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THE STATE OF LOCAL IMMUNITY IN BACKGROUND DISEASES OF THE CERVIX

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ABSTRACT

The article is devoted to the modern understanding of the etiopathogenesis of background and precancerous diseases of the cervix. The most important role in the occurrence of background and precancerous diseases of the cervix is played by environmental factors, i.e. exogenous and modifying factors, which may include trauma, inflammation, viral infection.

Background and precancerous diseases of the cervix occupy one of the leading places in the structure of gynecological pathology and represent a risk of cervical cancer.Cervical cancer ranks 3rd among malignant neoplasms of the female genital organs. In recent years, there has been an increase in the incidence of cervical cancer in patients younger than 40 years. It is known that the process of carcinogenesis is multi-stage and the preclinical existence of a tumor usually lasts for years. According to clinical studies, the transition of dysplasia to insitu cancer lasts about 3-8 years, another 10-15 years pass before the development of microinvasive cancer. In this regard, one of the primary tasks of gynecology, the ultimate goal of which is to reduce the incidence of cervical cancer, is the early diagnosis and treatment of background and precancerous diseases of the cervix.

The cervix has an autonomous immune system, represented by local and humoral immunity [11, 8]. Local immunity is formed by lymphoid structures and macrophages of the cervical stroma, immunoglobulins of classes A, M, G and locally secreted SIDA [2,4]. The first line of defense is IgA and IgM: IdM has hemolytic properties and neutralizing activity against bacteria and large viruses, and IgA is a typical immunoglobulin of the mucous membranes, whose main function is to block the adhesion of microorganisms to the epithelial cells of the mucous membrane [7,8]. IgG provides secondary immunity by blocking macrophages and stimulating suppressor tlymphocytes [2,4]. A significant role in protecting the genital tract is played by the complement system produced by the mucous membrane of the cervix and vagina. The complement attaches to IgA, which leads to the opsonization of microorganisms and subsequent phagocytosis by neutrophils. The state of local immunity is a decisive factor in determining the severity, duration and recurrence of inflammatory diseases of the cervix, papillomavirus lesions and CIN [1,3,5,7,9].

However, the immune system of pregnant women targets external stimuli even more aggressively, while forming immunoresistance to the fetus [1,4]. Steroid hormones have a

modulating effect on the function of local immunity of the cervix. Thus, estrogens contribute to an increase in the thickness of the vaginal epithelium, the secretion of mucins of the complement system. It was found that vaginal dysbiosis develops against the background of estrogen deficiency: the concentration of lactobacilli decreases and the number of fecal group bacteria increases [8]. There is no consensus on the effect of progesterone on local immunity. Thus, a number of authors believe that progesterone weakens the immune system; others, on the contrary, believe that when progesterone is administered, the number of Langerhans cells increases [2,4,6,8,10]. Given the dependence of the immune status on the level of estrogens, it can be assumed that against the background of estrogen deficiency, progesterone increases the risk of developing inflammatory diseases of the cervix and weakens local immunity, and against the background of normal or slightly elevated estrogen levels during pregnancy, this effect is absent.

The cervix and vagina belong to the organs located on the border of a woman's internal environment and an aggressive external environment. The protection of a woman's internal environment is provided by anatomical features, such as a closed genital slit and vaginal walls, the folding of the vaginal mucosa, closed external and internal pharynx, the length of a narrow cervical canal about 3 cm, the folding of its mucosa and the presence of thick mucus in the lumen. In addition, the cervix has an autonomous immune system consisting of lymphoid structures and macrophages of the stromal tissues of the cervix, humoral factors penetrating through the vascular wall from the blood – immunoglobulins of classes A, M, G, as well as locally secreted immunoglobulin A (sIgA). Class A immunoglobulins play a special role in immunological protection. Secretory Ig A is a typical mucosal immunoglobulin synthesized by plasmocytes of the interstitial tissue of the glands, it has the ability to neutralize viruses, i.e. it is the first antiviral barrier. The degree of protection of the mucous membranes correlates with the titer of locally formed antibodies [7]. The secretory system of immunoglobulin A is also a protection against autoimmune diseases and neoplasms, it affects the processes of adsorption and adhesion of microbial cells to the epithelium of the mucous membranes. According to the literature, the form and outcome of inflammation depend entirely on the usefulness of the immune response. When a woman's genitals are infected, the content of immunoglobulins in the cervical canal increases significantly, especially sIgA, since it blocks the adhesion of bacteria to epithelial cells and inactivates the resulting intermediate metabolic products and large molecules [2]. Literature data on the level of sIgA in cervical mucus in women with inflammatory diseases of the genitals are ambiguous. Thus, in patients with VZOMT in combination with vaginitis, an increase in the amount of secretory immunoglobulin A was found. This was explained by the presence of vulvovaginitis and accompanying dysbiosis. A direct correlation has been established between the increased level of SIdA in vaginal secretions and the severity of the inflammatory process of the vagina. The authors have suggested that the cause of sIgA activity is associated with the presence of vulvovaginitis, vaginal dysbiosis and is a phase of the immune response to the introduction of an infectious agent [3, 4]. In chronic vaginitis, the level of sIgA decreases, which is considered as a manifestation of a sharp suppression of local immunity in the chronic stage of vaginal inflammation [1,3].

