VAGINITIS AND CERVICITIS: MODERN APPROACHES AND VIEWS ON THE CHOICE OF AN EFFECTIVE TREATMENT METHOD

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Annotation. *Among gynecologic diseases in women of reproductive age the leading place is occupied by inflammatory diseases of the lower genital tract (70%), most of which are inflammatory processes of the vagina and cervix. The article presents the results of proteomic studies of cervicovaginal fluid in the early diagnosis of inflammatory diseases of the lower genital tract and the possibility of using cytokine biomarkers in clinical practice to predict the pathological state and the choice of further tactics of treatment of patients. The effectiveness of a combined preparation based on chlorhexidine and dexpanthenol, which has a pronounced antimicrobial, regenerating and metabolic action and is used in the treatment of acute and chronic vaginitis, is considered.*

Keywords: *inflammation, chronic vaginitis, pathologic condition, vagina.*

ВАГИНИТЫ И ЦЕРВИЦИТЫ: СОВРЕМЕННЫЕ ПОДХОДЫ И ВЗГЛЯДЫ НА ВЫБОР ЭФФЕКТИВНОГО МЕТОДА ЛЕЧЕНИЯ

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Аннотация. *Среди гинекологических заболеваний у женщин репродуктивного возраста ведущее место занимают воспалительные заболевания нижних отделов полового тракта (70%), большую часть из которых составляют воспалительные процессы влагалища и шейки матки. В статье представлены результаты протеомных исследований цервиковагинальной жидкости в ранней диагностике воспалительных заболеваний нижних отделов полового тракта и возможности использования цитокиновых биомаркеров в клинической практике для прогнозирования патологического состояния и выбора дальнейшей тактики лечения пациенток. Рассмотрена эффективность применения комбинированного препарата на основе хлоргексидина и декспантенола, обладающего выраженным антимикробным, регенерирующим и метаболическим действием и применяемого при лечении острых и хронических вагинитов.*

Ключевые слова*: воспаление, хронический вагинит, патологическое состояние, влагалище.*

VAGINIT VA SERVITSIT: SAMARALI DAVOLASH USULINI TANLASHDA ZAMONAVIY YONDASHUVLAR VA QARASHLAR

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Annotatsiya. *Reproduktiv yoshdagi ayollarda ginekologik kasalliklar orasida etakchi o'rinni pastki jinsiy yo'llarning yallig'lanish kasalliklari (70%) egallaydi, ularning aksariyati vagina va bachadon bo'yni yallig'lanish jarayonlari. Maqolada pastki genital yo'llarning yallig'lanish kasalliklarini erta tashxislashda servikovaginal suyuqlikning proteomik tadqiqotlari natijalari va patologik holatni bashorat qilish va bemorni keyingi davolash taktikasini tanlash uchun klinik amaliyotda sitokin biomarkerlaridan foydalanish imkoniyati keltirilgan. Aniq mikroblarga qarshi, regenerativ va metabolik ta'sirga ega bo'lgan va o'tkir va surunkali vaginitni davolashda qo'llaniladigan xlorheksidin va dekspantenolga asoslangan kombinatsiyalangan preparatni qo'llash samaradorligi ko'rib chiqiladi.*

Kalit so'zlar: *yallig'lanish, surunkali vaginit, patologik holat, qin.*

Introduction.

Data from a number of authors indicate a variety of etiological factors leading to the development of vaginitis and cervicitis: infectious of specific etiology (gonorrhea, chlamydia, syphilis, tuberculosis, actinomycosis, granuloma inguinale, lymphogranuloma); viral (herpes simplex virus; fungal, caused by Candida spp., protozoal trichomoniasis, amebiasis); inflammation associated with systemic inflammatory diseases (nodular polyarteritis, Behcet's syndrome) and neoplasia; infectious of nonspecific etiology (bacterial vaginosis, mechanical, physical, chemical injuries) [1, 2].

Particular attention has recently been paid to non-specific vulvovaginitis (NVV), in which one opportunistic microorganism displaces other members of the microbial community, which is accompanied by a pronounced local leukocyte reaction and other

signs of inflammation. The main etiologic factors of NVV are mainly representatives of enterobacteria (E. coli, Klebsiella, Proteus, Bacteroides, Staphylococci, Streptococci, etc.). NVV may be associated with poor hygiene, trauma to the external genitalia and vagina, allergic conditions, concomitant gynecological and extragenital pathology. Clinical manifestations of NVV are hyperemia and edema of the mucous membrane of the vulva and vagina, leucorrhoea. In some cases, NVDs occur with scanty clinical symptoms, and are exacerbated by intercurrent diseases and hypothermia.

