- α , interleukin (IL) - 1b and IL-18. Mechanisms of innate antimicrobial resistance are supported by immune system effectors-Toll-like receptors (TLRs) [17-19].

Results and discussions

Microbial agents binding to TLRs activate macrophage-monocyte cells that produce pro inflammatory cytokines that provide an innate immune response aimed at eliminating bacteria and viruses [19]. Expression of TLRs in the genital tract has been proven [18], and it is believed that immune responses against pathogens in the endometrium are carried out due to activation of TLRs types 2, 3, 4, and 9. In addition to TLRs, other effectors of the immune system are involved in innate immunity reactions: dephenzines, secretory inhibitors of leukocyte protease, which depend on hormonal fluctuations [18]. Activation of TLRs and other effectors in the immune system leads to the expression of a large number of hemokines and proinflammatory cytokines, which are involved in protecting the body from bacterial and viral infections, carry out communication between the immune, endocrine, and hematopoietic systems, and regulate a single protective response [18]. In conditions of persistence of the microorganism, factors of innate immunity maintain the inflammatory status. Probably, the genetic predisposition to hyper expression of the innate immunity factors may be one of the reasons for the preservation of the inflammatory response after the elimination of the infectious pathogen. Thus, the persistence of the microorganism or the features of the local immune defense become the basis for the development of a cascade of secondary injuries, as a result of which the inflammatory reaction does not end, the regeneration of the any tissue does not occur, and a pronounced cellular imbalance occurs. Typical manifestations of this imbalance include: an increase in the content of killer cells (CD56+, CD16+); a decrease in T-suppressors (CD8+); a change in the ratio between proinflammatory and regulatory cytokines; an increase in HLA-DR+; and an increase in IgM, IgA, and IgG titers. Elevated levels of IL-1 and IL-6 are associated with the expression of steroid sulfatase, which affects the biological activity of estrogens in the endometrium and causes impaired transferability and normal cephalic tissue transformation. The complexity of the situation lies in the fact that for normal reproduction, inflammation is a necessary component that ensures endometrial proliferation and implantation. So, royal naturale killers (NK) cell populations of lymphocytes (CD56bright and CD16dim) are normally found both in the endometrium outside the gestation and in the decidual tissue. Apparently, NK cells play a significant role in the onset of pregnancy, although their exact functions remain unknown [20]. Changes in the number or function of NK cells may play a role in early pregnancy loss. Immunohistochemical analysis showed an increased density of CD56 bright CD16-NK cells in the middle secretory phase of the endometrial cycle in women suffering from idiopathic prenatal

miscarriage[21, 22]. Consequently, in CE, we are not talking about the existence of inflammation as such, but about a violation of the balance of inflammatory and coanti-inflammatory factors in relation to the phases of the menstrual cycle and reproductive disorders, i.e., endometrial dysfunction. But long-term dysfunctional state inevitably leads the organ to structural changes. Endometrial dysfunction caused by inflammation is accompanied by disorders of vascular homeostasis and reparative processes in the uterus. A change in the balance of vasoconstrictor and vasodilator components of glandines creates a deficiency of endothelins, worsens vaso constriction, increases the content of nitric oxide in the endometrium – a powerful vasodilator, an antiplatelet agent released from the vascular endothelium, and finally enhances angio genesis, increasing the density of endometrial vessels. Microcirculation disorders occur, exudation and fibrin deposition in the endometrial stroma are activated. Against the background of local fibrinolytic activity depression, increased angiogenesis provokes hyperplasia of connective tissue and the formation of fibrotic junctions. As a result, the basis is created for the formation of structural changes in the endometrium – dystrophic, hyperplastic (more often focal) or sclerotic processes. In the implementation of the latter, the pathological distribution of collagens of type 1, 3 and 4 takes part, reflecting the rearrangement of the components of the extracellular matrix and their regulators in endometrial damage in women with CE. A trigger of similar stromal disorders, normally defined by the triad of "lymphocyte-macrophage-fibroblast", is a direct focus of the inflamed endometrium [23].

