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## NEW TENDENCIES IN DIAGNOSTICS AND TREATMENT OF DISEASES OF THE CERVIX (LITERATURE REVIEW)

In the problem of resolving the pathology of the cervix in recent years, a lot of information about etiology, causes of origin, diagnosis and treatment has been accumulated. The article summarizes the new possibilities of diagnosis and treatment of the pathology of the cervix, which contributes to a significant improvement in the resolution of the problem of the pathology of the cervix. There are 4 main groups of etiologic factors that lead to morphofunctional changes in the cervical epithelium. In the course of a violation of the transformation of the epithelialization of the cylindrical epithelium, the violation of local and humoral immunity is important. The definition of apoptosis index is a new modern method for predicting the development of precancerous and cervical cancer. Routine but informative methods for diagnosing cervical pathologies such as cytological and colposcopic, in recent years, have been replenished with an important immunohistochemical diagnostic method for detecting p16INK4a cellular protein, as well as by fluorescence spectrometry. The presented complex of diagnostic researches allows us to choose the method of adequate treatment of pathological processes taking into account the age of the patient, the nature and degree of severity of epithelial changes, the type of cervical and vaginal flora, as well as the hormonal status of the patient and concomitant pathology.

**Key words:** pathology of the cervix; routine and modern methods of diagnosis and treatment.

### НОВІ ТЕНДЕНЦІЇ В ДІАГНОСТИЦІ ТА ЛІКУВАННІ ЗАХВОРЮВАНЬ ШИЙКИ МАТКИ (ОГЛЯД ЛІТЕРАТУРИ)

У проблемі вирішення патології шийки матки за останні роки накопичилося досить багато інформації щодо етіології, причин виникнення, діагностики та лікування. У статті коротко подана інформація про нові можливості діагностики та лікування патології шийки матки, що сприяє значному покращенню вирішення проблеми патології шийки матки. Виділяють 4 основні групи етіологічних факторів, які призводять до морфофункціональних змін епітелію шийки матки. У процесі порушення трансформації епітелізації циліндричного епітелію мають значення порушення місцевого та гуморального імунітету. Визначення індексу апоптозу є новим сучасним методом прогнозування розвитку передракових процесів та раку шийки матки. Рутинні, але інформативні методи діагностики патології шийки матки, такі, як цитологічний та кольпоскопічний, в останні роки поповнилися важливим для діагностики імуногістохімічним методом для виявлення клітинного протеїну p16INK4a, а також методом флуоресцентної спектрометрії. Представлений комплекс діагностичних досліджень дозволяє обрати метод адекватного лікування патологічних процесів з урахуванням віку хворої, характеру і ступеня вираженості епітеліальних змін, виду цервікальної і піхвової флори, а також гормонального статусу хворої і супутньої патології.

**Ключові слова:** патологія шийки матки; рутинні та сучасні методи діагностики та лікування.

### НОВЫЕ ТЕНДЕНЦИИ В ДИАГНОСТИКЕ И ЛЕЧЕНИИ ЗАБОЛЕВАНИЙ ШЕЙКИ МАТКИ (ОБЗОР ЛИТЕРАТУРЫ)

В проблеме решения патологии шейки матки за последние годы накопилось достаточно много информации по этиологии, причинах возникновения, диагностике и лечению. В статье кратко представлена информация о новых возможностях диагностики и лечения патологии шейки матки, что способствует значительному улучшению решения проблемы патологии шейки матки. Выделяют 4 основные группы этиологических факторов, которые приводят к морфофункциональным изменениям эпителия шейки матки. В процессе нарушения трансформации эпителизации цилиндрического эпителия имеют значение нарушения местного и гуморального иммунитета. Определение индекса апоптоза является новым современным методом прогнозирования развития предраковых процессов и рака шейки матки. Рутинные, но информативные методы диагностики патологии шейки матки, такие, как цитологический и кольпоскопический, в последние годы пополнились важным для диагностики иммуногистохимическим методом для выявления клеточного протеина p16INK4a, а также методом флуоресцентной спектрометрии. Представленный комплекс диагностических исследований позволяет выбрать метод адекватного лечения патологических процессов с учетом возраста больной, характера и степени выраженности эпителиальных изменений, вида цервикальной и влагалищной флоры, а также гормонального статуса больной и сопутствующей патологии.

**Ключевые слова:** патология шейки матки; рутинные и современные методы диагностики и лечения.

Diseases of the cervix – the most common pathology that an obstetrician-gynecologist faces on an outpatient appointment.

The variety of pathological conditions of the cervix is reflected in modern colposcopic, cytological and histological classifications. There are several of them today:

- МКН-10;

- Classification of a colposcopic picture was proposed by E. V. Kokhanevich in 1997, which was officially approved by the Ministry of Health of Ukraine in the Order No. 676 of December 31, 2004 and is quite common among Ukrainian clinicians;

- Classification of colposcopic terms, adopted in Rio de Janeiro in 2011 at the 4th World Congress of the International Society for Colposcopy and Cervical Pathology, replacing the Rome Classification of 1990;

- Cytological classification by Richart (1968);

- Classification by Papanicolaou;

- Terminal system Bethesda (2014 and edited in 2016).

