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Challenges in the diagnosis of cervical pathologies

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ABSTRACT

This review deals with the current state of affairs in the diagnosis of cervical squamous intraepithelial lesions. Transformation of classifications of cervical pathologies is considered. The role of cytological (liquid-based and conventional cytology), molecular biological (Digene Hybrid Capture test), immunohistochemical (p16INK4α, Ki-67), and histologic methods in the diagnosis of cervical lesions is discussed. Particular attention is paid to the diagnosis of human papillomavirus infection. Performance indicators of screening programs based on primary determination of human papillomavirus (HPV) DNA in comparison with common cytological methods are presented. Tropism of HPV to various parts of the cervix, which predisposes to the formation of deep multifocal lesions, as well as the influence of the physical status of HPV on the treatment strategy and risks of relapse are considered.

Keywords: cervical squamous intraepithelial lesions, cervical intraepithelial neoplasia, HPV, diagnosis

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Проблемы диагностики патологий шейки матки

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РЕЗЮМЕ

Статья посвящена современному состоянию проблемы диагностики плоскоклеточных интраэпителиальных поражений шейки матки. Рассмотрены вопросы трансформации классификаций и терминологии патологий шейки матки. Обсуждается роль цитологических (жидкостная и традиционная цитология), молекулярно-биологических (Hybrid Capture Diegene Test), иммуногистохимических (p16INK4α, Ki-67) и гистологических методов в диагностике поражений шейки матки. Особое внимание уделено диагностике папилломавирусной инфекции, приведены показатели эффективности скрининговых программ, основанных на первичном определении ДНК вируса папилломы человека (ВПЧ) в сравнении с общепринятыми

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цитологическими методами. Рассмотрена тропность ВПЧ к различным отделам шейки матки, предрасполагающая к формированию глубоких мультифокальных поражений, а также влияние физического статуса ВПЧ на лечебную тактику и риски рецидивов.

Ключевые слова: плоскоклеточные интраэпителиальные поражения шейки матки, цервикальная интраэпителиальная неоплазия, ВПЧ, диагностика

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

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INTRODUCTION

Squamous intraepithelial lesions of the cervix are some of the most common pathologies among women of reproductive age in clinical practice. The leading etiological factor in these pathologies is human papillomavirus (HPV) infection and its direct cytopathic effect on the cervical epithelium. The main challenge in the diagnosis and treatment of cervical pathologies is high frequency of persistent latent HPV infection involving endocervical glandular lesion, which, in turn, leads to incomplete elimination of the virus, incomplete excision of altered tissues, and, as a consequence, a high relapse rate. Currently, the search for optimal approaches to diagnosing and assessing the prognosis of these pathologies is underway, also through improving screening programs.

CHRONOLOGY OF CHANGES IN CERVICAL PATHOLOGY TERMINOLOGY

The term “dysplasia” in relation to cervical pathology was coined in 1953, and in 1956, it was proposed for the histologic classification of cervical diseases [1]. Dysplasia is characterized by intense atypical cell proliferation in the basal and parabasal layers (cellular and nuclear polymorphism, increased mitosis) with impaired stratification of the epithelium, but without involving the surface layer and stroma. Depending of the altered epithelial layer, weak, moderate, and severe dysplasia are differentiated. Carcinoma *in situ* was considered separately and, according to the FIGO classification, belonged to stage 0 cervical cancer. It was subsequently proven that there are no clear histologic differences between carcinoma *in situ* and severe dysplasia, and a possible similarity of cytological changes was confirmed [2].

In 1973, R.M. Richart proposed a unified concept of neoplastic changes in the cervix. On this basis, the term “cervical intraepithelial neoplasia” (CIN) was proposed to describe the stages of tumor progression [3]. Inclusion of carcinoma *in situ* in the group of severe dysplasia, based on similarities in genetic cell abnormalities, prognosis, and clinical outcomes, made a significant difference for the classification compared to the previous approach.

In 1974–1976, doubt was put on the concept of CIN as obligate precancer following the H. Hausen’s definition of the etiological role of HPV in the development of cervical dysplasia and cancer [4], the pathogenesis of viral damage, the regenerative potential of tissues, and the possibility of self-elimination of the virus.

In 1988, the National Cancer Institute (USA) developed and introduced a new classification for cervical smears – The Bethesda System (TBS) for reporting cervical pathology, heralding the introduction of the term “squamous intraepithelial lesion” (SEL) [5]. According to this approach, dysplastic changes in the cervix are divided into “low-grade squamous intraepithelial lesion (L-SIL)”, corresponding to CIN I, and “high-grade squamous intraepithelial changes” (H-SIL), corresponding to CIN II–III, including carcinoma *in situ* (CIS).

