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CURRENT ASPECTS OF DIAGNOSIS AND MANAGEMENT OF CERVICAL INTRAEPITHELIAL NEOPLASIA (CIN)

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Abstract. This article provides a comprehensive analysis of contemporary approaches to the diagnosis and treatment of cervical intraepithelial neoplasia (CIN) within the framework of updated international protocols. The pathogenetic role of high-risk human papillomavirus (hrHPV) and the mechanisms of epithelial malignant transformation are examined. The diagnostic value of co-testing (cytological examination in conjunction with HPV typing) and the role of p16 and Ki-67 immunohistochemical markers in differentiating dysplasia grades are analyzed in detail. Management strategies for patients with varying degrees of lesions (CIN I–III) are addressed, specifically focusing on the criteria for selecting between conservative surveillance and surgical excision. The study findings confirm that a personalized approach based on risk stratification allows for minimizing the iatrogenic impact on women's reproductive health without increasing the risk of oncological progression.

Keywords: cervical intraepithelial neoplasia, CIN, human papillomavirus, HPV, co-testing, p16/Ki-67, cervical screening, risk stratification, surgical excision.

Introduction. Despite the implementation of screening and vaccination programs, cervical intraepithelial neoplasia remains one of the most pressing issues in modern gynecology. [1] Timely identification of precancerous conditions allows for the prevention of invasive cervical cancer (CC) in nearly 100% of cases; [1, 2, 3, 4, 5, 6] however, the choice of the optimal treatment method remains a subject of debate, particularly in women of reproductive age.

Purpose and objectives of the study. To summarize and systematize current data regarding the etiopathogenesis, early visualization methods, and morphological verification of CIN, as well as to evaluate the effectiveness of various patient management strategies to optimize clinical outcomes. [1, 7] To achieve this goal, several research objectives were established. Primarily, the study is aimed at investigating the role of HPV persistence as a trigger for neoplastic transformation and evaluating the effectiveness of modern screening models. A crucial aspect is determining the diagnostic significance of p16 and Ki-67 immunohistochemical studies as a tool for verifying abnormal changes. [2, 5] Additionally, the study involves a comparative analysis of the efficacy of surgical methods, such as loop electrosurgical

excision procedure (LEEP) and conization, in comparison with conservative surveillance strategies.[7, 8] Furthermore, the research aims to justify the role of vaccination as a component of the comprehensive treatment of patients with already diagnosed lesions.

The results of the study and their discussion. Cervical Intraepithelial Neoplasia (CIN) is a precancerous condition characterized by impaired differentiation and proliferation of atypical cells within the stratified squamous epithelium of the cervix. [9, 10] Despite significant progress in vaccine prevention, cervical cancer (CC) remains one of the leading causes of mortality among women of reproductive age. [1, 3, 7]

Etiology and Pathogenesis. The primary etiological factor of CIN is the prolonged persistence of high-risk human papillomavirus (hrHPV) strains (predominantly types 16 and 18). [9, 10, 11, 12, 13] The process of malignant transformation is associated with the integration of viral DNA into the host cell genome, leading to the hyperexpression of E6 and E7 oncoproteins. These proteins inactivate tumor suppressors (p53 and pRb), which triggers an uncontrolled cell cycle. [14]

Classification. According to modern terminology, CIN is classified by the degree of epithelial involvement:

- **CIN I** (Mild Dysplasia): Atypical cells occupy the lower third of the epithelial layer. The superficial and intermediate layers are preserved. The risk of developing cervical cancer is approximately 1%. It often regresses spontaneously (in up to 60% of cases).
- **CIN II** (Moderate Dysplasia): Atypical changes are primarily detected in the lower two-thirds of the epithelial thickness. The probability of developing a malignant process is 5%.
- **CIN III** (Severe Dysplasia or Carcinoma in situ): Involvement of the entire epithelial thickness without breaching the basement membrane. It exhibits pronounced morphological changes: cells in all layers of the epithelium develop large nuclei and an abnormal frequency of mitosis; cells mature and differentiate only in the superficial layer. The risk of tumor occurrence increases to 12-15%. [1, 5, 7, 10, 15]

