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FEATURES OF THE COURSE AND TACTICS FOR THE MANAGEMENT OF PATIENTS WITH DYSPLASTIC CONDITIONS OF THE CERVIX DUE TO VAGINAL MICROBIOCENOSIS DISORDERS

Boboyeva A.I., Aliyeva D.A.
"Republican Specialized Scientific and Practical Medical Center for Maternal and Child Health" State institution

Цель: Определить оптимальную тактику ведения и изучить особенности ведения пациенток с диспластическими изменениями шейки матки, выявленными на ранних стадиях скрининга шейки матки на фоне бактериального вагиноза и ИПВ-инфекции.
Материал и методы: В исследовании приняли участие 47 женщин в возрасте от 19 до 49 лет. Все пациенты были разделены на 2 группы. Первую группу составили 27 пациентов с АСК-УЗИ (эпителиальные клетки с атипией неизвестного значения) цитологического заключения. Во вторую группу вошли 20 женщин с интраэпителиальными изменениями низкой степени злокачественности (LSIL).
Результаты: Наиболее частое нарушение биоценоза влагалища у обследованных женщин обеих групп связано с концентрацией Candida albicans (46%) выше 108. Следующими по частоте являются Mycoplasma hominis (25%) и Gardnerella vaginalis (16,5%). В единичных случаях обнаружены Escherichia coli, стафилококки и Prevotella bivia.
Выводы: Персистирующая инфекция ИПВ, вызванная высокоонкогенными видами, способствует развитию диспластических процессов и рака шейки матки. В процессе формирования ЦИН ИПВ, обладающая высоким раковым риском, поражает столбчатый эпителий зоны трансформации и стволовые клетки, расположенные под эндоцервиксом. Вирус использует для размножения метапластический эпителий, в том числе в эндоцервикальных криптах, а при нарастании генетических заболеваний начинает размножать эпителиальные клетки.
Ключевые слова: цервикальная дисплазия, бактериальный вагиноз, папилломавирусная инфекция, микробиоценоза влагалища.

Objective: To determine the optimal management tactics and study the features of managing patients with dysplastic changes in the cervix, detected in the early stages of cervical screening in the context of bacterial vaginosis and HPV infection. ***Material***

and Methods: The study involved 47 women aged 19 to 49 years. All patients were divided into two groups. The first group consisted of 27 patients with an ASC-US (atypical squamous cells of undetermined significance) cytological diagnosis. The second group included 20 women with low-grade squamous intraepithelial lesions (LSIL). ***Results:*** The most common disorder of vaginal biocenosis among the women in both groups was a high concentration of *Candida albicans* (46%) above 10^8. The next most frequent findings were *Mycoplasma hominis* (25%) and *Gardnerella vaginalis* (16.5%). *Escherichia coli*, staphylococci, and Prevotella bivia were found in isolated cases. ***Conclusions:*** Persistent HPV infection caused by highly oncogenic strains contributes to the development of dysplastic processes and cervical cancer. During the formation of CIN, HPV, which has a high cancer risk, affects the columnar epithelium of the transformation zone and the stem cells located beneath the endocervix. The virus uses the metaplastic epithelium for replication, including in endocervical crypts, and with the increase of genetic mutations, it begins to induce abnormal epithelial cell reproduction.

Keywords: cervical dysplasia, bacterial vaginosis, human papillomavirus infection, vaginal microbiocenosis.

Microbiocenosis refers to a stable community of microorganisms in a specific environment. The existence of microbiocenosis in the skin has been known for a long time. The vaginal mucosa, vaginal microflora, and vaginal secretions form an integrated but dynamic ecosystem.

The microflora includes many microorganisms that form a relatively stable community, as well as bacteria (transient microorganisms) that enter from the environment. Temporary microbes are unable to survive in the genital mucosa for long and generally do not cause pathological conditions if natural resistance mechanisms and immune responses maintain barrier functions and prevent excessive microbial reproduction. It is known that the normal vaginal microbiome is dominated by lactobacilli, which help prevent the development of vaginal infections by producing lactic acid, hydrogen peroxide, and bacteriocins, while also outcompeting harmful microorganisms [1, 2, 3].

For women's reproductive health, population stability and normal microbiocenosis are essential components. The well-organized function of these mechanisms, also known as colonization resistance, protects against sexually transmitted infections (STIs) and the overgrowth of opportunistic microorganisms [3].

Most representatives of the normal microflora, such as Lactobacillus and *Bifidobacterium* species (making up 80-90% of the flora), do not cause inflammation due to the absence of pathogenic factors. These bacteria act as a buffer that limits the growth of opportunistic microorganisms (which make up 10-20% of

the microflora) and the spread of pathogens.

Protective mechanisms of colonization resistance include:

- healthy competition with foreign microorganisms for nutrients;
- production of antimicrobial substances (e.g., short-chain fatty acids, peroxides, bacteriocins, lysozyme);
- neutralization of microbial xenobiotics via adsorption and biotransformation.
- blocking of adhesion receptors;
- stimulation of immune responses against pathogens;
- production of immunostimulants and activators of phagocytic and enzymatic activity;

Protection against exogenous (e.g., gonococci, chlamydia) and endogenous opportunistic microorganisms is also provided by other physical and chemical factors: the acidic vaginal environment, which is essential for normal microflora function and acts as an antipathogenic barrier, and the production of antimicrobial substances like lysozyme and lactoferrin.