The negative for intraepithelial lesion or malignancy (NILM) category was introduced to indicate a normal cytological pattern. The new classification is etiologically and pathogenetically

substantiated and correlates with the mechanisms of initiation and course of the disease, depending on the high- or low-risk HPV types. Later it was proposed to use TBS categories for the morphological description of the histologic material. Therefore, the use of a unified terminology for histologic and cytological impressions increases the evidence-based diagnosis.

Currently it is recommended to use L-SIL as a diagnostic category to describe changes associated with transient HPV infection, while H-SIL is used to define a true precancerous lesion. However, some ambiguous morphological findings may be included in the Atypical squamous cells (ASCs) category, depending on qualitative and quantitative criteria. This category includes atypical squamous cells of undetermined significance (ASC-US) and atypical squamous cells – cannot exclude H-SIL (ASC-H), differentiated according to the expected lesion grade (L-SIL or H-SIL, respectively) [6]. To describe endocervical epithelial cell abnormalities, the terms "atypical glandular cells" (AGC), "atypical glandular cells, favor neoplastic", and "adenocarcinoma *in situ*" (AIS) were proposed.

According to the International Classification of Diseases (ICD), 11th revision (2022), the abbreviation CIN was completely excluded from use. CIN I was replaced by the term "low-grade squamous intraepithelial lesion of the cervix". The description of L-SIL states that it is a "a condition of the cervix caused by chronic infection," so L-SIL is not currently considered as cervical dysplasia. CIN II and CIN III are grouped in the category of high-grade squamous intraepithelial lesion of the cervix and represent the class *Carcinoma in situ of cervix uteri*. The headings "Cervical intraepithelial neoplasia grade II" and "Cervical intraepithelial neoplasia grade III" were completely excluded from the new edition [7]. The abbreviation SIL has officially replaced the abbreviation CIN in clinical practice.

Thus, over the past 70 years, several approaches to cervical lesion classification have been proposed. Despite the shift in the emphasis toward the development of a clinically oriented classification (TBS) and attempts to standardize the terminology, the existing uncertainty in the use of CIN and SIL demonstrates the lack of unified approaches to the diagnosis and treatment of cervical pathologies.

EPIDEMIOLOGY

The Information Center on HPV and Cancer of the Catalan Institute of Oncology and the International Agency for Research on Cancer have published epidemiological data on the global prevalence of HPV infection caused by HPV types 16 and 18 in women over 15 years, depending on the results of cytological screening. Women with normal cytology results were infected by HPV in 3.9% of cases, and HPV was detected in 25.8% of women with L-SIL. Almost every second woman with H-SIL was infected by HPV (51.9%) [8].

According to D. Egemen et al. (2020), 87% of L-SIL, 95% of H-SIL, and 54% of ASC-US cases are associated with other highly oncogenic HPV serotypes, including those mentioned before [9]. The prevalence of HPV types 16 and 18 in the Russian Federation was 9.4% among women with NILM, 35.1% in women with L-SIL, and 56% in women with H-SIL [10]. It should be mentioned that these highly oncogenic serotypes are the most common both in the Russian Federation and worldwide.

Carriers of HPV infection are most often detected in the group of women aged 20–29 and 30–39 years, as well as in the age group of 40–49 years [11]. The prevalence of cervical lesions varies depending on the population and averages 1.5–7.7% for L-SIL and 0.4–1.5% for H-SIL [12–14]. About 1.7% of cytological smears are classified as L-SIL, 0.3% – as H-SIL, 4.1% – as ASC, and 0.21% – as AGCs [9].

THE ROLE OF HPV INFECTION

The predominant HPV-associated etiology of cervical cancer is proven [4]. Along with common knowledge about the pathogenetic processes caused by HPV persistence, it is necessary to understand the physical status of HPV and its tropism to various parts of the cervix. It is known that high-risk HPV affects pluripotent stem and proliferating cells in the emerging transformation zone, as well as in the superior canal and endocervical crypts [15].

According to J.Y. Chen et al. (2018), glandular lesions were observed in 82.57% of HPV-infected women. The persistence of HPV in the cervical crypts in 80.77% of cases was combined with positive margins after resection and leads to relapse after surgery. Relapse in the initial absence of glandular lesions was observed only in 18.23% of patients with

positive margins [16]. The depth of crypt lesions in 94% of cases did not exceed 5 mm laterally to the cervical canal, however, their location at a distance of up to 4 cm from the ectocervix may be the cause of incomplete excision of the endocervical component [17].

Women with positive endocervical margins are at high risk for recurrent lesions. In addition, negative margins after cold-knife conization do not guarantee the absence of future relapses [18].