- Histological classification of background diseases, precancerous conditions and cancer of the cervix [1,2].

In addition, colposcopists have developed their own classification of colposcopic pictures of pathological conditions of the cervix (Bauer, Vespi, Burghart), which are widely used by their compatriots-clinicians [2].

There are four main groups of etiologic factors that lead to morphofunctional changes in the cervical epithelium:

1. Mechanical injuries and chemical effects on the cervix;
2. Hormonal deficiency of ovarian function;
3. Infectious diseases of the cervix and vagina, especially viral and chlamydial etiology;
4. Violation of the immune status [3].

Background processes of the cervix relate to the optional precancerous processes. They constitute, according to various authors, from 15 to 52.4 % of gynecological diseases and 80 % of all diseases of the cervix [4, 5]. Earlier, the fact that ectopia of the cylindrical epithelium of the cervix was observed in healthy women and until 22–23 years of age passed independently, without the use of any methods of treatment [6, 7]. But, for today, more and more authors in their writings tend to the fact that even the presence of ectopia of cylindrical epithelium in young women who did not give birth, requires additional examination and careful observation. This is primarily due to an increase in the factors of the development of cervical cancer: early onset of sexual activity and, accordingly, early infection with the human papillomavirus and other sexually transmitted infections, a large number of sexual partners (more than 3), ignoring the bar oral contraceptives, abortions, chronic inflammatory diseases of the reproductive system, prolonged, uncontrolled use of hormonal contraceptives, as well as smoking, in which the carcinogenic substances – nitroimidazoles and kotanin – are formed in the vagina. In the process of breaking the transformation of the epithelialization of the cylindrical epithelium, all these factors lead to the development of dysplasia, and in the future – cervical cancer [5, 8, 9]. After all, the action of the human papilloma virus only initiates the tumor process, but is not sufficient for its progression.

However, there is evidence of changes in immune status, mainly about a decrease in the number of T-helper subpopulations. Violations of local and humoral immunity appear already at the stage of background cervical diseases. [10]. There was a lack of cyclical changes in the content of all classes of immunoglobulins in cervical mucus in women with cervical pseudo-erosions, while in healthy ones, these variations are determined.

AF Cooper et al. found that, with ectopy of the cylindrical epithelium of the cervix with proliferation of the cylindrical epithelium, accumulation of immunoglobulins occurs in the zones of cellular infiltration, which consists of lymphocytes and macrophages; infiltrates are also located around small vessels. All this testifies to the possibility of forming in the tissues of the cervix a reaction of the hypersensitivity of the slowed-down type, and a close connection of immunomorphological phenomena with the proliferation of the epithelium in ectocervix – about the possibility of the influence of immunoglobulins on processes that support the existence of pseudo-erosions. Great importance in protecting the epithelium from viruses belongs to interferons that affect the course of the inflammatory process and the state of immunity of cervical tissues. Interferon gamma produced by activated lymphocytes promotes the expression of adhesion molecules in human papillomavirus cells in flat

epithelium cells, in particular the ICAM-1 molecule, which is essential for epithelial-lymphocytic interaction and migration of lymphocytes to the focal point of the lesion. Interferons are involved in the activation of natural killers, increase their liveness and enhance the activity of cytotoxic lymphocytes. There are data on the suppression of the development of a number of experimental tumors in the introduction of leukocyte interferon [11].

Definition of apoptosis index is a new, modern method of predicting the development of precancerous processes and cervical cancer in patients with cervical diseases and associated HIV-infection. In particular, a high level of expression of E7 protein, telomerase, cyclin B1 and K67 is a factor of unpleasant prognosis in cervical diseases requiring urgent active treatment measures

It should be noted that by 1996 the incidence of CWM in the world had a tendency to decrease, but now this pathology increases with each passing year. According to the WHO, in the next 5–10 years, the mortality rate from CWM will increase by 25 %. There are 2 peaks of CWM development: 30–39 years and 60–64 years. According to various authors, the increase in the incidence of cervical cancer among women under 30 years of age is from 2.1 % to 5 % per year [12].

According to the literature, background diseases of the cervix are found in 15–52.4 % of gynecological patients and amounted to 80 % of all diseases of the cervix.

Taking into account that now with the aim of improving the quality of medical care there is an active reform of the healthcare sector with an emphasis on family medicine, it is the family doctors who will most often be the first to diagnose cervical cancer. And it depends on them how this disease will proceed in the future.