The cervix and vagina represent a single ecological system, the anatomical structure and function of which contribute to the maintenance of normal biocenosis, which protects the female reproductive system from the introduction of pathogens of specific or non-specific etiology and the occurrence of an inflammatory process. Early onset of sexual activity, neglect of barrier methods of contraception, promiscuity, and violation of the anatomical integrity of the cervix are cofactors for infection with STIs with the subsequent development of chronic cervicitis [3].

Cervicitis of non-specific etiology is characterized by an inflammatory process of the cervix, which often becomes chronic. In this regard, much attention is paid to the search for diagnostic markers of inflammation in order to predict and treat the disease.

Local immunity and vaginal microflora.

The human microbiota is a complex ecosystem of diverse microorganisms consisting of bacteria, viruses and fungi that reside predominantly in epidermal and mucosal habitats throughout the body, such as the skin, oral cavity, lungs, intestine and vagina. The female reproductive tract has a unique microenvironment consisting of diverse microbial communities. The nature of the vaginal microbiota is well known. The primary function of the vaginal microbiome is to protect against pathogens and other toxic factors, while maintaining a symbiotic relationship with commensal microbes. These characteristics are common to all mucosal tissues of the genital tract, since in addition to its role in defense, it plays a critical role in reproduction by mediating local immune tolerance to fetal/paternal antigens, trophoblast invasion and angiogenesis [4]. The mucous membranes of the genital tract play an important role in creating protection against the invasion of pathogenic microorganisms. One of the barrier mechanisms is the secretion of glycocalyx, which is a complex multicomponent system, the structure of which is determined by a group of proteoglycans, glycoproteins and glycosaminoglycans. As a result of this process, the mucous membrane is moistened and the adhesion of bacteria to epithelial cells is prevented [4–9]. The term “local immunity” refers to a complex of adaptive reactions of various natures that provide protection for body tissues that communicate with the external environment. An important role in the formation of immunity is played by a single structured system called “mucosal-associated lymphoid tissue” (MALT). The function of this system is aimed at maintaining the body's homeostasis and the formation of immunity, and is realized through the cellular (macrophages, neutrophils, and lymphocytes) and humoral links (immunoglobulins, eicosanoids (prostaglandins and leukotrienes), lactoferrin, lysozyme, properdin, complement, cytokines, etc.).

The bulk of the normal vaginal microflora is made up of lactobacilli (Lactobacillus crispatus, Lactobacillus iners, Lactobacillus jensenii). The microflora also contains obligate anaerobic microorganisms in lower concentrations.

Glycogen, which is metabolized to glucose, is necessary for the production of lactic acid, which maintains the pH of the vaginal environment at a low level (3.8–4.5), and is then used by the vaginal flora [6–9]. In addition, certain types of lactobacilli, such as Lactobacillus crispatus, are capable of producing hydrogen peroxide in high concentrations, which are lethal to pathogenic microorganisms.

A number of factors suppress the growth of foreign bacteria and have an antimicrobial effect that helps maintain normal vaginal microflora. This property is possessed by bacteria that produce a wide range of antimicrobial peptides (bacteriocins), lysozyme, and amino acids. In addition, microorganisms of the resident flora can compete with non-resident bacteria for the availability of nutrients [4, 5, 9, 10].

The adaptive mechanisms of local immunity of the lower genital tract are well known.

Dendritic cells (DC), located in the mucous membranes of the genital tract, are important regulators of the immune response, capable of presenting antigens to T lymphocytes and initiating both innate and adaptive immune responses [6, 11]. DC have a powerful antigen-presenting ability to stimulate naive and effector T cells [11–18]. During the development of the adaptive immune response, T cells come into direct contact with DC, from which they receive a peptide antigen presented in a complex with MHC class I and II molecules on the surface cell membrane of DC.

Plasma cells (plasma cells) secrete immunoglobulins IgG and secretory IgA into the cervicovaginal fluid, forming humoral (non-cellular) immunity. In turn, immunoglobulins promote activation of other immune system cells by preventing bacterial adhesion and opsonization of pathogens [5].

Thus, cervicovaginal fluid (CVF), consisting of secretions from the sebaceous, sweat, Bartholin and Skene glands, plasma transudate, exfoliated epithelial cells, bacterial products, cervical mucus, endometrial fluid and fallopian tubes, is an important component of local immunity of the female genital system [12]. By washing the lower parts of the female

genital organs and moisturizing the mucous membrane, CVF creates a physical barrier to microbial invasion.