Clinical signs of HE reflect processes occurring in the endometrium, although the symptoms are usually scanty. Menstrual cycle disorders can be caused by prepost, and intermenstrual blood discharge (more often by blood anointing) [24]. Severe menstrual bleeding is possible, often accompanied by dysmenorrhea, but a number of authors do not find an association of CE with pelvic pain or abnormal uterine blood flow [25]. The intensity of inflammation is not related to the age of patients or the duration of symptoms [24], but the presence of CE itself is more likely in women with a history of sexually transmitted infections (STIs) and PID [24]. Diagnosis of CE is not an end in itself and is performed exclusively in those situations where there are clinically significant signs of endometrial dysfunction: idiopathic infertility, habitual miscarriage, repeated ECG failures or symptoms that reduce the quality of life. To confirm the diagnosis, it is recommended to perform ultrasound examination of the pelvic organs with Dopplerometry of uterine vessels; hysteroscopy and histological examination of the endometrium in the late proliferative phase of the menstrual cycle; microbiological research; and a number of immune histochemical studies.

Echographic signs of CE include: thinning of the M-echo and changes in the endometrial structure; unevenness of the closure line; expansion of the uterine cavity due to liquid content, visualization of gas bubbles in the uterine cavity; diffuse focal and cystic changes in the subendometrial zone of the myometrium. The effectiveness of ultrasound in the diagnosis of CE remains a subject of debate, varying in the judgments of researchers from indisputable reliability to questionable value, which encourages a differentiated application of the method [26, 27]. Measurement of endometrial thickness is important not so much in the diagnosis of CE as in determining the prognosis of fertility, especially in the context of assisted reproductive technology programs. Thus, a poor prognosis for the onset of beremia is established if the anteroposterior M-echo size is less than 8 mm during the implantation window [5, 28, 29]. The endometrial structure is evaluated for the same purpose: if the endometrial thickness in the secretory phase of the cycle is less than 8 mm, but more than 7 mm, with its normal structure and in the absence of Doppler signs of myocardial and endometrial ischemia, the prognosis for pregnancy is determined as favorable [30, 31]. Doppler imaging is also aimed not at diagnosing CE, but at establishing optimal conditions for participation in assisted reproductive technology programs, although the approaches to the optimal endometrial blood flow are controversial [32-35]. Obviously, the contradictory opinions are explained by the lack of detailed data on the peculiarities of uterine vascular blood flow in HE, but the task of determining these features is not even set due to the lack of clear diagnostic criteria for HE itself. Direct visualization of signs of CE is performed during liquid menohysteroscopy, which allows you to identify signs of inflammation and structural disorders of the endometrium, including characteristic micropolyps and intrauterine adhesions. Histological examination of endometrial biopsy claims to be the "gold standard" for the diagnosis of but the incompleteness of the understanding of the biological basis and etiopathogenesis of CE is hindered by identification of morphological criteria of the disease.

In addition, there is no uniform approach to the methods of biopsy material collection [25], and the interpretation of histological sections can be too subjective [36].

Criteria for the morphological diagnosis of CE are: inflammatory infiltrates consisting primarily of lymphoid elements, located more often around glands and blood vessels, less often diffusely; focal infiltrates have the form of "lymphoid follicles" and are located not only in the basal, but also in all parts of the functional layer, in comp. they also include leukocytes and histiocytes; the presence of plasma cells; focal fibrosis of the plasma, which occurs during a long course of chronic inflammation, sometimes covering large areas; sclerotic changes in the walls of the spiral arteries of the endometrium. But even these seemingly established signs are being challenged. In particular, plasma cells are detected not only in CE, but also in the asymptomatic course of infections, as well as in fertile healthy women; however, plasma cells are detected in hormone-mediated intrauterine disorders associated with changes in vascular architectonics against the background of anovulation, or acute disintegration [37, 38]. In addition to morphological examination, it is possible to perform an immune histochemical assessment of the endometrium [22, 39], but this also does not allow a convincing diagnosis of CE. Thus, there is no single approach to the diagnosis of CE, and even a morphological study has a number of limitations that do not allow it to be used as the "gold standard" for disease verification [40]. And since the diagnosis of CE itself does not determine the management tactics of patients, which is built up depending on the characteristics of reproductive disorders, clinical picture, the presence of infectious diseases and other factors, its determination can be carried out on the basis of clinical and laboratory data without histological confirmation.

Differences in the morphological interpretation of CE are due to the presence of variants that are determined by the characteristics of general and tissue reactivity, the etiological factor, the severity of the disease, the presence of exacerbations and the degree of their severity. Long-term course of CE leads to the formation of secondary morphofunctional changes in the endometrium, which consist in the activation of sclerotic processes with damage to the extracellular matrix, a violation of the mediator functions, cell-cell interactions, changes in the angioarchitectonics of tissue tectonics, and the development of its ischemia. Disorders of endometrial functions are accompanied by violation of the immune barrier, which predisposes to relapses of an infectious lesion involving conditionally pathogenic microflora of the vaginal-cervical ecosystem.

