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Petro TOKAR
Doctor of Philosophy, Assistant at the Department of Obstetrics, Gynecology and Perinatology, Bukovinian State Medical University, tokar.petro@bsmu.edu.ua
ORCID: 0000-0002-5862-4532

CERVICAL DYSPLASIA: CURRENT INSIGHTS IN PATHOGENESIS, DIAGNOSIS, PROGNOSIS, PREVENTION AND MANAGEMENT

The aim of the study. *To conduct a systematic analysis of current knowledge about the pathogenesis, diagnosis, prognosis, prevention and clinical management of cervical dysplasia; to identify key risk factors, the role of oncogenic types of human papillomavirus (HPV), the diagnostic value of molecular markers, as well as the cost-effectiveness of screening and treatment strategies based on current clinical guidelines.*

Methodology. *The study was based on a systematic review of the literature for 2010-2024, including the results of randomized controlled trials, meta-analyses, and FIGO, ESGO, WHO guidelines on the diagnosis, risk stratification, and treatment of cervical dysplasia. The evidence was summarized with a focus on the clinical and economic effectiveness of biomarker support, screening programs, and tactical approaches to the management of patients with CIN1-3.*

Scientific novelty. *It has been established that the integration of highly specific biomarkers (p16INK4a, Ki-67), HPV genotyping and modified screening strategies (HPV testing in combination with cytology) can improve diagnostic accuracy and individualize treatment approaches. The high clinical and cost-effectiveness of excisional treatments for HSIL, as well as the potential for using thermal ablation in patients with limited access to health care services, were revealed.*

Conclusions. *A comprehensive strategy to combat cervical dysplasia should include early vaccination, the introduction of high-precision molecular diagnostic methods, and algorithmic management of patients according to the degree of dysplasia and associated risk factors. Early diagnosis, risk stratification using biomarkers, and the use of cost-effective therapeutic interventions can significantly reduce cervical cancer morbidity and mortality and ensure the preservation of women's reproductive health.*

Key words: *cervical dysplasia, pathogenesis, human papillomavirus (HPV), cervical cancer, screening strategies, treatment, prevention.*

Петро Токар. ДИСПЛАЗІЯ ШИЙКИ МАТКИ: СУЧАСНІ УЯВЛЕННЯ ПРО ПАТОГЕНЕЗ, ДІАГНОСТИКУ, ПРОГНОЗУВАННЯ, ПРОФІЛАКТИКУ ТА ТАКТИКУ ВЕДЕННЯ

Мета дослідження. *Провести систематичний аналіз сучасних уявлень про патогенез, діагностику, прогнозування, профілактику та клінічне ведення дисплазії шийки матки; визначити ключові чинники ризику, роль онкогенних типів вірусу папіломи людини (ВПЛ), діагностичну цінність молекулярних маркерів, а також економічну ефективність стратегій скринінгу й лікування з урахуванням сучасних клінічних рекомендацій.*

Методологія. *У дослідженні використано систематичний огляд літератури за 2010–2024 роки, включаючи результати рандомізованих контрольованих досліджень, метааналізів і клінічних настанов FIGO, ESGO, WHO, що стосуються діагностики, стратифікації ризику та лікування дисплазії шийки матки. Проведено узагальнення доказів з акцентом на клінічну та економічну результативність біомаркерного супроводу, скринінгових програм і тактичних підходів до ведення пацієнток із CIN1–3.*

Наукова новизна. *Установлено, що інтеграція високоспецифічних біомаркерів (p16INK4a, Ki-67), генотипування ВПЛ та модифікованих стратегій скринінгу (тестування на ВПЛ у поєднанні з цитологією) дозволяє покращити діагностичну точність та індивідуалізувати підходи до лікування. Виявлено високу клінічну та економічну ефективність ексцизійних методів лікування при HSIL, а також потенціал використання термоабляції у пацієнток з обмеженим доступом до медичних послуг.*

Висновки. *Комплексна стратегія боротьби з дисплазією шийки матки повинна включати ранню вакцинацію, впровадження високоточних методів молекулярної діагностики та алгоритмізоване ведення пацієнток відповідно до ступеня дисплазії й супутніх факторів ризику. Рання діагностика, стратифікація ризиків за допомогою біомаркерів і застосування економічно обґрунтованих лікувальних втручань дозволяють значно знизити захворюваність і смертність від РШМ та забезпечити збереження репродуктивного здоров'я жінок.*

Ключові слова: *дисплазія шийки матки, патогенез, вірус папіломи людини (HPV), рак шийки матки, стратегії скринінгу, лікування, профілактика.*

