

Review

The current state of cervical diseases prevention in women of reproductive age taking into account the vaginal biocenosis – review

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Received: 26 November 2022 / Accepted: 30 May 2023

Abstract

In recent years, cervical pathology has taken a leading place in the structure of cancer in the whole world. The variety of pathological lesion forms of the lower part of internal genital organs requires a personalized approach to solving complex treatment tactics. The study of the ectopic columnar epithelium (ECE), which according to the literature, is about 40% and results from the ineffective treatment of previous cervical pathology, represents great interest on practical grounds in gynecology. At first glance, all benign processes do not occur as a significant cancer risk. However, they do significantly impact reproductive health and leave much to be discussed about treatment and prevention. According to most researchers, vaginal biocenosis is a complex micro-ecosystem, where the key role belongs to the vaginal microflora, which in turn changes dynamically during the cycle and age of women and depends on many factors: anatomical and histological structure of the genital area, immune response and others. The modern classification of benign cervical and vaginal tumors includes various conditions and diseases. Further observation and treatment require verification of squamous epithelial cells with atypia of unclear genesis, especially in women of reproductive age with HPV infection on the background of aberrant microbiocenosis of the vagina. Thus, in our opinion, the state of modern medical knowledge in the direction of expanding the study of disorders of the microbiocenosis of the vagina in the prevention of cervical oncological pathology is a promising study. Namely, the study of the interaction of micro- and macroorganisms among women of reproductive age with benign pathology under HPV load and different cytological pictures will allow to develop a mathematical model for predicting the pathological process progression and become a prerequisite for quality prevention.

Keywords: microbiocenosis of the vagina, bacterial vaginosis (BV), human papillomavirus (HPV), ectopic columnar epithelium (ECE), benign pathology of the cervix.

Introduction

Women's health, in general, and reproductive health, in particular, are integral to preserving Ukraine's gene pool in the context of the demographic crisis. Reproductive health (RH) includes not only the absence of diseases or disorders in the system but is also associated with a state of complete physical, mental and social well-being (as defined by the WHO). Various factors have a negative impact on the reproductive

sphere: social and economic conditions, lifestyle, environmental problems, burdened heredity, as well as the quality and availability of medical services [1–3].

Diagnosis of cervical cancer

Cervical pathology in the structure of oncogynecological morbidity in the world occupies a leading place and is 15% in this group, and mortality reaches 8% [4–6].



Diagnosis of cervical cancer (CC) has evolved from the first detection of abnormal cells in a Pap smear and the sensational report by Trout about the possibility of cytological screening for this pathology and the creation of the first colposcope by H. Hinselmann until Harald Zur Hausen discovered the role of human papillomavirus (HPV) in the pathogenesis of CC and the introduction of co-testing into the routine work of obstetricians and gynecologists and the development of HPV vaccines.

Factors of cervical cancer

According to clinical epidemiology, the pattern of early onset of sexual activity and the number of partners in the initiation of cervical oncopathology was revealed. Uncontrolled sexual behavior on the background of dyshormonal disorders has increased the risk of cervical cancer. Violations of a healthy lifestyle and tobacco dependence (more than 10 cigarettes/day), as a rule, were observed in most women with precancerous pathology of the cervix [7, 8].

According to the literature, traumatic injuries of the cervix due to abnormal childbirth and abortion, chronic inflammatory diseases of the reproductive sphere against the background of TORCH infections dominate among the factors of obstetric and gynecological history of cervical cancer (CC) [9, 10].

The development of the cytological direction of cervical cancer screening has allowed to clearly classify the cervix pathology into groups of benign diseases, dysplasia and cancer. The combination of this method with a colposcopic examination (easy and difficult) allowed us to draw parallels between cytological changes and colposcopic pictures, which significantly improved the quality of medical care in terms of early diagnosis verification in terms of cancer vigilance [11, 12]. However, suppose the role of cervical dysplasia in the disease progression to cancer is thoroughly studied; in that case, the place of benign pathology, particularly ectopic columnar epithelium (ECE), on the background of HPV infection remains open for research [13].

Classification of cervical and vaginal tumors

The modern classification of benign cervical and vaginal tumors includes various conditions and diseases. Among the latter are the most common erosions, congenital transformation zone, endometrioid heter-

otopias, atrophic processes, leukoplakia, warts, cysts, and polyps. The variety of pathological damage forms of the lower internal genitals requires a personalized approach to solving complex treatment tactics [14, 15]. Thus, the differentiation between a true erosion and pseudo erosion of the cervix from the colposcopic expediency point of view does not matter. In women's reproductive age, the endocervix's surface is covered with single-row columnar epithelium (CE). The location of the last one outside the external os is called ectopic CE. This colposcopic picture is a characteristic of puberty age and is observed in the initial stages of childbearing. Quite often in sexually active women, against the background of sexually transmitted infections, ectopic CE is observed on the surface of the exocervix around the external os of the cervix in the form of single islets or large areas extending to the entire surface of the vaginal cervix.