When dysbiosis occurs, these protective mechanisms are disrupted, breaking down barriers to bacterial infections. When lactobacilli levels drop, over ten known colonization resistance mechanisms disappear. Facultative opportunistic bacteria, at high titers, exhibit invasive potential and can induce an inflammatory response.

The formation of bacterial infections proceeds as follows: Initially, a dysbiotic process develops in the vagina due to adverse factors like weakened immunity, hormonal imbalances, or infection with STIs. Disruptions in the interaction between the microflora and genital tissues are often accompanied by damage to mechanisms that maintain local immunity, while apoptosis weakens.

Increased cell survival leads to the accumulation of chromosomal aberrations in the nuclei of infected epithelial cells. This is further exacerbated by certain facultative microbiota, such as mycoplasmas, which inhibit nucleic acid biosynthesis, leading to DNA damage. These processes, in turn, may trigger autoimmune reactions, tumorigenesis, and secondary infections in affected tissues. It is no coincidence that bacterial vaginosis is now linked to an increased risk of carcinogenic processes in the cervix [4, 5, 6, 7].

Cervical intraepithelial neoplasia (CIN) is a precancerous condition of the cervix. In women of reproductive age, the prevalence of cervical pathology is 17-29% [1, 4].

The development of the neoplastic process in cervical epithelium is linked to human papillomavirus (HPV) infection. HPV infection in epithelial tissues leads to the integration of viral DNA into the cell genome and subsequent expression of viral oncogenes (E6 and E7). This initiates a viral carcinogenesis model. In transformed cells, complex, multistep mechanisms of genetic mutations are activated, disrupting

cell cycle regulation [2].

Intraepithelial neoplasia of the cervix is often a morphological response to chronic vaginal inflammation linked to disturbed microbiocenosis. Different infectious agents typically coexist. Most patients with CIN present with a combination of infections, highlighting significant microbiocenosis disruption, which in turn may impair regenerative processes in the cervical squamous epithelium [6].

Therefore, the dominant factor in CIN development is a chronic infectious process, forming the pathogenic basis for cervical intraepithelial neoplasia. In many countries, cytological screening is the primary method due to its cost-effectiveness. The Bethesda system, developed to standardize terminology in economically developed countries, is used to describe cytological findings. This system accurately determines further diagnostic and treatment recommendations. According to this classification, CIN is categorized as LSIL or HSIL based on the severity of intraepithelial lesions.

Objective: To determine the optimal management tactics and study the features of managing patients with dysplastic changes in the cervix, detected in the early stages of cervical screening in the context of bacterial vaginosis and HPV infection.

Research materials and methods: In the study, 47 women aged 19 to 49 years old with an abnormal cytological appearance of the cervical sample taken during examination at the polyclinic of the consultation polyclinic of the Republican Specialized Maternal and Child Health Scientific and Practical Medical Center "Family and Marriage" a woman participated. All patients were divided into two groups. The first group consisted of 27 patients with an ASC-US (atypical squamous cells of undetermined significance) cytological diagnosis. The second group included 20 women with low-grade squamous intraepithelial lesions (LSIL).

As part of the comprehensive examination of patients with diseases of the female genital organs, a cytological examination was performed for women on the initial request for specialized medical care. At the preanalytical stage of cytological research, a special Cervex-Brush® Combi brush was used to properly collect the material, its removable part was placed in a preservative medium, and the traditional method of smear preparation prevents it from losing the properties of the cellular material. Thin-layer cytological preparations obtained in a cytocentrifuge were stained according to the method of G. N. Papanicolaou with gradual application of hematoxylin according to Harris, Papanicolaou OG6 and EA50. The received cytological preparations were placed under the cover. The study was carried out using a light microscope AxioScope A.1 (Carl Zeiss, Germany) x100 to x1000 magnification. The results of the study were evaluated according to the Bethesda terminological classification. All obtained cytological preparations are of appropriate quality and contain a sufficient amount of metaplastic cells of the transformation zone

and/or cervical gland epithelium.

To determine the composition and quantitative ratio of the microflora of the genital organs, molecular biological studies were conducted using the polymerase chain reaction method. The examination included 16 indicators (total bacterial mass, normal flora – Lactobacillus spp., Enterobacterium spp., Staphylococcus spp., Streptococcus spp., Gardnerella vaginalis, Porphy- romonas spp., Prevotella bivia, Sneathia spp., Eu- bacterium spp., Leptotrihiaspp., Megasphaera spp., Dialister spp., Veilonella spp., Clostridium spp., Lachnobacterium spp., Mobiluncus spp., Corynebacterium spp., Peptostreptococcus spp., Ureaplasma (urealyt- icum + parvum), Mycoplasma (hominis + genitalium), Candida spp. The test for human papillomavirus (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59) with high carcinogenic risk was carried out using the PCR method with specific primers.