According to M. Arbyn et al. (2017), the presence of high-risk HPV after treatment increased the relapse risk to 28.4%, while a negative result reduced the risk to 0.8%. When positive resection margins were combined with a positive HPV status, the risk of relapse was 53%. With negative resection margins and persistent HPV, the risk of relapse was 13%, and 1% with a negative HPV status, regardless of the resection margin state [19].

CYTOLOGY, HISTOLOGY, IMMUNOHISTOCHEMISTRY

A cytological examination of the cervical epithelium with interpretation of the results according to TBS is used in all cervical screening programs. The sensitivity and specificity of the cytological method for L-SIL detection is 80.31 and 68.46%, respectively, while for H-SIL, it is 97.14 and 85.58%. respectively [21]. However, approximately 30% of newly diagnosed cases of cervical cancer occur among women who were screened negative due to misinterpretation or sampling errors [22]. Comparing liquid-based and conventional cytology methods, a lot of authors state that liquid-based cytology improves the quality of cytological material, is more preferable in terms of cost-effectiveness, and also makes it possible to use the sample for subsequent HPV testing [22–24]. Positive predictive value (PPV) of these methods is comparable. Negative predictive value (NPV) is higher for liquid-based cytology [25]. A systematic review carried out in 1991–2007 as part of the European Quality Assurance Guidelines for Cervical Cancer Screening found that although liquid-based and conventional cytology had equal sensitivity and specificity in detecting dysplasia from stage CIN II (H-SIL), the specificity of liquid-based cytology in case of ASC-US was lower [26].

Cytological screening does not reveal any pathology in most HPV-positive women. It was established that among HPV-positive women with normal cytology results, dysplasia was diagnosed within 5 years in 6.4% of cases [27]. The affected glands often located deep in the cervical canal make obtaining adequate material for the cytological examination difficult. That is why the cytological examination is limited in the diagnosis of precancer and cancer of the cervix. Pathological changes in the obtained material may be mild or absent, since the process is often located deep in the crypts, while the squamous epithelium is practically intact [28].

In this case V.G. Cherenkov et al. (2019) insisted on obtaining the material for cytological and molecular studies not only from the transformation zone, but also from the crypts in the endocervix [29]. In addition, it is recommended to perform a biopsy involving the endocervical component before elaborating a treatment strategy, since it is persistence of HPV in the crypts that may cause subsequent progression of lesions as well as relapses, especially in case of H-SIL [30, 31].

The histologic method is the gold standard for cervical pathology diagnosis. Comparing the results of the cytological examination and the final histologic diagnosis, several authors noted significant discrepancies. In 20% of patients with L-SIL cytology, the presence of dysplasia was not confirmed, in 45.52% of cases, CIN I (L-SIL) was detected, in 20.89% of cases – CIN II (H-SIL), and in 04.47% of cases – CIN III (H-SIL). On the other hand, in 0.9% of H-SIL cases, the presence of dysplasia was not confirmed, CIN I (L-SIL) was detected in 15.09% of cases, CIN II (H-SIL) – in 16.98% of cases, CIN III (H-SIL) – in 50.94% of cases. Cervical cancer was detected in 5.6% of H-SIL cases [32].

A comparative analysis of the histologic findings after primary excisional biopsy in patients with previous targeted cervical biopsy showed a higher positive correlation with CIN I (L-SIL) and CIN III (H-SIL) compared to CIN II (H- SIL). Cervical cancer was revealed by excisional methods in 1.8% of patients with CIN III (H-SIL), diagnosed previously by targeted biopsy [33].

Applying immunohistochemical markers of cell proliferation, such as ki-67 and p16/INK4a, can help to improve the accuracy and information value

of a routine histologic examination and reduce the frequency of false-positive and false-negative results. HPV DNA replication begins with the formation of oncoproteins E6 and E7 promoting the functional inactivation of the retinoblastoma protein (pRb) genes, which has an antiproliferative effect through the expression of the p16/INK4a protein [34].

The transforming effect of HPV leads to overexpression of this protein, controlled by pRb through negative feedback [35]. Ki-67 is a nuclear non-histone protein actively expressed during cell division (cell proliferation marker) [36]. Overexpression of Ki-67 is associated with the severity of dysplastic changes in the cervix, but not with HPV infection [37]. It is known that an increase in dysplastic changes of the cervix is associated with an increase in the expression of these markers [38]. Most L-SIL cases are associated with elevated levels of Ki-67. Approximately in one third of L-SIL cases, strong diffuse expression of p16INK4a can be found in the lower part of the epithelial layer [39]. However, it has been proven that not every p16INK4a-associated damage of the cervical epithelium is caused by HPV.