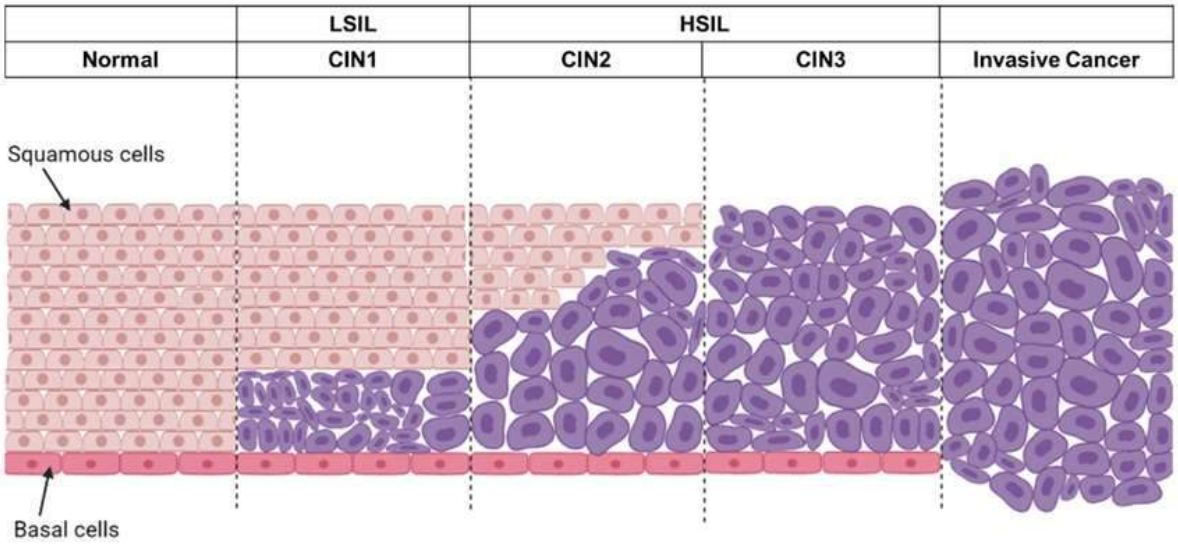

Figure 1. An overview of the progression of cervical cancer
data generated [16]

Table 1. Correlation between Cytological Findings (Bethesda System) and Histological Diagnosis (CIN)

<table>
<tr><td></td><td></td><td colspan="5">Unambiguous interpretation</td></tr>
<tr><td rowspan="5">Cytological findings</td><td rowspan="5">The Bethesda System for Reporting Cervical Cytology</td><td>NILM
Negative for intraepithelial lesion or malignancy. Negative for reactive cellular changes associated with inflammation and repair. [8, 17]</td><td>LSIL
Low-Grade squamous intraepithelial lesion</td><td colspan="3">HSIL
High-Grade Squamous intraepithelial lesion</td></tr>
<tr><td colspan="5">Borderline interpretation</td></tr>
<tr><td colspan="5">ASC (Atypical squamous cells)</td></tr>
<tr><td colspan="2">ASC-US
Atypical squamous cells of undetermined significance</td><td colspan="3">ASC-H
Atypical squamous cells, cannot rule out HSIL</td></tr>
<tr><td>Histological Diagnosis</td><td>The Cervical Intraepithelial Neoplasia System</td><td>Normal</td><td>HPV</td><td>CIN I</td><td>CIN II</td><td>CIN III</td></tr>
</table>

Data generated by author

Diagnostics. The modern diagnostic algorithm is based on a three-step approach:

1. Screening: PAP test (liquid-based cytology is preferred) and HPV testing (Co-testing). [4, 5, 11, 12]
2. Colposcopy: Visualization of pathological areas (acetowhite epithelium, punctation, mosaicism) using acetic acid and Lugol's (Schiller test) solutions. [2, 5, 14]
3. Histological confirmation: The "gold standard" — targeted (punch) biopsy or excision followed by pathomorphological examination. [3, 4, 18]

Table 2. Performance of Diagnostic Methods

Diagnostic method	Sensitivity	Specificity
Cytology (PAP test)	50–70%	90–95%
HPV test	95–98%	85–90%
Colposcopy	80–90%	70–80%

Data generated [14]

Additional tools may include:

4. Immunohistochemical (IHC) study for p16 and Ki-67. [2, 5, 19]
5. Testing for E6/E7 oncoproteins. [14]

During colposcopy with acetic acid or Lugol's solution, clinicians evaluate the characteristics of the lesion margins, surface relief, lesion size, and vascular patterns. [14] A targeted biopsy is performed during colposcopy to verify the type of CIN. [14, 20] In an excisional biopsy, a larger volume of tissue is removed (compared to a punch biopsy) using LEEP (Loop Electrosurgical Excision Procedure) or conization [2, 7, 8].

Factors that negatively affect the quality of the cervical cell sample include menstruation, abnormal uterine bleeding, inflammatory diseases of the vagina and cervix, sexual intercourse within 24 hours before sampling, pronounced genitourinary syndrome, pregnancy, postpartum and lactation periods, physical manipulations or chemical irritation, previous colposcopy with acetic acid less than 24 hours before sampling, radiotherapy, and recent surgical interventions on the cervix. [18]

Immunohistochemical studies (p16/Ki-67) allow for the differentiation of low-risk changes (LSIL, CIN I) from high-risk ones (HSIL, CIN II/III). [5, 14, 19, 20, 21] P16 is a tumor suppressor protein whose expression significantly increases in cells infected with high-risk HPV due to the interaction of viral E6/E7 oncoproteins with the pRb protein. [2, 5] High levels of Ki-67 indicate uncontrolled cell proliferation, which is characteristic of high-grade dysplasia. [20]