Cervical cancer and cervical dysplasia remain the leading cause of morbidity and mortality worldwide, with an estimated incidence of 470,000 [14]. Approximately 230,000 women die from cervical cancer each year; more than 190,000 of these women come from developed countries in South America, sub-Saharan Africa, and the Far East [18]. In the United States, the incidence of invasive cervical cancer is significantly lower; the American Cancer Society estimates that in 2020, 604,127 women were diagnosed with cervical cancer and 4,170 died [2, 14]. The differences in incidence are mainly due to the use of cytological screening in many industrialized countries in the second half of the 20th century [4]. In the United States, the main burden of cervical disease is manifested as a significantly higher number of precancerous lesions, including mild cervical intraepithelial neoplasia (CIN1) (more than 1.4 million

new cases) and high-grade lesions (CIN2/3) (330,000 new cases) [5]. And in Ukraine, in particular, in 2023, the total number of newly diagnosed cases of cervical cancer was 2962 cases. Of the total number of cervical cancer patients, 1075 women died [2, 8].

Overall, the clinical management of patients with precancerous and malignant cervical lesions is a significant burden on the healthcare system. While improved methods are needed to improve the accuracy of cervical cancer screening, it is also important to consider that the majority of cervical cancer deaths worldwide occur among women who have never been screened [13, 21].

In the cervical cancer prevention strategy, special attention is paid to the timely diagnosis of precancerous conditions, in particular, pathological changes in the squamous epithelium. Sometimes, some medical terms can cause anxiety for people who do not have the necessary knowledge. For example, the diagnosis of cervical dysplasia (CU) in the understanding of some patients becomes synonymous with inevitable cancer [6, 10].

Cervical dysplasia is a common precancerous lesion that affects 1% to 2% of women worldwide [11]. Over the past decade, significant progress has been made in the diagnosis and treatment of cervical dysplasia. It is known that the incidence of cervical cancer (CC) in women aged 15-29 years has increased significantly in recent years. Every year, approximately 500,000 women worldwide are diagnosed with invasive cervical cancer, and every two minutes one of them dies as a result of this pathology [11, 14]. The progressive increase in morbidity and the number of patients with common forms of this pathology necessitate the creation of new and improvement of existing methods of diagnosis and treatment of precancerous conditions of the cervix.

The association between precancerous and malignant lesions of the cervical epithelium and human papillomaviruses (HPV) is well established [8, 14]. There are more than 100 identified HPV types, and they are divided into high-risk (HR-HPV) and low-risk (LR-HPV) categories based on their association with cervical cancer [8, 9]. Although most women with HR-HPV infection have only transient infections that do not lead to malignant transformation of the cervical mucosa, HR-HPV is the etiologic agent of almost all cases of cervical cancer. Dunne et al. found that although the overall prevalence of HPV infection (including low- and high-risk types) among US women aged 14 to 59 years was 26.8% (n = 1921), the prevalence of high-risk HPV was 15.2%. In addition, there was a marked peak in HR-HPV infection in women aged 20 to 24 years with a prevalence of 29% [10]. The vast majority of HPV infections (up to 90%) regress spontaneously, without treatment, in a few months [11, 12]. However, if the viral infection persists, the risk of developing precancerous lesions increases, as well as the risk of developing invasive carcinoma [12, 13]. This emphasizes the importance of accurate diagnosis, as well as the identification of those lesions with the highest risk of progression.

Colposcopy-guided biopsy is still considered the "gold standard" in the evaluation of cervical lesions; however, histologic evaluation of these lesions is limited to the interpretation of morphology with little or no information on the risk of persistence, progression, or regression. In addition, histologic assessment of cervical lesions is complicated by interobserver variability [14]. The main categories of interpretation include distinguishing between normal dysplasia (CIN) of any grade and mild lesions (CIN1) from severe lesions (CIN2/3). Errors in histologic diagnosis lead to either overtreatment of patients who will not benefit from intervention or, conversely, undertreatment of patients with clinically significant high-grade lesions who have received false negative diagnoses.

The life cycle of HPV and the molecular events leading to cellular transformation, although not fully understood, have provided insight into potential biomarkers that can be used as additional tests to improve the diagnostic accuracy of cervical lesions and to identify patients at risk of cancer progression.

The purpose of the study is to analyze the current understanding of the pathogenesis, diagnosis, prognosis, prevention and management of patients with cervical dysplasia based on a literature review; to identify risk factors, the role of human papillomavirus (HPV), biomarkers, methods of diagnosis and prevention of cervical cancer.

Materials and methods. All of this data was collected through an extensive literature review and the latest research.

