



DYNAMICS OF CLINICAL AND IMMUNOLOGICAL INDICATORS OF WOMEN WITH CERVICAL INTRAEPITHELIAL NEVIA PLASIA UNDER THE INFLUENCE OF IMMUNOCORRIGATING THERAPY

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ABSTRACT

Background: In the structure of gynecological diseases cervical pathology is 15-40%. Almost all of these infections occur against the background of a secondary immunodeficiency state and provoke its further development, aggravating the course of the disease. **Objective:** The results of complex examination and treatment of cervical intraepithelial neoplasia (CIN) in 64 women were studied. **Methods:** The level of cellular immunity parameters (CD3+, CD4+, CD8+, CD16+, CD25+ and CD95+) in the dynamics of treatment was studied. **Result:** It was identified that the evidenc- of immunological defect correlated with the nature of pathological changes in the cervical intraepithelial tissue, indicating the involvement of the immune system in the pathogenesis of CIN. Immunocorrection was showed out using the medicine "Bioflazid" in combination therapy. **Conclusion:** The recieved data confirm the effectiveness of "Bioflazid" in complex treatment, in which there is a positive dynamics of not only clinical indicators, but also the parameters of the immune system.

KEYWORDS: Cervical intraepithelial neoplasia, immunity, immunocorrection.

INTRODUCTION

In the structure of gynecological diseases cervical pathology is 15-40%.^[1,3] The most common cause of pathological conditions of the cervix is infectious processes, accompanied by long-term persistence of the pathogen in the genital tract.^[1] Inflammatory diseases have an extremely adverse effect on the reproductive function of women.^[4,6]

The complexity of effective treatment of cervical diseases is associated with the spread of infectious processes due to the associative nature of the microflora, in particular, the development of bacterial, viral-bacterial, viral-fungal-bacterial and other varieties of mixed forms of infection.^[5,6] Often mixed forms of infectious pathology have a potentiating effect^[10,11] and contribute to the formation of chronic, torpid for treatment, often recurrent diseases.^[3]

Clinically, this is accompanied not only by the development of local foci of infection with signs of chronic inflammation, but also the development of degenerative, atypical and other pathological processes.^[4] It is also noted that these infections do not leave behind a stable immunity. Observed repeated reinfection and relapses, which occur in symptomatic or inapparently the form.^[5,6] Among gynecological patients with inflammatory diseases of the genitals, their viral

nature was established in 25.4% of cases. Genital herpetic infection was detected in 16.8%, chlamydial urogenital infection in 21.8% and cytomegalovirus infection in 8.6% of cases.

Almost all of these infections occur against the background of a secondary immunodeficiency state and provoke its further development, aggravating the course of the disease.^[2,7] At the same time, there are changes in the cellular and humoral parts of the immune system, a decrease in the level of interferons, insufficiency in the phagocytosis system, as well as severe damage to immune cells of the mucous membranes, which manifests itself in the form of intestinal dysbacteriosis and vaginal microbiocenosis. This is natural in chronic viral and bacterial infection, and is an indicator of the reactivity of the body as a whole.^[8]

This leads to the fact that in recent years in gynecological practice immunocorrecting drugs are increasingly used.^[7,8] Immunomodulators are widely used in the treatment of herpetic infection, persistent papillomavirus infection and other infectious diseases of the genital tract.^[5] The most widely used drugs interferon series, interferon inducers, cytokine preparations.^[2]

The aim of the study was to conduct a comparative analysis of the parameters of cellular immunity in

women with infectious and inflammatory diseases of the cervix associated with cervical intraepithelial neoplasia.