Research results:

The most frequent violation of the vaginal biocenosis in examined women in both groups is associated with the concentration of Candida albicans (46%) higher than 108. The next frequency is Mycoplasma hominis (25%) and Gardnerella vaginalis (16.5%). In isolated cases, Escherichia coli, staphylococci and Prevotella bivia were detected.

Results of clinical and laboratory examination of patients with abnormal cytological image

Criteria	**Types of cytological findings**			
	ASC-US (n=27)		**LSIL (n=20)**	
	Abs	**%**	**Abs**	**%**
Sexual infections				
Bacterial vaginosis	**17**	**63**	**16**	**80**
IPV	**18**	**67**	**19**	**95**
Genital candidiasis	**8**	**30**	**4**	**20**
Trichomoniasis	**-**	**-**	**1**	**5**
	-	**-**	**-**	**-**
Colposcopic image:				
Abnormal severity level 1	**10**	**37**	**12**	**60**
Abnormal severity level 2	**-**	**-**	**4**	**20**

non-specific sign	**4**	**15**	**4**	**20**
inadequate	**13**	**48**	**-**	**-**
Transformation zone				
I	**6**	**22**	**9**	**45**
II	**4**	**15**	**5**	**25**
III	**8**	**30**	**3**	**15**

Escherichia coli, Staphylococcus and *Prevotella bivia* were found in isolated cases. Associations of pathogenic and conditionally pathogenic microflora were often observed (Table 1). At the same time, the detection rate of IPV with high oncogenic risk was 2 times higher in the group of patients with LSIL.

Half of the patients in the first group had a mild degree of cervical epithelial dysplasia, 10% anomalous severity level 1 colposcopic image.

During the extended colposcopy in the second group, 60% of patients had an anomalous weight level 1 colposcopic image. In most of the patients in this group, the colposcopic image has non-specific signs, in 1/3 it was insufficient, which is related to the intensity of the inflammatory process and changes in the cervix. At the same time, 1/5 of the patients in the second group had a transformation zone of type I-II, which made it difficult to diagnose the pathological process of the cervix. In patients with a nonspecific colposcopic image, various degrees of leukoplakia may be hidden under the layer. Therefore, multifocal biopsy was performed for patients with type I or II transformation zones. Cervical excision was performed in patients with type III transformation zone.

In the second group, the presence of abnormal colposcopic picture was determined by clear changes of grade II in the form of a thick layer of aceto-white epithelium, rough mosaic and tuberose of the epithelial layer.

All patients underwent etiotropic therapy, taking into account the identified pathogens, as well as ablative procedures for types I and II of the transformation zone and excision procedures of type III, as well as drugs aimed at restoring vaginal microbiocinosis (probiotics, immunity). but correctors). Women diagnosed with HPV infection were treated with antiviral and immunostimulating drugs along with drugs aimed at restoring vaginal biocenosis.

After 3-6 months of treatment, patients in both groups underwent repeated cytological examination and expanded colposcopy. Regression of cytological signs of ASC-US and LSIL was observed in more than 90% of cases and was associated with elimination of the infectious agent and regression of abnormal colposcopic images. In 20 women with signs of cytological atypia, colposcopy was performed with biopsy and control histological examination, if the abnormal signs of the colposcopic image

remained, morphological signs of immature metaplasia in 11 cases, leukoplakia without signs of dysplasia in 2 cases, and IPV infection in 6 cases. CIN I was confirmed by histological signs, CIN II in 1 case.

Some patients have persistent IPV infection and recurrence of bacterial vaginosis. The number of these women in the group with a previously diagnosed LSIL cytological image was higher than in the first group, which may indicate an initially torpid combined course of the infectious process or be determined by compatibility factors during therapy.

Conclusions: Persistent IPV infection caused by highly oncogenic species contributes to the development of dysplastic processes and cervical cancer. In the process of CIN formation, IPV with a high cancer risk affects the columnar epithelium of the transformation zone and the stem cells located under the endocervical. The virus uses metaplastic epithelia for reproduction, including in endocervical crypts, and with the increase of genetic diseases in them, it initiates the proliferation of β-epithelial cells. Infection of cervical epithelial cells with IPV is necessary, but not sufficient, for their malignancy.

In addition, the pH level of vaginal contents, in turn, depends on Lactobacillus spp. and affects the process of squamous metaplasia. Thus, the presence of at least one and possibly multiple infections together with IPV accelerates the development of CIN and is a risk factor for invasive cervical cancer.

The results of the study showed that for CIN I, it is necessary to adhere to conservative treatment tactics with mandatory control in the form of a combined test (cytological examination + IPV test) and extended colposcopy. Targeting or biopsy after extended colposcopy should take into account the nature of the transformation zone and the presence of highly oncogenic IPV infection.

The tactics of treatment of patients of reproductive age with histologically confirmed CIN I in the ambulatory stage should be aimed at conservative treatment and normalization of the vaginal biocenosis, which helps to implement the soft, organ-preserving principles of therapy.

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