The traumatic nature of true cervical erosions is characteristic of the atrophic and attenuated epithelium at the period of menstrual function attenuation. In women of childbearing age, this picture is mostly not found. Violating the architecture of the multi-layered superficial epithelium in the reproductive period is associated with inflammation of various origins [16].

Clinical forms of cervical cancer

Various clinical forms of temporary nature inflammation (acute, chronic) lead to disruption of the exocervix cytological landscape with subsequent desquamation of destroyed cells and defect replacement with columnar or squamous epithelium. As a result of productive inflammation, the glandular epithelium and stroma grow, which is the reason for the appearance of numerous papillary growths – polyps and genital warts (against the background of HPV infection) [17].

According to the literature, the study of the ECE recurrence problem is about 40%, and 20% is the result of ineffective treatment of previous cervix pathology is of great interest on practical grounds in gynecology. At first glance, such benign processes do not pose a significant cancer risk, but they significantly affect reproductive health and leave much to be discussed about treatment and prevention.

The connection between cervical cancer and oncogenic HPV presence leaves no doubt, but the stratification of cervical oncological pathology risks in the case of a positive test for oncogenic strains of papillomavirus infection with a normal cytological picture (NILM - negative for intraepithelial lesions and malignancy or

malignancy) and atypical squamous cells of undetermined significance (ASC-US – Atypical squamous cells of undetermined significance) stay polemic [18, 19].

According to the latest international guidelines, screening for cervical cancer using the Pap test and/or HPV PCR test is recommended to start at the age of 21–25, regardless of sexual orientation or sexual behavior. The study of factors that can hypothetically potentiate the spontaneous elimination of the HPV pathogen and thus prevent the development of clinically significant forms of cervical pathology has a considerable scientific interest.

Verifying squamous epithelial cells with atypia of unclear genesis requires further monitoring and treatment. The management of this pathology varies in many countries and involves a number of additional financial costs and the use of medical resources. Most information sources note the relevance of the next colposcopic examination after co-testing. There are no clear recommendations on the timing of surveillance and management of ASC-US women with/without HPV. The introduction of inexpensive cervical examination by a gynecologist with the help of a colposcope has significantly improved the diagnostic panel of cervical cancer. Evaluation of the color and epithelium landscape, the state of the vascular pattern, location and nature of the junction of squamous and columnar epithelium, the presence of pathological formations of the cervix during the examination and advanced colposcopy gives a realistic picture of its condition and offers optimal observation and treatment [20].

Colposcopic signs severity

Particular attention is paid to the examination of the contact point of the cervical canal epithelium and the vaginal part of the cervix uteri. The junction zone of the different epithelium has its own age characteristics. The displacement of this line onto the surface of the exocervix is a puberty characteristic. In reproductive age, the normalization of the joint area at the level of the external os, by transiting to perimenopause, this line moves into the depth of the cervical canal. These features should be taken into account when searching for abnormal colposcopic images.

Assessment of colposcopic signs severity is divided into three types: normal; abnormal, clinically insignificant and abnormal, clinically significant.

This division reduces errors in interpreting the colposcopic picture, but not in all cases gives a precise algorithm for the doctor. In most cases, this is due to

a number of objective circumstances of a personalized nature (socio-economic, medical).

Considering the presence of cyclical changes in the body of women of reproductive age associated with the functioning of a complex system of neurohumoral connections at different levels, the study of cervical pathology as a target organ should be carried out with a mandatory assessment of this regulation. According to the literature, menstrual disorders are often combined with cervical problems and manifestations of disharmony play a dominant role in changing the ecosystem of the reproductive tract.

Human microbiome project

The beginning of the XXI century was marked by the launch of a full-scale global Human Microbiome Project, which aimed to study fundamentally the amazing world of microorganisms (bacteria, viruses, fungi, protozoa) that inhabit the human body in natural habitats. Leading American scientists have been involved in creating a “map of eukaryotes”, studying not only the species composition of the last ones but also their genetic data, collective behavior and ways of interacting with the macroorganism. The precondition of this study was the awareness of the control possibility of the human body microbiota to keep optimal symbiotic relationships. The urgency of the potential impact of microbiota on humans is primarily due to the quantitative predominance of the last ones over somatic cells. According to some estimates, the number of cells in microbial populations is at least 100 trillion, and the total genome is about 9 million genes, which is hundreds of times greater than the genomic composition of cells in the human body. Acting as a powerful bioreactor, the microbiome performs numerous metabolic functions, supports vital immunoprotective processes, and affects the structural and functional state of internal organs, ensuring the body’s homeostatic state as a whole. It plays the role of a reliable protector of the human body from harmful microorganisms and exogenous factors through a complex system of interaction between micro- and macro-organisms [21].

Vaginal microbiome

Particular attention, from the point of view of reproductive health, is the research results by an interdisciplinary team of scientists from among clinicians,

microbiologists, geneticists, and statisticians in the study of vaginal microbiome (Vaginal Microbiome Consortium).