The relationship between the level of secretory immunoglobulin A and the degree of colonization of the vagina with lactobacilli has been established [6]. Most researchers traditionally note changes in the indicators of general and local humoral immunity in chlamydia and papilomovirus infection [7], focus on a decrease in the level of sIgA in cervical mucus, an increase in the amount of IgG and IgM [8]. The majority of patients suffering from dyshormonal processes of the cervix have vaginal pathology, manifested by the clinical picture of vaginitis and/or bacterial vaginosis, with a decrease in the concentration of lactobacilli, an increase in the concentration of conditionally pathogenic microflora, sexually transmitted pathogens, and microorganisms associated with dysbiotic conditions of this ecological niche [9]. It should be assumed that background diseases of the cervix, accompanied by a change in the structure of the epithelium of the vaginal part of the cervix, should contribute to a certain extent to a change in the local immunity system.

The purpose of this study was to assess the state of local immunity in women with background cervical diseases.

Materials and methods. 4 groups of women were examined. The first group (control) consisted of 20 gynecologically and somatically healthy women. The second group (II) included 14 women with cervical leukoplakia confirmed by histological examination. The third group (III) is represented by 20 patients with ectopia. The fourth group (IV) included 69 women with cervical ectopia in combination with sexually transmitted infections (STIs). The average age of group II patients did not significantly differ from the control group. The examination algorithm was as follows: smears for oncocytology, the degree of purity of the vaginal contents, the tank. seeding from the cervical canal, examination for STIs by polymerase chain reaction, simple and extended colposcopy. In the presence of a pathological colposcopic picture, a targeted biopsy was performed followed by a histological examination of the biopsy. Local immunity was assessed by the sIgA index in cervical mucus, which was taken with a syringe with a catheter, homogenized by adding a five-fold volume of phosphate-salt buffer, pH =7.36 centrifuged. The sIgA study was carried out in a supraventricular fluid. The collection of cervical mucus was carried out in all women in the periovulatory period. The concentration of sIgA was determined using the sIgA – ELISA-BEST kit, designed for the quantitative determination of secretory immunoglobulin A in biological fluids by solid-phase enzyme immunoassay. For statistical processing of the material, the Statistica for Windows, Realease 6.0 application software package from StatSoft Inc., USA (2012) was used. The results of the study and discussion of the data obtained showed that ectopias are more common in younger women. They are a predisposing factor that determines the risk of developing concomitant infection. Areas of cylindrical epithelium on the cervix are the optimal environment for colonization by cocci, chlamydia, ureaplasmas and mycoplasmas. Pathogens persist for a long time in the mucous membrane of the exo- and endocervix and cause a pronounced inflammatory reaction [10]. The vaginal environment, which is aggressive for the cylindrical epithelium (pH of the vaginal contents, abundant flora), also contributes to the occurrence of the inflammatory process in ectopic areas. Distribution of examined women by age In women with pathological processes on the cervix, in almost 50% of cases, smears of the 3rd-4th degree of purity were established in the absence of any clinical manifestations of infection, bacterial vaginosis was diagnosed in another 30%. Group IV patients complained of

abnormal discharge from the genital tract for a long time. The inflammatory process in the vagina was confirmed by bacterioscopic examination. Bacteriological examination of the contents of the cervical canal revealed epidermal staphylococcus (35%), epidermal streptococcus (30%), Staphylococcus aureus in 20% of cases, mixed infection was detected in 15% of women. Ureaplasmas (37.5%), mycoplasmas (37.5%), chlamydia (25%) were found in patients with cervical ectopia in combination with STIs.

All women underwent simple and extended colposcopy. When leukoplakia was detected, a histological examination of the biopsy was mandatory. Leukoplakia was histologically characterized by the presence of hyperkeratosis, acanthosis, and diffuse infiltration of connective tissue by lymphocytes. The main signs were hyper- and parakeratoses. Analysis of the sIgA concentration in the mucus of healthy women revealed a wide range of individual indicators from 5.0 mg/l to 151.6 mg/l. The average level was 51.6±8.8 mg/l. In the group of women with cervical leukoplakia, the average sIgA index was significantly higher than in the control group and amounted to 75.9±23.2 mg/l ($p<0.02$).

The presence of ectopia on the neck also led to increased secretion of sIgA. In this group, the indicators were 84.2±10.1 mg/l, which is also significantly higher than in the control group ($p<0.009$). In women suffering from vaginitis, the concentration of immunoglobulin increased slightly and averaged 69.9±20.5 mg/l. The range of individual fluctuations was 7.14±63.2 mg/l. An almost similar pattern was observed in cases of combination of ectopia with STIs with an average of 67.9±22.0 mg/l.

An increase in the concentration of SIDA in women with nonspecific vaginitis and ectopia on the background of STIs characterizes the degree of tension of local immunity, which should increase depending on the strength and duration of exposure to the infectious agent. In women with background diseases of the cervix, there were no clinical manifestations of infection, although in 50% of cases, dysbiotic changes in the vaginal biotope occurred during bacterioscopic examination of the vaginal discharge, which, as a rule, are combined with cervical pathology [9]. However, according to literature data, vaginal dysbiosis is accompanied by a decrease in the level of SIdA [2, 8]. It remains to be assumed that an increase in the concentration of secretory immunoglobulin A correlates with morphofunctional changes in the cervix, which is under the constant influence of the endocrine system. This correlation is direct and significantly significant: with ectopia, $r=0.2688$, $p=0.008$; with leukoplakia, $r=0.3225$, $p=0.020$. SIdA is an indicator of the physiological state of the body, determines the degree of deviation from the physiological norm and can serve as a marker of changes in the body's regulation system.

Thus, the results of the study allow us to conclude about the participation of secretory immunoglobulin A in the processes of exocervix regeneration, which is confirmed by a significant increase in its concentration in patients with background processes on the cervix.

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