American Journal of Medicine and Medical Sciences 2026, 16(6): 2805-2808
DOI: 10.5923/j.ajmms.20261606.08

Squamous Cell Intraepithelial Lesions of the Cervix: Possibilities of Early Diagnosis and Patient Management Tactics

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Abstract This article examines the role of human papillomavirus (HPV) in the etiology and pathogenesis of squamous intraepithelial lesions and cervical cancer. Current diagnostic capabilities and management strategies for patients with HPV-associated cervical diseases are presented. The results of studies on the safety and efficacy of a combination drug are analyzed.

Keywords Cervix, Human papillomavirus, Somatotype, Intraepithelial neoplasia, Constitutional affiliation

1. Introduction

Cervical cancer (CC) remains one of the most pressing issues in gynecological oncology. It is the third most common malignant neoplasm in women worldwide, the most common among women aged 15–39, and the most common cause of cancer death in developing countries [1,18]. The increasing incidence of the disease in women, with a trend toward younger age, is highly alarming, as this patient group represents not only a reproductively significant portion of the population but also a socially active group [2,17]. In recent years, the number of women aged 20 to 40 years (41.21%) with the disease has almost doubled. A particularly noticeable increase has been observed in the age group under 29, where the increase in this indicator over the past decade has amounted to 150% [3,16]. High-risk human papillomavirus (HRHPV) plays an important role in the carcinogenesis of cervical cancer [4,15]. Human papillomavirus infection (HPV) is one of the most common sexually transmitted infections, with infection rates among the sexually active population of the planet reaching 20–60% [5.8]. It is generally accepted that HPV infection is an early indicator of a precancerous condition [6], and HPV causes HPV-induced genital cancer in 15–20% of those infected [7,9,10]. The development of invasive cervical cancer is preceded by intraepithelial cellular atypical changes, designated as cervical intraepithelial neoplasia (CIN) of varying severity, and carcinoma in situ - conditions in which some cells exhibit signs of cellular and nuclear atypism and disruption of the anisotropy of the epithelial layer without destruction of the basement membrane and penetration of atypical cells into the underlying tissues. CIN is considered to be a pre-invasive analogue of invasive squamous cell carcinoma [1,10]. It is known that patients with dysplasia of the stratified squamous epithelium (SSE) belong to the high-risk group for the development of invasive carcinoma; however, the process of malignant transformation occurs over a sufficiently long period of time, which makes it possible to carry out appropriate treatment measures to prevent the development of cancer [2,11]. Currently, there is no method for predicting the course of CIN in a specific patient, determining the possibility of persistent persistence or progression to a higher degree or to invasive cervical cancer, indicating the exact duration of this process [2,12]. Obviously, the inadequacy of screening control and the limited capabilities of traditional examination methods significantly complicate the timely detection of preinvasive pathological cervical conditions. Particularly difficult is the diagnosis of latent and subclinical forms of HPV infection, which often coexist with clinically manifested conditions of the cervical epithelium, predisposing to relapses after removal of the visible tumor focus associated with the persistence of the virus in adjacent tissues. It is known that even conization of the cervix does not always provide a complete therapeutic effect, since unresected foci of neoplasia may remain in the remaining MSE, accounting for from 5 to 28% [13,17]. The above necessitates the search for new diagnostic and therapeutic methods for cervical pathology aimed at reducing chronic (persistent) papillomatous infections, which serve as precursors to invasive cancerous tumors [18].

Currently, pathological changes in the cervix are recorded as complicated clinical forms against the background of severe dysbiotic disorders, excessive colonization of the lower genital tract with opportunistic microflora, and often in combination with sexually transmitted infections (STIs)

Received: May 11, 2026; Accepted: May 29, 2026; Published: Jun. 1, 2026
Published online at http://journal.sapub.org/ajmms

[2,3,15]. Penetration of viruses into cells is facilitated by changes in the vaginal environment and the pathological condition of the superficial layers of the cervical epithelium. In this regard, infection with the human papillomavirus (HPV) is of particular importance, since the persistence of its highly oncogenic types leads to intraepithelial neoplasia and cervical cancer [1,4,8]. According to literature [1,2,16], it is a proven fact that since the 1990s, dysplasia and preinvasive cancer have been trending toward younger age. Physicians are faced with the task of preventing the progression of the pathological process from dysplasia to preinvasive and invasive cervical cancer.

For women with HPV-associated dysplasia of varying severity, determining the management strategy, selecting the optimal surgical treatment method, and administering modern antiviral therapy is important.