SUBJECTS AND METHODS OF RESEARCH

Subjects

64 women with CIN I and II degrees aged 25 to 49 years were followed up, which averaged 36.8 ± 6.7 years. The diagnosis was based on the clinical picture and laboratory and instrumental examinations. Surveyed women were divided into 2 groups: the 1st group consisted of 31 women who received only basic treatment, the 2nd group consisted of 33 women, to standard treatment which included a drug "Bioflazid". "Bioflazid" was administered per os, starting with 15-20 drops per day, increasing the dosage to 30 drops per day in three divided doses. Patients of the main group were also local treatment "Bioflazid" in the form of applications and vaginal trays. For the preparation of baths 1.5 ml of the drug was diluted in 10 ml of saline. The course of treatment is 4 weeks. The control group consisted of 20 healthy women.

Methods of research

Immunological studies included quantitative determination of lymphocytes with phenotype CD3, CD4, CD8, CD16, CD20, CD25 and CD95 using monoclonal antibodies LT series (too, "Sorbent", Russia). Statistical processing of the data was carried out on a personal computer using a package of applications.

The effectiveness of the proposed treatment was evaluated by comparative analysis of clinical, instrumental and laboratory data.

RESULTS

From anamnesis it was found that most patients had no previous pregnancies (75.0%), no births (28.6%). Concomitant gynecological pathology (menstrual cycle disorder, hyperandrogenia or chronic salpingooforit) was revealed in 37.5% of the examined women (Fig.1). Due to the fact that the presence of STIs and opportunistic flora is one of the cofactors of HPV-associated diseases of the cervix, vaginal contents were examined (PCR method). Changes in the biotope were observed in 71.9% of patients, including significant changes, respectively, were found in 18.8% of women. Determination of human papillomavirus DNA by PCR revealed HPV type 16 in the majority of patients - 81.3%, HPV type 18 was diagnosed less frequently - in 37.5% of patients. Infection with herpes simplex virus was observed in 34.4% of the surveyed women. For the first time, HPV was diagnosed in 78.6% of women.

The majority of patients, chronic cervicitis combined with a pathology of the vagina: a clinically pronounced symptoms of vulvovaginitis were diagnosed in 71.9% of patients.

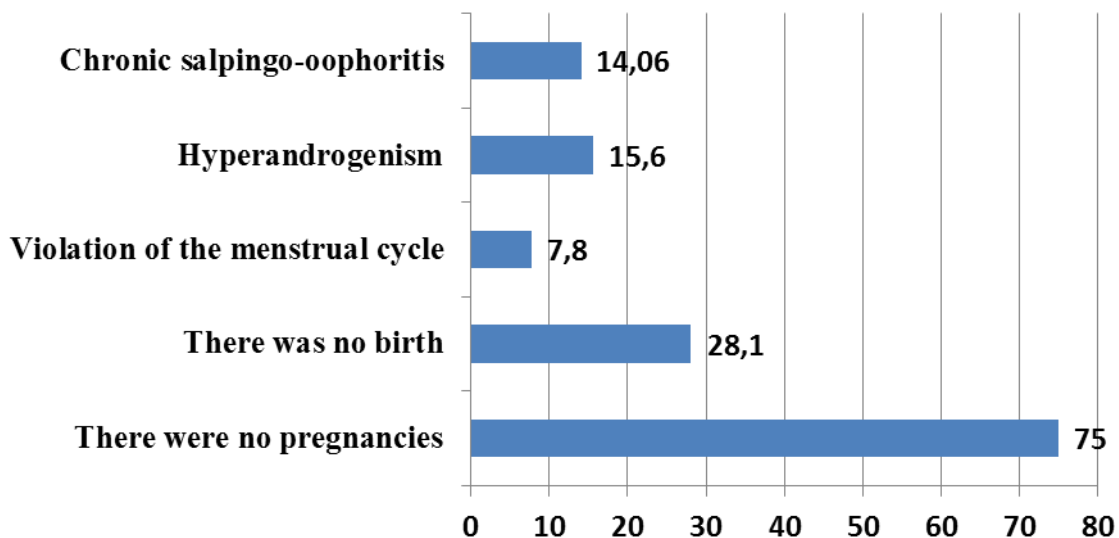


Fig. 1: Anamnestic patient data, (%).