Cervical cancer does not occur suddenly. The tumor undergoes developmental stages from the background processes to the precancerous (dysplasia) and only then the oncological disease develops. According to the WHO, the development of microinvasive cancer of the cervix is on average 7–12 years. Another 5 years is required for the transition to a common form [13]. Thus, the physician has enough time to detect the pathology in the initial stages – cervical intraepithelial neoplasia (CIN) and for their effective treatment. Back in 1990, the World Congress on Pathology of the Cervix and Colposcopy in Australia came to the conclusion that cervical cancer is a completely preventable disease.

To date, complex diagnostics of diseases includes: clinical, cytological, colposcopic, histological methods of examination, as well as, if there is evidence, additional – bacteriological, bacterioscopy, virological, hormonal, colpocytological methods, ultrasound examination of the pelvic organs.

Among the diagnostic methods, the most common and accessible cytological study it is inexpensive, safe, painless and is considered the main one in the diagnosis of inflammatory, pre-tumor and malignant diseases of the cervix. For the effectiveness of cytological screening in many countries of the world, the terminology system Bethesda-system was introduced. It was developed as a result of gaining new knowledge about the role of HPV in the development of CKM and most consistent with all stages of the development of cervical carcinogenesis.

Qualified colposcopy makes it possible to identify patients who need to be monitored, examined and further treated [14].

The use of microhistoscopy makes it possible to investigate the transition between a flat and cylindrical epithelium and to draw conclusions about it both macroscopically and microscopically with the help of life-time dyeing of tissues. Microcolposcopy is a method that complements cytological and colposcopic investigations, which allows to give a diagnostic assessment and conduct a topographic survey of suspicious areas, as well as localize the center of the lesion. This significantly facilitates the targeted biopsy, in addition, it allows the recognition of the endocervical transformation zone in cases where colposcopy does not produce sufficiently precise results. This method provides an opportunity for intraoperative microcoloscopic control of the edges of conization with the aim of treating all suspicious areas and not to miss any lesions inside the transformation zone. [15]

In recent years, cytological studies have been replenished with important immunohistochemical methods for diagnosis, which are becoming widespread in the world, since it is known that the violation of regulatory mechanisms of apoptosis can lead to proliferation of cells with neoplastic changes. The immunohistochemical method for detecting cellular protein p16INK4a is highly effective in almost 100 % of cases with CIN 1-2 [16].

In the presence of risk factors for cervical cancer in patients with ectopia, a comprehensive diagnosis is required that necessarily involves histological examination and pathogenetic treatment.

One of the new methods of early and differential diagnosis of the pathology of the cervix, which aims to reduce the use of invasive methods (in particular, biopsy), is fluorescence spectrometry. The method is based on the use of a laser as a source of light and the ability of the cervical epithelium to autofluorescence. Depending on the type of pathology of the cervix, autofluorescence occurs at different wavelengths and has different intensity of the maximum spectrum. Fluorescent spectrometry, performed under the control of colposcopy and comparable with the results of cytological study, makes it possible to reduce the frequency of groundless biopsies of the cervix.

The presented complex of diagnostic researches allows us to choose the method of adequate treatment

of pathological processes taking into account the age of the patient, the nature and degree of severity of epithelial changes, the type of cervical and vaginal flora, as well as the hormonal status of the patient and concomitant pathology.

The choice of the method of treatment of patients with diseases of the cervix depends on the type of pathology, the duration of the disease, the magnitude of pathological changes, the presence of concomitant pathology, the previous treatment of the disease. It is also necessary to consider the presence of risk factors for cervical cancer. The performed therapy is more effective, the earlier it was started.

The existing methods of treatment of background diseases of the cervix are now divided into conservative and surgical methods. Conservative in turn can be divided into pharmacotherapeutic and physiotherapeutic. The surgical method of treatment is based on the destruction of the pathological focus in a mechanical way. This method can also be divided into 2 subspecies: destructive methods (diathermocoagulation, cryodestruction, laser destruction, radio waves destruction) and excisional (knife, laser, electric and radio wave excision). Each method has its own indications and contraindications, disadvantages and pride.

Also, in the treatment of background cervical processes, low-energy laser radiation or laser-magnetic therapy is used to stimulate and accelerate the reparative regeneration of the renal surface of the cervix and to prevent complications after destructive treatments. In addition, low-energy laser radiation has a positive effect on the process of normalization of the function of the ovaries, especially in patients with hypofunction of ovaries [17].

**CONCLUSIONS.** Consequently, when conducting women with cervical cancer, it is important to conduct a detailed examination to identify the etiological factors involved in the development of pathological processes and to develop an adequate plan for the management of such patients.

**PERSPECTIVES OF FURTHER RESEARCH.** It is planned to introduce actively into practical medicine very informative but expensive methods of studying the pathology of the cervix: the identification of highly oncogenic strains of papillomavirus infection, liquid cytology and immunohistochemical methods. The introduction of these methods into the practice of obstetrician-gynecologists to maximize the coverage of women of all ages will significantly reduce the incidence of cervical cancer.

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