The aim of this study is to improve approaches to selecting an appropriate treatment method depending on the severity of HPV-associated cervical dysplasia (CDM).

2. Materials and Methods

A total of 2,328 women living in Bukhara were examined, including 234 women aged 23 to 54 years (mean age of the subjects was 38.3 ±6.7 years) with CDM of varying severity combined with HPV. A medical history was significant in 189 (35.2%) women, including gastrointestinal, cardiovascular, and endocrine diseases. Smoking rates were 29.2%. The average age at menarche was 12.3 ±1.2 years; only 3.2% of women began menstruating after the age of 16. At the initial consultation, 93.3% of women had a regular menstrual cycle, 2.2% were in menopause or postmenopause, and 4.5% had menstrual disorders. All women were sexually experienced. Early onset of sexual activity (before the age of 18) was reported by 16.7% of women. The number of sexual partners ranged from 1 to more than 50. Anamnesis collection revealed that 57.1% of women had regular sexual activity, human papillomavirus infection (HPV) was detected in 18.2%, 100% had given birth, and 74.3% had artificial abortions. Contraception was used by 54.9%, more than half of them used coitus interruptus, and barrier methods of contraception were used by 38.4% of women. Examination for STIs was conducted in 100% of cases. In addition to the detection of HPV, which served as the selection criterion for the study groups, other STIs were detected in 61.2% of women, and pelvic inflammatory disease in 25.7%. We qualitatively assessed the colposcopy results using the M. Coppleson system, and quantitatively, using the Richard Reid scoring system (modified Reid colposcopic index), which allows for the differential diagnosis of various cervical lesions. We analyzed 534 colposcopy reports. The first group consisted of 235 (44.0%) examined women with minimal epithelial damage (Reid score 0-2); the qualitative Coppleson score corresponded to stages 1-2. Histological examination of the material revealed chronic exocervicitis without signs of dysplasia in 5 (0.01%) women of the first group, CIN 1 in 34 (6.68%), CIN 1-2 in 152 (28.6%), CIN 2 in 27 (5.2%), and CIN 2-3 in 17 (3.2%). The second group included 270 (50.6%) patients whose colposcopic picture corresponded to a moderate degree with a transition to a high degree of epithelial damage (4-6 points according to Reid), and the qualitative assessment corresponded to stage 2-3 of cervical dysplasia according to Coppleson. Histological examination of the material revealed CIN 1 (dysplasia 1) in 52 (9.9%) examined women of the second group, CIN 1-2 (dysplasia 1-2) in 159 (29.9%), and CIN 2-3 (dysplasia 2-3) in 59 (11.4%). The third group included 29 (5.4%) patients with a high degree of epithelial damage (6-8 points according to Reid), the qualitative assessment according to Coppleson corresponded to stage 2-3. Analysis of the results of the histological examination of the material revealed that CIN 1-2 (dysplasia 1-2) was detected in 3 (0.01%) patients of the third group, CIN 2-3 (dysplasia 2-3) in 19 (3.7%), and CIN 3 (dysplasia 3 and cancer in situ) in 7 (1.4%). Colposcopic evaluation of results cannot replace histological examination; however, it can be used to predict dysplasia and preclinical forms of cancer with high accuracy. This examination facilitates the correct selection of the biopsy site and is used in the differential diagnosis of numerous benign diseases. Patients underwent various surgical treatments: diathermocoagulation was performed in 127 patients, cryosurgery in 186, laser vaporization in 32, cone electrosurgical excision of the cervix in 17, radiowave excision in 142, and knife amputation of the cervix in 30. For differentiation, we used a control histological examination of cervical tissue samples obtained using methods allowing this analysis (cone electrosurgical excision of the cervix, radiowave excision, and knife amputation of the cervix). In 142 patients who underwent radio wave excision, the incidence of high (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68) and low (6, 11, 42, 43, 44) oncogenic risk HPV types was 83 (58.5%) and 59 (41.5%), respectively. Patients with HPV who underwent radio wave excision of the cervix received antiviral therapy. Before the manipulation and dynamically, the concentration of cytokines - interleukins (IL): -8, -6, -4, -1 and IL-IR (receptor antagonist to IL-1) in the mucus of the cervical canal was determined.