The significance of infection in the persistence of chronic endometrial inflammation is often disputed, and the argument in this discussion is the evidence of endometrial sterility in patients with confirmed CE. Indeed, the undoubted role of the infection factor in the etiology of endometritis does not exclude its presence in the chronic inflammatory process. However, the predisposition of such patients to infectious relapses and the low-symptomatic development of endometritis justify the point of view on conducting antibacterial therapy at the slightest signs of exacerbation or even in the presence of conditionally pathogenic microflora in the vaginal discharge, which creates the potential for these exacerbations. If there are doubts about the feasibility of prescribing antibiotics to a clinician, it is worth asking what exactly they are going to treat: antibiotics are a means of treating infectious diseases, including not only PID, but also vaginal infections. On the other hand, CE, infertility, and habitual miscarriage in the absence of clinical and laboratory signs of infection do not require antibiotic therapy [41]. Therefore, in addition to antibiotic therapy, a comprehensive program for the treatment of CE and related disorders

It provides for the correction of immune disorders and prevention of structural changes in the endometrium, mainly dystrophic and sclerotic processes [42, 43].

If infectious invasion is suspected or there is a high risk of infection, patients with CE should be prescribed antibiotics in accordance with the principles of PID treatment. Traditional risk factors for PID are considered among the factors that determine the expediency (necessity) of using antibiotics in patients with CE: a large number or frequent change of sexual partners, a history of STIs in the patient or her sexual partner, instrumental interventions on the uterus that can lead to a violation of the cervical barrier, termination of pregnancy, intrauterine contraceptive administration, hysterosalpingography, IVF [44]. Antimicrobial therapy for PID is always empirical, since the identification of a microbial agent is difficult, microbiological research is often uncorrected, and its implementation takes time [8, 45, 46]. Medications used in patients with CE should have a wide range of effects and be effective against *N. gonorrhoeae* and *C. trachomatis*, (a negative result of routine testing does not exclude the presence of these obligate pathogens in the upper reproductive tract), drugs with activity against anaerobic

infection are prescribed at the same time. Treatment should be initiated as soon as a suspected diagnosis of PID is made, because prevention of long-term consequences depends on early administration of antibiotics. Since isolated endometritis has no pronounced clinical symptoms, its treatment is usually performed on an outpatient basis using oral medications. It has been shown that in women with mild to moderate PID, oral antibiotics have similar efficacy to that of parenteral drugs, but the duration of the course of treatment should be 2 weeks, both in outpatient and inpatient settings. A differentiated approach to the selection of antimicrobial therapy is valid for detecting etiologically significant infections in microbial associations [47] in patients who do not have clinical signs of PID and are receiving antibiotic therapy for other reasons. In recent years, the use of therapy methods that increase the body's non-specific resistance and normalize the immune system's activity has significantly increased in the complex of treatment measures for CE. Somehow, the vector of the course of the disease changes from an infectious lesion to the formation of

If there is a persistent inflammatory reaction, the question arises of changing the treatment direction from antibiotic therapy to immunomodulators, drugs that improve endometrial trophism, and physiotherapeutic factors [48-50]. But this shift should not be taken literally, as a sequence of actions involving the end of one stage before the start of another. The formation of pathological inflammatory reaction should be prevented at the very beginning of its development, even during antibiotic therapy, which is simultaneously designed to improve the results of the use of antibacterial or antiviral agents.

Even at the initiation of antibiotic therapy, the question arises of ensuring its maximum availability. Any lesion, including an infectious lesion, is confined to healthy tissues by fibrin deposition during a local inflammatory response. The mechanism of development of the product phase of inflammation is associated with stimulation of fibroblasts by products of connective tissue destruction and cytokines synthesized by macrophages.