Studies on the level of immunocompetent cells showed that the quantitative content of the total pool of T - lymphocytes in patients with CIN was significantly reduced ($P < 0.01$) (Fig.2). Analysis of subpopulation composition in these patients revealed that CD4+ lymphocyte levels were 1.17 lower than control values, and the number of CD8+ cells was 1.3 times higher than in women in the control group ($P < 0.01$).

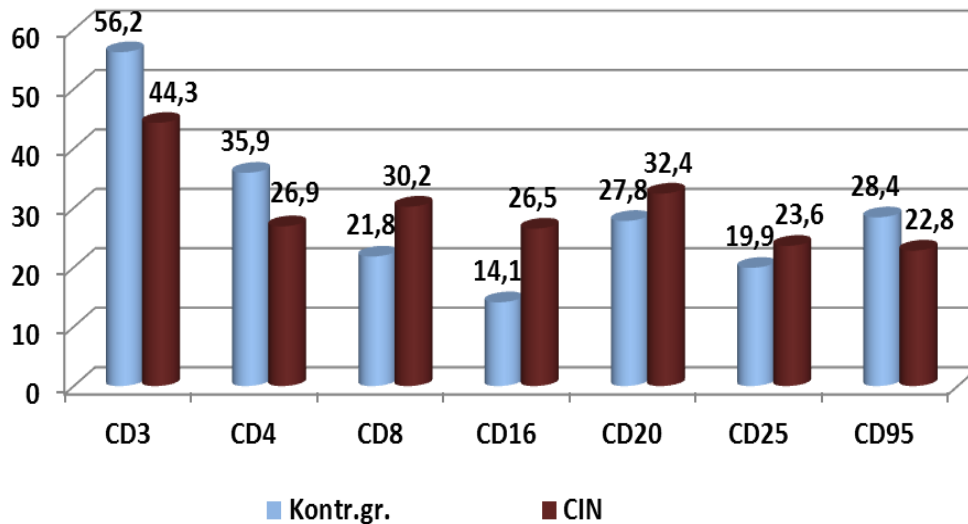


Fig. 2: Parameters of cellular immunity in examined women, %.

The level of lymphocytes with CD20 marker was significantly increased in comparison with the data of the control group ($P < 0.05$). CD25+ cell activation was observed in women with CIN ($P < 0.01$). The increase in the number of lymphocytes carrying the receptor for IL-2 (CD25+), and the level of secretion of IL-2 in patients with CIN should be considered as an adaptive reaction from the body to the course of the disease. Apoptosis processes play a significant role in the regulation of the immune response.^[7,8] Suppression of apoptotic cell death may be a possible factor increasing lymphocyte proliferation.^[2]

Our studies revealed a significant decrease in CD95+ lymphocytes in women with CIN in contrast to the indicators of women in the control group ($P < 0.01$). It is known that upon contact of NK cells in cell target received signal molecules, including the process of apoptosis (Yarilin, 1999) i.e., revealed in the present study, reduced levels of CD95+ may be due to, among other factors, increased content of natural killer cells.

Our studies have shown the presence of changes in the state of immunity in women with cervical intraepithelial

cervical neoplasia. Thus, the severity of immunological disorders is correlated with the nature of pathological changes in the cervical intraepithelial tissue. Since lymphocytes of subpopulation composition play an important role in the formation of antitumor immunity, the change in their level with the aggravation of clinical manifestations indicates the involvement of the immune system in the pathogenesis of CIN. In this regard, it can be assumed that the peculiarities of the immune system can play a significant role in ensuring predisposition or resistance to malignant tumors.

In the dynamics of basic treatment using hormones and antiviral therapy for 4 weeks there was a positive dynamics of clinical and immunological parameters. However, these changes did not reach the data level of the control group (table.1).