The E6/E7 oncoprotein test is more specific than conventional HPV DNA testing. [21] E6 and E7 are viral oncoproteins that inhibit the activity of two crucial cellular suppressor proteins, p53 and pRb. This leads to uncontrolled cell division and the formation of precancerous or cancerous changes. Detecting high levels of E6/E7 is a strong indicator that the HPV infection is causing active cellular transformation with a high risk of progression to CIN III or invasive cancer. [14, 20, 21]

Depending on the oncogenic potential, viruses are classified into high-risk and low-risk types. High-risk HPV strains include types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. [15] Types 16 and 18 alone account for 70% of cervical cancer and 80% of vulvar and vaginal cancer. [10, 11, 12, 14] Detection of high-risk HPV increases the risk of cervical cancer 70-fold. [11]

Treatment Strategy and Management. Active surveillance of women with histologically confirmed cervical precancerous lesions involves regular monitoring to assess the risk of progression, especially in young women. The choice of strategy depends on the degree of neoplasia, visualization of the transformation zone (TZ), comorbidities, extension to the cervical canal or vagina, the patient's age, and reproductive plans, with a possible transition to minimally invasive treatment if more severe changes are detected. [3, 8, 15]

The primary indications for treatment remain histologically verified HSIL or CIN II+, except in special circumstances: patients concerned about the potential impact of treatment on future pregnancy outcomes, women under 25 years of age, and pregnant women. Immediate treatment without biopsy (the "see-and-treat" approach) is possible only in non-pregnant patients over 25 years old under special circumstances (limited access to care, disability, etc.) and only with informed consent. [1, 7, 8, 14, 15]

1. Conservative Strategy (Surveillance)

Primarily applied for CIN I. Repeat cytological examination and HPV testing are recommended every 6–12 months. In young women (under 25) with CIN II, surveillance for 12 months is also possible, provided there is adequate colposcopic visualization. [1, 2, 3, 12]

2. Surgical Treatment

Indicated for CIN II–III and persistent CIN I (lasting more than 2 years).

- Ablative methods: Cryodestruction, laser vaporization (effective only with full visualization of the transformation zone).
- Excisional methods: LEEP/LLETZ or cold-knife conization. These methods provide tissue samples for histology, which is critical for ruling out microinvasion. [3, 8, 22]

Table 3. Management strategies and treatment modalities for histologically confirmed CIN

PAP test		
CIN I		CIN II-III
21-29 years old: Repeat Pap test in 12 months	30-65+ years old: Colposcopy	Colposcopy
	Confirmation of CIN1	Confirmation of CIN II-III
	Surgical treatment	Surgical treatment

Data generated by author

Table 4. Clinical triage and follow-up for NILM, ASC-US, and ASC-H findings

PAP test				
	LSIN			HSIL
	NILM	ASC-US		ASC-H
21-29 years old	PAP test every 2 years	Pap test every 12 months		Immediate referral for colposcopy with biopsy without additional testing, is performed in all age groups
		If results are negative then co-testing every 5 years or PAP test every 3 years	If results are positive then colposcopy	Excisional therapy may be performed depending on colposcopic findings and biopsy results
30-65+ years old	Co-testing (PAP test + HPV test) every 5 years			

Data generated by author

Histologically verified CIN II exhibits a higher frequency and rate of regression compared to CIN III, which justifies deferring treatment in young women. [4, 21] The primary rationale for delaying the treatment of CIN II is the potential risk of adverse obstetric outcomes, specifically preterm birth, following excisional therapy or ablation. [1, 7, 8]

CIN III is considered a direct precursor to cervical cancer and always necessitates treatment. [4, 20] With informed consent, immediate treatment using an excisional procedure can be performed in a single visit ("see-and-treat") for non-pregnant patients aged 25 and older, as well as for older women with an immediate risk of developing cancer between 25–100% based on their history and current results: cytologically confirmed HSIL regardless of HPV testing, or HPV-positive results with cytologically verified ASC-H. [8, 9, 12, 14]

Ablation may be considered for the treatment of extensive cervical lesions or those extending to the vagina, provided that all other criteria for ablation are met.

Adjuvant HPV vaccination is recommended for previously unvaccinated individuals aged 27 to 45 undergoing treatment for CIN II+. This intervention reduces the frequency of recurrence, ensures treatment efficacy, and provides long-term protection for the patient. [10, 11, 15, 19, 22]

Conclusions. The analysis conducted suggests that the effectiveness of cervical cancer prevention directly depends on the accuracy of primary screening, where HPV testing demonstrates a higher predictive value compared to isolated cytology. It has been established that the management of patients with cervical neoplasia must be differentiated: an active surveillance strategy is entirely justified and safe for young women diagnosed with CIN II, provided there are favorable colposcopic findings, thereby minimizing the risks of future obstetric complications.

At the same time, surgical treatment in the form of radiowave excision (LEEP) remains the priority for HSIL, ensuring high radicality with relatively low surgical trauma. Ultimately, the integration of vaccination into treatment and follow-up protocols creates a synergistic effect, significantly reducing recurrence rates and ensuring long-term protection for the patient.

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