Results and discussion. A systematic analysis of published data shows that the key elements of effective control of dysplasia incidence are scalable screening programs with simultaneous access to molecular diagnostic methods, including HPV genotyping, and wide vaccination coverage of young people [20, 32]. The prevalence of CIN1 and CIN2/3 precancerous changes shows high variability depending on the level of screening coverage: with regular screening at least once every 3 years, the frequency of HSIL detection decreases by more than 2.5 times. For example, in Nordic countries with national screening programs, the rate of invasive cervical cancer is less than 6 cases per 100,000 women, while in countries with low coverage it exceeds 30 per 100,000 [8, 15, 23].

The key pathogenetic factor in the development of cervical dysplasia is the persistence of oncogenic HPV types. Most transient infections are self-limited within 12-18 months, but approximately 10-15% of women progress to dysplastic changes [17, 29, 31]. Leading

studies have shown that the highest level of HPV-16 infection is observed in women aged 20-24 years, with a peak prevalence of up to 29%, which necessitates early vaccination before the onset of sexual activity [6, 8]. In addition, population-based studies have confirmed that HPV infection with types 16, 18, 31, 33, and 45 increases the risk of CIN2+ by 4-7 times [25, 33].

Histologic verification of lesions remains the "gold standard," but the accuracy of diagnosis depends largely on the interpretive agreement between pathologists. Studies have shown that p16INK4a and Ki-67 assessment significantly improves the objectivity of CIN2/CIN3 stratification, avoiding both undertreatment and overtreatment [1, 3, 9]. A meta-analysis of 12 studies with a total sample of more than 9,000 women showed that the combined use of p16/Ki-67 has a sensitivity of up to 92% and a specificity of up to 85% in detecting HSIL [15, 17].

Methods of treating cervical dysplasia, including ablative and excisional interventions, have been evaluated in a number of multicenter studies [21, 26]. According to the updated FIGO and ESGO guidelines, LEEP/LLETZ remain the methods of choice for HSIL, providing complete regression of pathology in 93-95% of cases [14]. At the same time, the recurrence rate within 2 years after the intervention is no more than 4.8% [12, 32]. In a prospective study of 1,400 patients with CIN2+, it was proven that the incidence of long-term obstetric complications (including preterm labor) after LEEP was 7.4%, while the incidence of cold knife cone was 12.1% [10, 18].

A therapeutic alternative in the form of thermal ablation demonstrates efficacy of up to 88% in patients with CIN1/2 at low risk, especially in countries with limited access to surgery [19, 20]. Economic modeling conducted in South Africa showed that the implementation of the HPV testing-treatment with thermoablation strategy can reduce healthcare costs by 35% compared to the classic cytology-histology-surgery algorithm [33].

From an economic point of view, the introduction of universal HPV vaccination in girls aged 9-14 years has one of the highest cost-effectiveness rates of all cancer prevention strategies [5, 19]. According to cost-effectiveness models, every $1 invested in vaccination avoids $3-7 in future costs. In Ukraine, potential healthcare cost savings could reach more than UAH 500 million annually if 80% of the target population is vaccinated [1, 6]. Similar economic benefits are also confirmed when using combined screening and treatment programs that provide an algorithmic approach to patient management involving primary care [25].

In addition, the cost-effectiveness of organizing centralized molecular diagnostic laboratories reduces the average cost of an HPV test by almost 45%, which allows it to be included in national healthcare packages. Model calculations in Poland and Hungary have shown that the transition to HPV testing as primary screening for women aged 30-65 years reduced costs by 21-26% without losing clinical effectiveness [7, 24, 30].

Given the synergistic effect of factors such as low socioeconomic status, lack of regular gynecological surveillance, and low awareness of women, a strategy to combat dysplasia should include not only a medical component but also effective educational, communication, and organizational tools [31]. The results of the systematic analysis suggest that a multidisciplinary approach to the prevention and treatment of cervical dysplasia should be the basis of a modern health care model focused on preserving women's reproductive health and reducing cancer incidence [18, 23].

Conclusions. Despite progress in HPV-related cervical disease management, there remains a need for reliable molecular biomarkers to improve screening accuracy and clinical triage. Studies show that combining HPV DNA testing, genotyping, and p16INK4a immunohistochemistry significantly enhances diagnostic precision and risk assessment. Advanced detection of HPV mRNA and viral load may identify persistent infections linked to disease progression. Effective prevention of cervical dysplasia requires integrating these diagnostic tools with accessible vaccination and screening programs. Tailored treatment based on dysplasia grade and patient risk factors ensures early intervention and better outcomes.

Practical significance. The practical significance of the study lies in the possibility of creating effective individualized approaches to the examination and treatment of patients at risk of cervical disease. Early detection of pathological changes in the cervix makes it possible to develop effective treatment programs aimed at preventing the development of precancerous conditions and cervical cancer, improving the quality of life of patients. The use of modern cervical cancer biomarkers and screening programs is a reliable way to prevent cancer.

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