The determination was carried out by a solid-phase enzyme immunoassay according to the method of Caltag Laboratories, USA. Obtaining and preparing cervical mucus for the study of the cytokine spectrum was carried out by collecting mucus using a brush, fixing the washing in a physiological solution in a ratio of 1:10 and storing the samples in polypropylene Eppendorf tubes (volume 2 ml). Interleukins produced by cells of the lymphoid system are predominantly pro-inflammatory: IL-1 (IL-1α and IL-1β), IL-8, IL-6, while IL-4 and IL-IR are anti-inflammatory cytokines. Pro-inflammatory interleukins and, in particular, IL-1, quickly respond to tissue damage and infection and are a trigger for the development of primary immune reactions, which determines the appropriateness of their assessment as diagnostic markers of the disease and criteria for the effectiveness of the therapy. In 93 (65.5%) of 142 patients

with planned subsequent radio wave excision of the cervix and identified inflammatory diseases or other STIs, first-stage therapy was carried out, which consisted of prescribing antiseptics followed by prevention of dysbiotic conditions. The most frequently encountered STIs in association with HPV were Candida spp. - in 42 (45.2%), Gardnerella vaginalis - in 34 (36.6%), the association of Gardnerella vaginalis + Ureaplasma urealyticum - in 12 (12.8%) and Trichomonas vaginalis - in 5 (5.4%). Then, using random sampling, 142 patients were divided into three representative groups: in group 1, antiviral therapy was carried out before surgical treatment; In the 2nd group — against the background of surgery with its continuation in the postoperative period, in the 3rd group the treatment was only surgical. In accordance with the plan, 142 patients were divided into three groups: Group 1 — 47 (33.1%) patients, Group 2 — 47 (33.1%) and Group 3 — 48 (33.8%). The first-stage therapy, carried out by 65.5% of the subjects, included the administration of antiseptics intravaginally for 6-10 days, followed by the introduction of probiotics for 6 days. pH was monitored during therapy: if before the start of therapy the pH was 5.9 ± 0.03, then after the introduction of antiseptics the pH was 5.8 ± 0.02. The use of probiotics contributed to a significant decrease in the pH level. Thus, after 6 days of probiotic administration, the pH level was 4.7 ±0.03, with a significant difference between the pH values before and after probiotic administration (p=0.01). After completing the first-stage therapy, an STI test was again performed, and if the results were negative, the patient was included in the observation group. Antiviral therapy included the use of Panavir suppositories and gel, which is a direct-acting antiviral drug with immunomodulatory properties. Its use increases the body's nonspecific resistance to various infections. In addition, the experiment demonstrated the anti-inflammatory effect of Panavir. The method of administration was as follows: Panavir suppositories containing 200 mcg of the active ingredient are administered rectally for 10 days, one suppository daily at night. A thin layer of 0.002% Panavir gel is simultaneously applied to the vaginal and cervical mucosa for 5 days. The drug is well tolerated in therapeutic doses. It suppresses viral activity in the early stages, relieves clinical symptoms, restrains the spread of the lesion, protects against secondary infection, and strengthens local immunity. In Group 1, Panavir suppositories and gel were administered 10 and 5 days before the planned surgery, respectively; in Group 2, therapy was administered starting on the first postoperative day with suppositories as described above, and starting on the third postoperative day, the gel was added (by intravaginal administration directly to the cervix) for 5 days. Immunological parameters were monitored before and after therapy in Groups 1 and 2, and only before therapy in Group 3. Follow-up in all three groups was performed 3 months after surgery and compared with each other. As can be seen, we obtained better results in terms of a decrease in the concentration of proinflammatory interleukins at the local level in the first group of subjects (who received Panavir before surgery) compared to the indicators in the second group (Panavir was prescribed simultaneously with surgery and with prolonged treatment in the postoperative period). When comparing the results before and after treatment, a significant difference was noted in all indicators in both groups ($p < 0.01$). Moreover, the indicators in the first group significantly differed from similar interleukin indicators in the second group after treatment ($p < 0.05$).

In addition, we analyzed delayed interleukin levels in all three groups of patients who underwent radiofrequency excision of the cervix. In the women receiving Panavir (Groups 1 and 2), local interleukin levels remained virtually unchanged compared to the data obtained after the end of therapy. In Group 3, women who did not receive antiviral therapy, interleukin levels did not differ significantly from those at baseline. Three months after the end of treatment, a significant difference was found between Groups 1 and 2 ($p < 0.05$), as well as between Groups 1 and 3 ($p < 0.01$). A significant difference was also found between Groups 2 and 3 ($p < 0.05$).

Thus, radiofrequency excision is the most optimal surgical correction method for cervical dysplasia requiring surgical treatment. An assessment of the cytokine status at the local level in the association of dysplasia with HPV indicates the feasibility and effectiveness of antiviral therapy on the eve of surgical treatment, and the drug of choice in this case may be Panavir in the form of gel and suppositories.

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