Fibrosis is a universal process based on the accumulation of extra cellular matrix proteins and compaction of connective tissue with the formation of scarring, which usually occurs as a result of chronic inflammation, while sclerosis is a replacement of the organ parenchyma with a dense connective tissue, accompanied by the death of functional elements. Fibrin deposition is associated with two adverse consequences. First, the attempt of the organization to limit the focus of inflammation, which is understandable from the point of view of preventing the spread of infection beyond its borders, worsens the access of medicines and reduces the ineffectiveness. Secondly, in the presence of repeated episodes of inflammation and its chronic course, fibrosis leads to hemodynamic disorders and morphological changes in the stroma with impaired endometrial function. Therefore, the suppression of fibrin formation is one of the priority tasks of CE therapy. The most common method of influencing connective tissue with the aim of preventing its hyperplasia is depolymerization of the extracellular matrix by enzymes such as hyaluronidase.

Hyaluronidase cleaves the main component of the interstitial connective tissue substance, hyaluronic acid - a mucopolysaccharide, which includes acetylglucosamine and glucuronic acid, and which is a cementing substance of connective tissue.

Under the action of hyaluronidase, hyaluronic acid is reduced to glucosamine and glucuric acid with a simultaneous decrease in its viscosity. At the same time, tissue and vascular permeability are increased, and the diffusion of liquids in the interstitial space is facilitated. Unfortunately, the therapeutic effect of enzyme preparations is low due to the instability and rapid destruction in biological media, pyrogenicity, toxicity with parenteral administration, and antigenic foreignness to the body. The task of stabilizing the enzyme and improving its pharmacological characteristics was solved by creating Longidase prepartate, a conjugate of hyaluronidase with a high molecular weight carrier, which resulted in a prolonged, thermostable form of hyaluronidase that is resistant to denaturation and inhibitors. At the same time, the pharmacological carrier has its own biological activity, acting as an immunomodulator, detoxifier, and antioxidant with moderately pronounced anti-inflammatory properties.

Longidase ®: therapeutic possibilities and efficacy

Drug bovgialuronidase azoximer (Longidase ®) It exhibit santifibrotic properties, weakens the course of the acute phase of inflammation, regulates (increases or decreases, depending on the initial level) the synthesis of inflammatory mediators (IL-1 and FNЛ-α), increases the humoral immune response and the body's resistance to infection. As an enzyme preparation, Longidase ® solves two important tasks for the treatment of CE: it improves tissue permeability for antibiotics and prevents excessive fibrin deposition resulting in tissue sclerosis [1, 51]. Together with the biologically active carrier azoximer, bovgialur onidase becomes multifunctional drug capable of suppressing the acute phase of inflammation, preventing reactive

growth of connective tissue, and causing the reverse development of fibrosis (but not sclerosis!). fabrics [52]. Experimental preclinical tests of Longidase demonstrated the absence of antigenic properties, allergizing, embryotoxic, teratogenic and carcinogenic effects.

Longidase® is available in two dosage forms-lyophilizate for the preparation of a solution for injection containing 3000 IU and rectal /vaginal suppositories-3000 IU, which are widely used in outpatient practice. The drug is prescribed by 3000 IU intramuscularly once every 3 days for 5-10 injections, and in the form of rectal or vaginal suppositories-1 suppository after 2 days with a total course of 10 injections. If necessary, maintenance therapy is prescribed.

Clinical studies of the effectiveness of Longidase have demonstrated its significant therapeutic potential in CE. When comparing the results of treatment of patients with CE in the period of infectious exacerbation using antibacterial therapy or complex therapy, including Longidase, the microbial and scape of the cervical canal and uterine cavity significantly differed, characterizing the best microbiological outcome in patients who received complex therapy [53]. In another comparative study.

Conclusion

A study of the use of Longidase in complex therapy of CE, accompanied by the formation of intrauterine splices, yielded results indicating a high anti-adhesive effectiveness of the drug when used after the destruction of intrauterine synechiae [54].

These data expand the possibilities of treatment of CE and associated diseases and reproductive disorders. Close attention to chronic inflammation should not remain a purely theoretical interest. The fact that immunomodulatory and enzyme therapies do not have a convincing evidence base does not justify the absence of effective monitoring of the formation of chronic inflammation and its harmful consequences. Many issues related to CE are far from being resolved, and the accumulation of information should occur not only in the field of theoretical research, but also in the practical activities of clinicians, of course, provided that unregistered medicines are used. Longidase ® is a medicinal product that has passed the entire required set of preclinical and clinical studies and received registration and an International unpatented Name (INN) All peaceful health organizations. The safety and proven efficacy of Longidase allow for increased use of this preparation in the treatment of intrauterine pathology associated with inflammation.

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