Table 1: Dynamics of cellular immunity parameters in examined women, ($M \pm m$), %.

Indicators	Control gr., n=18	Source data	Women with CIN	
			Basic therapy	Basic therapy + "Bioflazid"
CD3+	56,2 ± 1,2	44,3 ± 0,7*	51,6 ± 1,0* ^	55,8 ± 1,2*
CD4+	35,9 ± 0,7	26,9 ± 0,8*	31,9 ± 0,9* ^	34,5 ± 0,7*
CD8+	21,8 ± 1,1	30,2 ± 0,7*	26,8 ± 1,1* ^	24,9 ± 1,1*
CD16+	14,1 ± 1,6	26,5 ± 1,2*	20,3 ± 1,2* ^	16,1 ± 1,6*
CD20+	27,8 ± 1,0	32,4 ± 0,9*	32,4 ± 0,9* ^	27,6 ± 1,0*
CD25+	16,9 ± 0,8	23,6 ± 0,5*	29,8 ± 1,0* ^	20,9 ± 0,8*
CD95+	28,4 ± 1,1	22,8 ± 1,2*	25,3 ± 0,9* ^	27,4 ± 1,1*

Note: * significantly in relation to the control group

^ Significance in relation to the group before treatment ($P < 0,05-0,001$)

In the group of women who received bioflazid, the number of CD3+cells ($P<0.05$), T-helper /inducers ($P<0.01$) and T-suppressors/cytotoxic lymphocytes ($P<0.01$) significantly increased, and the level of killer activity significantly decreased ($P<0.01$). The content of lymphocytes with activation markers was normalized ($P<0.01$).

DISCUSSION

Thus, the main preventive measures aimed at early detection and overcoming the progression of HPV-associated cervical pathology may be:

- regular PAP test screening;
- colposcopic examination;
- HPV and viral load detection;
- antiviral therapy "Bioflazid" when the initial changes of the cervical epithelium, aimed at the normalization of the cytological picture and the suppression of viral activity.

To achieve good results, it is important to observe the dosage and duration of treatment. As noted above, the most dangerous in terms of the progression of dysplasia is the persistence of HPV, in which the virus is embedded in the genome of the epithelial cell. Antiviral action in this case should last several months to capture several cycles of complete renewal of the epithelium.

It is known that 57% of CIN I spontaneously regress ("pass themselves"), 32% remain in the form of CIN I for a long time, 11% progress in CIN II, CIN III, and only 0.5% — in invasive carcinoma. Unlike mild dysplasia, CIN III turns into invasive cancer in 12% of cases within 2 years, and regresses quite rarely.^[1,3] The effectiveness of treatment was evaluated in three stages. Immediately after completion of therapy, the clinical efficacy of treatment was analyzed, the pH level of vaginal contents was determined. After 5-7 days after the end of treatment, PCR examination and colposcopy were performed, after 3 months, extended colposcopy, swab sampling on HPV, STI, cytological examination of smears from the cervix were performed. Immediately after completion of therapy, there was relief of clinical manifestations of vulvovaginitis and cervicitis, cessation of pathological vaginal discharge, absence of discomfort during sexual intercourse and urination in 90.6% of patients of group 1 and 96.4% of group 2, which was statistically significant compared with the initial picture at the beginning of the study ($p<0.05$). The normal pH of the vagina after completion of therapy was 26 (81,3%) patients receiving the combined treatment, "Bioflazid" per os and locally. The absence of infectious agents in the vaginal biotope after 3 months was found in 78.1% of patients of group 1 and 82.1% of group 2. Adverse and side effects during treatment were not recorded, all patients completed the study in full. Thus, the search for new approaches to the treatment of patients with cervical pathology associated with various infections in recent years continues to be relevant. The data obtained confirm the effectiveness of the use of "Bioflazid in complex treatment, in which there is a positive dynamics of not

only clinical indicators, but also the parameters of the immune system.

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