P.P. Pereira et al. (2022) demonstrated the possible immunopositivity for p16 and Ki-67 in healthy tissues, as well as in areas of tubal metaplasia of the cervix and cervical endometriosis [40]. Thus, simultaneous detection (coexpression) of both p16INK4α and Ki-67 proteins (dual stain) has the greatest diagnostic value. Simultaneous detection of p16/Ki-67 can be a reliable method for risk stratification among HPV-positive women, especially in cases of CIN II–III (H-SIL) [41]. The degree of coexpression correlates with the severity of cervical lesions and indicates the disease progression [42].

UNRESOLVED ISSUES IN THE DIAGNOSIS OF CERVICAL PATHOLOGY

The issues of diagnosis, treatment, and prevention of squamous and glandular cervical lesions remain highly relevant in the Russian Federation and around the world. It is explained by many factors, including the need to optimize screening, treatment, and prevention programs [43].

The International Federation of Gynecology and Obstetrics (FIGO) recommends a cytological examination (up to 60 years old) and testing for HPV (up to 65 years old) as screening every 5 years. The Society of Gynecologic Oncology and American Society for Colposcopy and Cervical Pathology (ASCCP) have recommended only primary HPV screening for women aged 25 years and older since 2015. The World Health Organization (WHO, 2014) recommends HPV testing, a cytological examination, and a visual inspection with acetic acid at least once for every woman aged 30–49 years [25]. PCR methods for HPV diagnosis are increasingly replacing cytology as the main screening test in the USA, Australia, and England [44–46].

The mainstay for the diagnosis of persistent HPV infection is the detection of viral DNA in cervical scraping by PCR (Hybrid Capture Digene HPV test) with determination of the critical DNA concentration (viral load) and assessment of the physical status, the oncogenic risk (high or intermediate), and the type of infection (single or multiple).

Despite the described cases of HPV-negative lesions of the cervix, including malignant ones, L. Rodríguez-Carunchio et al. (2015) in most cases associated the detection of such lesions with diagnostic artifacts and false-negative results. This fact was confirmed by the detection of viral DNA when using more sensitive PCR diagnostic methods [47].

According to T. Malagón et al. (2020), the use of Hybrid capture-based technology for the HPV diagnosis reduces the risk of subsequent occurrence and progression of cervical dysplasia to a greater extent than the use of other PCR methods among women with normal cytology findings [27].

According to a Cochrane Library review, the sensitivity of Hybrid capture-based detection of precancerous lesions of the cervix is higher than that of cytological diagnostic methods. Precancerous lesions will be diagnosed in 20 screened women out of 1,000. The HPV test will identify 18 women in this group, while the cytology test will identify 15. A negative HPV test result is more reassuring than a negative cytology result, because the cytology test has a higher chance of being false-negative [48].

There are controversies regarding the choice of the screening method for the age group of 25–30 years old. The results of numerous studies indicate that transient HPV is common among this age group, and self-elimination of the virus reaches 90%. HPV persistence is more often observed for 2 years or

more in the age group of 30 years and older, which is one of the risk factors for lesion progression [49–51]. Consequently, HPV screening before the age of 30 might be associated with a high rate of false-positive results, which can lead to unnecessary treatment. Despite this, primary HPV screening among women of this age group is associated with higher CIN III (H-SIL) detection compared to cytological methods. According to O. Feldstein et al. (2023), it should be considered as the main diagnostic approach in this age [52].

Y.J. Tai et al. (2017) assessed the links between the risk of disease progression and the diagnostic and treatment approaches among 53,000 women with L-SIL [53]. These approaches included repeated cytology, colposcopy, cervical biopsy or cervical curettage, cryotherapy, and excisional methods. It revealed that cryotherapy and excisional procedures significantly reduced the risk of lesion progression, presumably due to the effective elimination of HPV. C. Firnhaber et al. (2017) and G. St-Martin et al. (2021) also supported the active diagnostic and treatment strategy in cases of L-SIL. [54,55].

On the other hand, C. Buick et al. (2020) and C. J. Min et al. (2020) indicated that there is no need for in-depth screening and subsequent treatment of young women with L-SIL due to a low risk of malignancy and a high probability of spontaneous elimination of HPV in this age group [56, 57].

CONCLUSION

Direct pathogenetic links of squamous intraepithelial and glandular lesions with the progression of cervical cancer dictate the need to search for new diagnostic approaches in order to timely identify and treat these conditions and reduce the risk of their progression.

Long-term latent HPV persistence, especially in the cervical crypts, leads to an increased risk of occurrence and recurrence of squamous intraepithelial and glandular lesions. Modern diagnostic and treatment approaches should be aimed at increasing the efficiency of cervical lesion diagnosis by assessing the degree of involvement of the cervix and especially cervical crypts in the pathological process, as well as by determining the optimal volume of excision. These issues can be solved by a comprehensive assessment of cytological, molecular biological, histologic, and immunohistochemical findings that have high sensitivity and specificity for the diagnosis of cervical pathologies.

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