Inflammation is part of a nonspecific immune response, representing a vascular tissue reaction to any damage. The inflammatory process has a protective and adaptive nature, aimed at destroying the agent that caused the damage and restoring the damaged tissue. Morphological changes that characterize the inflammatory process consist of three interrelated components: alteration, exudation and proliferation.

Acute and chronic inflammatory process.

A long-term inflammatory process can acquire a chronic course, i.e., become chronic [13].

In acute inflammation, including vulvovaginitis, cervicitis, vascular tissue returns to normal activity by liquefying and removing exudate and cellular debris by macrophages and the lymphatic system. If the damaging agent is not neutralized during the acute process, an immune response develops, which leads to chronic inflammation.

The nature of the inflammatory process determines the severity of pathological changes in the stromal and epithelial components of the cervix.

In chronic cervicitis in the stratified squamous epithelium, transient disturbances of the nuclear-cytoplasmic ratio, changes in the form of hyperkeratosis, acanthosis, cell polymorphism, a decrease or absence of glycogen in the cells of the stratified squamous epithelium (SPE) are possible. Similar changes occur in cervical intraepithelial neoplasia.

Most often, chronic cervicitis is combined with cervical pathology, contributes to the violation of differentiation of metaplastic epithelium, long-term persistence of high-oncogenic risk HPV and, ultimately, the development of CIN in 13.2% of cases. Isolated chronic cervicitis is diagnosed in 39.7% of cases.

Cytokines and other inflammatory markers are involved in local and systemic changes developing against the background of the inflammatory process. It is not possible to completely suppress the inflammatory response in the chronic process, and, therefore, the synthesis of cytokines remains quite high. This leads to the formation of a vicious circle, in which the balance between pro- and anti-inflammatory cytokines is disturbed. In this case, anti-inflammatory agents (glucocorticoids, catecholamines), not being able to eliminate the source of inflammation, significantly suppress Th1 lymphocytes, while having virtually no effect on Th2 cells. The production of cytokines (IL-4 and IL-5), which are mediators of the synthesis of low-affinity IgE antibodies by plasma cells, increases as a result of the resulting shift in favor of Th2.

Fibroblasts, endothelial and other somatic cells, as well as many proteins and / or glycoproteins that are produced by activated lymphocytes and the monocyte-macrophage system, form a cytokine network.

Common properties that unite cytokines are: participation in the formation of immune and inflammatory reactions (serve as mediators); act as growth factors, influencing cell proliferation and differentiation; form a regulatory network and have multifunctional activity with overlapping functions.

Ensuring the coordinated action of the immune, endocrine and nervous systems in the development of an inflammatory reaction is one of the most important functions of the cytokine system. A number of studies have shown that a massive release of proinflammatory cytokines (IL-1β, IL-6, IL-12, TNF-α, IL-8) occurs at the site of infection.

Choice of therapy.

The choice of an effective method of therapy is of great importance in the management of patients with infectious processes of the genitals (vulvovaginitis, cervicitis).

The individual choice of a drug depends on the clinical course of the disease, the results of clinical and laboratory studies, as well as on the characteristics of the drug's action, indications and contraindications for its use, the possibility of purchasing the drug, etc. The main routes of drug administration are systemic and local (local).

Local therapy has a number of advantages: rapid penetration into the source of infection and rapid action, no systemic effects, minimal risk of side effects, the possibility of use in patients with extragenital pathology (especially in localized forms of the infectious process: acute vulvitis, vaginitis, cervicitis or exacerbation of chronic processes of the vagina and cervix), convenience and ease of use.

Currently, in mixed vaginal infections with a dominant role of opportunistic microorganisms and anaerobes-bacteroids, it is preferable to use combination drugs that can eliminate a wide range of pathogenic microorganisms. One of such drugs is Depantol®. The active ingredients of Depantol® vaginal suppositories are chlorhexidine bigluconate, dexpanthenol and polyethylene oxide base (PEO), due to which it has an antiseptic, regenerating and metabolic effect (antiseptic + reparant complex) [16]. Chlorhexidine is active against most pathogens of vaginal and cervical infections (Treponema pallidum, Chlamidia spp., Ureaplasma spp., Neisseria gonorrhoeae, Gardnerella vaginalis, Bacteroides fragilis, Escherichia coli, Staphylococcus spp., Streptococcus spp.), including yeast, dermatophytes, protozoa (Trichomonas vaginalis) without developing resistance to it [16], which corresponds to the "Strategy for preventing the spread of antimicrobial resistance". Dexpanthenol stimulates the regeneration of mucous membranes due to the effect on cellular metabolism, acceleration of mitosis and increase in the strength of collagen fibers. Dexpanthenol also has pronounced anti-inflammatory properties. An important fact is the absence of cross-resistance of

both components and systemic antibiotics. The active PEO base, in turn, has a destructive effect on biofilms and creates the prerequisites for clinically rapid relief of discomfort. Depantol® is officially registered for the treatment of acute and chronic vaginitis, exo- and endocervicitis, bacterial vaginosis and is widely used in obstetric and gynecological practice [16].