According to the classification of E.F. Kira, there are 4 types of basic nosological forms of vaginal biocenosis:

1. Normocenosis is characterized by the dominance of lactobacilli and the absence of pathological flora and is a physiological type;
2. The intermediate type occurs against the background of a moderate decrease of lactobacilli, the appearance of gram-positive cocci and gram-negative rods, as well as a moderate increase in the number of leukocytes, monocytes, macrophages, and epithelial cells. This variant of vaginal biocenosis is often observed in healthy women, rarely accompanied by complaints and clinical manifestations;
3. Vaginal dysbiosis is characterized by replacing lactoflora with abundant polymorphic conditionally pathogenic microbial picture and the appearance of “key cells”;
4. Inflammatory type of smear - vaginitis, occurs as a result of an inflammatory reaction to the presence of specific or nonspecific microflora in the vagina biotope.

The vaginal biocenosis is a complex microecosystem, where the key role belongs not only to the vaginal microflora but also to the anatomical and histological structure of the genital area. The vital activity of the “healthy” flora of the vagina depends on a number of cyclic hormonal, immunological, and age-related changes in the reproductive tract and others. The surface layer of the multi-layered squamous epithelium of the vagina, rich in glycogen, serves as a strategic center of the nutrient substrate, and it is a source of energy and flexible processes of lactobacilli.

The variability of the species composition of the vaginal flora can be influenced by various medical and socio-economic factors: inflammatory diseases of the genital organs, hormonal disorders, tumor pathology of the reproductive sphere, antibiotics, contraceptive use, low socio-economic status, nutritional imbalance, ethnicity and other [21]. On the other hand, nowadays, it is well known that the microbiome can significantly change the physiological processes of the host.

Bacterial vaginosis

The most common reason for women to see a doctor is the appearance of abnormal vaginal discharge with

an unpleasant odor, which often causes itching, and dyspareunia. According to various authors, the share of bacterial vaginosis (BV) among vulvovaginal infections is from 12% to 80%. Such a wide range of this pathology is firstly due to ethnic characteristics and environmental and climatic factors. Despite the widespread prevalence of this pathology, only in 1984, at the First International Symposium on Vaginitis in Stockholm, BV was set apart into an independent nosological form.

Determination of BV means a sharp increase of anaerobic flora against the background of lactoflora depletion and the inflammatory picture absence of the genital mucosa. The main etiological factors of vaginosis are not only *Gardnerella vaginalis* but also other bacteria: *Streptococcus agalactiae*, *Escherichia coli*, type of *Bacteroides* species, *Peptostreptococcus Prevotella*, *Mobiluncus* and opportunistic pathogens *Staphylococcus epidermidis*, *Enidercidus*.

Diagnosis of BV according to the Amsel criteria assumes the presence of three criteria out of four:

- Homogeneous liquid discharge from the vagina of white-grey color;
- The presence of key cells in the microscopy of native smears;
- pH of the vaginal environment is more than 4.5;
- Positive amine test (appearance of fishy odor when mixing equal proportions of potassium hydroxide and vaginal secretions).

The Hay/Ison criteria are also based on the results of Gram-stained smear microscopy and evaluation of the relationship between *Lactobacillus* spp. and other microflora of the vagina. There are 4 levels of violation:

- Grade 0 (normal result: *Lactobacillus* morphotypes predominate);
- Grade 2 (intermediate result: available mixed flora (*Lactobacillus* and *Gardnerella/Mobiluncus*);
- Grade 3 (BV): *Gardnerella* or *Mobiluncus* morphotypes predominate, key cells are present, *Lactobacillus* in small numbers or absent;
- Grade 4: does not apply to BV; there are only gram-positive cocci without lactobacilli (aerobic vaginitis).

According to the Nugent scoring system, diagnostic criteria and scoring allow diagnosing BV with a high probability.

Treatment of bacterial vaginosis

Developed schemes for medical treatment of BV using metronidazole and clindamycin did not give high

efficiency and were associated with the phenomenon of biofilm formation. In the community, microorganisms (*Gardnerella vaginalis*, *Streptococcus agalactiae*, *Esherichia coli*, types *Bacteroides*, *Peptostreptococcus Prevotella*, *Mobiluncus*, *Staphylococcus epidermidis*, *Enterococcus faecalis*) will show symbiosis due to mechanisms of the acidic environment of the vagina and create obstacles to overcoming infection with standard treatment regimens.

Along with the development of diagnostic tools BV, the direction of prevention of dysbiotic disorders of the reproductive tract is developing, and the prospect of correcting the biocenosis from the outside is modeling. Taking into account the important social and economic aspects (the cost of treating BV in the United States of America is \$ 4 million annually) and the medical side of pregnancy complications (a miscarriage factor) and the development of comorbid reproductive pathology (HPV persistence cofactor), successful treatment and prevention of BV is an urgent issue of modern gynecology [21].

Conclusion

The state of modern medical knowledge in the direction of expanding the study of the role of microbiocenosis disorders of the vagina in the prevention of cervix oncopathology is a promising study. In our opinion, the study of the interaction of micro- and macroorganisms in women of reproductive age with benign pathology under HPV load and different cytological pictures will develop a mathematical model for predicting the progression of the pathological process and become a prerequisite for quality prevention.

Conflict of interest

The authors declare no conflict of interest.

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