It has been established that chlorhexidine has no effect on the resistance of bacteria to antibiotics [17]. Many years of experience in use and the results of scientific research have not provided statistically significant evidence of the emergence of chlorhexidine-resistant microorganisms. The increase in the resistance of microorganisms to the bactericidal effect of chlorhexidine directly depends on the doses used. As studies show, the use of chlorhexidine in the range of single doses (0.2–2 mg) can cause the emergence of strains of microorganisms for which the minimum inhibitory concentration (MIC) is higher compared to the initial values. In this regard, chlorhexidine in a single dose of 16 mg (vaginal suppositories and vaginal tablets Hexicon®, vaginal suppositories Depantol®) has an advantage over low-dose forms. An additional strong argument in favor of choosing the local medicinal products Depantol® and Hexicon® in the form of vaginal suppositories is their hydrophilic polyethylene oxide (PEO) suppository base (98% – PEO 1500 and 2% – PEO 400), which has an adsorbing effect. The osmotic effect of PEO lasts much longer – for 15–20 hours, at human body temperature it spreads over the vaginal mucosa and ensures uniform distribution of the active substance. Due to its hydrophilicity, the substance adsorbs pathological secretions well, promotes cleansing of the mucous membrane of the genital tract and penetration of the active substance into tissues [19, 20].

A systematic review and meta-analysis of randomized controlled trials to evaluate the effect of daily care using chlorhexidine (CHX) wipes on overall rates of hospital-acquired bloodstream infections (HABSI) and catheter-associated bloodstream infections (CABI) in adults and children in the intensive care unit showed a positive effect on gram-positive and gram-negative microorganisms. The studies were unblinded cluster-randomized crossover trials that included 22,850 patients from 15 adult and 10 pediatric intensive care units. A statistically significant reduction in the overall number of HABSI was found in patients using CHX wipes (OR: 0.74; 95% CI: 0.60–0.90; p = 0.002) (I2 = 36%) [21]. In the study by M. Climo et al. the incidence of CAI was 53% lower in the group with CG compared to the control group [22]. S. Bleasdale et al. found a lower risk of CAI in the group with CG compared to the control group [23]. The study by A. Milstone et al. also found a decrease in the incidence of bloodstream infections in patients with a central catheter (p = 0.03) [24].

The results of a comparative study showed that the use of Depantol® at 36–37 weeks of pregnancy in women with risk factors for soft tissue injury can significantly reduce the incidence of birth trauma due to the normalization of cellular metabolism, increased strength of collagen fibers, elasticity and extensibility of the birth canal [25]. The use of vaginal suppositories Depantol® helps to reduce the number of repeated biopsies and the physiological course of the postcoagulation period in physiosurgical treatment of cervical pathology, which ensures normal epithelialization of the cervix and reduces the number of complications [26-28]. It is important that the drug does not have a negative effect on the level of lactobacilli. A randomized, double-blind, placebo-controlled study examined dexpanthenol on the function of the epidermal barrier in vivo. Seven-day treatment with dexpanthenol improved hydration of the stratum corneum and reduced transepidermal water loss. The results showed that local use of dexpanthenol improves the protective function of the skin [29]. Dexpanthenol penetrates well into the skin and mucous membranes, promotes moisturizing and strengthening the protective barrier. It prevents skin irritation, stimulates regenerative processes and promotes the healing of various injuries. Dexpanthenol increases the molecular mobility of lipid and protein segments of the stratum corneum, modulates the expression of certain genes, and causes rapid wound healing [29]. Consequently, the use of a drug containing chlorhexidine and dexpanthenol for the treatment of vaginitis, cervicitis, accompanied by microtrauma as a result of inflammation, promotes their healing and restoration of the integrity of the vaginal mucosa and cervix.

Thus, one of the effective options for treating inflammatory processes in the lower genital tract is the use of combination drugs that not only have a broad spectrum of antimicrobial activity, anti-inflammatory action, but also increase the protective barrier of the mucosa. The complex drug Depantol® for topical use, which is approved for use during pregnancy, including the first trimester, fully meets these criteria.

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