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NEW DAY IN MEDICINE**

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**FEATURES OF THE CLINICAL COURSE AND PARACLINICAL CHARACTERISTICS  
OF CERVICAL DISEASES DEPENDING ON INFECTION  
OF PATIENTS WITH HPV TYPES 16/18**

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✓ **Resume**

*Based on the conducted analysis, the effectiveness and feasibility of using a set of modern non-invasive methods for the early diagnosis of cervical lesions associated with the human papillomavirus were substantiated and determined, allowing for the determination of the scope and timing of both diagnostic and therapeutic measures.*

*In patients with pathological changes in the cervix, infected with human papillomavirus types 16 and 18, compared with uninfected patients, colposcopic and cytological signs of severe intraepithelial neoplasia are significantly more often detected.*

*Keywords: cervix, human papillomavirus, intraepithelial neoplasia.*

**ОСОБЕННОСТИ КЛИНИЧЕСКОГО ТЕЧЕНИЯ И ПАРАКЛИНИЧЕСКОЙ  
ХАРАКТЕРИСТИКИ ЗАБОЛЕВАНИЙ ШЕЙКИ МАТКИ В ЗАВИСИМОСТИ ОТ  
ИНФИЦИРОВАНИЯ ПАЦИЕНТОК ВПЧ 16/18 ТИПОВ**

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✓ **Резюме**

*На основании проведенного анализа обоснована и определена эффективность и целесообразность использования комплекса современных неинвазивных методов ранней диагностики поражений шейки матки ассоциированных с вирусом папилломы человека, позволяющих определить объем и сроки проведения как диагностических, так и лечебных мероприятий.*

*У пациенток с патологическими изменениями на шейке матки, инфицированных вирусом папилломы человека 16 и 18 типов, по сравнению с неинфицированными, достоверно чаще выявляются кольпоскопические и цитологические признаки тяжелой интраэпителиальной неоплазии.*

*Ключевые слова: шейка матки, вирус папилломы человека, внутри эпителиальная неоплазия.*

**OPV 16/18 TURLARI BILAN BEMORLARNING INFEKSIYASIGA QARAB, BACHADON  
BO'YNI KASALLIKLARINING KLINIK KECHISINING XUSUSIYATLARI VA PARAKLINIK  
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✓ **Rezyume**

*O'tkazilgan tahlil asosida, inson papillomavirusi bilan bog'liq bo'lgan bachadon bo'yni shikastlanishlarini erta tashxislash uchun zamonaviy invaziv bo'lmagan usullar to'plamidan foydalanish samaradorligi va maqsadga muvofiqligi asoslandi va aniqlandi, bu esa diagnostika va terapevtik choralarning ko'lami va vaqtini aniqlash imkonini berdi.*

*Bachadon bo'yni patologik o'zgarishlari bo'lgan, 16 va 18-turdagi inson papillomavirusi bilan kasallangan bemorlarda, infeksiyalanmagan bemorlarga nisbatan, og'ir intraepitelial neoplaziyaning kolposkopik va sitologik belgilari sezilarli darajada ko'proq aniqlanadi.*

*Kalit so'zlar: bachadon bo'yni, inson papillomavirusi, intraepitelial neoplaziya.*

**Relevance**

Detection and surgical treatment of patients with pathological changes in the cervix have long been the only way to prevent cervical cancer [1,3,5,7,9]. It has now been proven that highly oncogenic human papillomavirus (HPV) types, primarily types 16 and 18, cause cervical intraepithelial neoplasia and cervical cancer [WHO]. Vaccination appears to be the most promising method for preventing cervical cancer, but is only possible in women with unified status. For patients infected with the human papillomavirus, the only real way to prevent the development of intraepithelial neoplasia, and consequently cervical cancer, is through the detection of HPV infection—a highly reliable, accessible, and informative method. The sharp increase in human papillomavirus (HPV) infection in the population, its high contagiousness, and the ability of this pathogen to cause malignant cervical pathology pose a challenge to gynecological practice [2,4,6,8,10].

According to WHO, CDC, and European guidelines, destructive methods are used to treat both the clinical manifestations of HPV infection and associated diseases. To date, there is no consensus on the management of LSIL due to the regression of this disease and frequent complications of surgical intervention [3,13]. The advisability of prescribing immunomodulatory drugs remains controversial [1,11,12]. There are a sufficient number of studies examining the effectiveness of immunotherapy for papillomavirus infection, but its selection is often empirical, without taking into account the immunological status of the body. In this regard, a comprehensive study of the state of the immune system is of interest, in particular, the determination of lymphoid cells, the phagocytic activity of neutrophilic leukocytes, and the concentration of immunoglobulins in the peripheral blood during the development of the infectious process. Despite a significant body of research substantiating the rationale for various destructive interventions on the cervix in cases of HPV persistence for more than two years, the issue of reducing recurrence through combined immunocorrection and destructive treatment remains the most significant [2,14,15,16,17,22]. Therefore, research aimed at identifying rational diagnostic methods and a substantiated differentiated approach to treating cervical diseases associated with HPV infection in women of reproductive age is relevant.

Squamous intraepithelial lesions (SIL) of the cervix are a leading cause of gynecological pathology among women of reproductive age [4,18]. The human papillomavirus (HPV) plays a major role in the development of cervical SIL. According to the literature, the peak incidence of HPV infection occurs between the ages of 15 and 30 years and accounts for 18.6%. After age 30, HPV infection declines (9.9%), while the incidence of SIL and cervical cancer increases [4,19, 20, 93, 167, 195]. In our country, over the past decade, the number of newly identified cases of cervical cancer has increased by 23.9%, which is a serious threat to the reproductive health of the female population [1,21, 23].

The results of numerous publications indicate that women under 30 years of age are characterized by a transient infection, with self-elimination of the human papillomavirus reaching 90%, while women over 30 years of age experience a persistent course of infection [1,24]. It is known that prolonged persistence of human papillomavirus infection (HPV) for 2 years or more is a risk factor for the development of cervical cancer. However, to date, there is not a single effective personalized diagnostic method capable of predicting the course of cervical SIL in a specific patient with a clear indication of the time and duration of the process [4]. The rationale for using currently available diagnostic methods is ambiguous due to their different diagnostic sensitivity and specificity. The lack of universally accessible and highly effective methods for diagnosing and predicting cervical SIL often increases unnecessary, often repeated, aggressive surgical procedures on the cervix and associated complications [3,7,24].

From a clinician's perspective, the need for timely diagnosis and prediction of the severity of cervical SIL is not only a medical but also a socio-demographic problem of our time.

Of undoubted interest is the prevalence of this virus in patients with underlying and precancerous cervical diseases, a common risk group for carcinogenesis in Uzbekistan. We found no studies on the incidence of infection, clinical features, and paraclinical examination results in patients with endocervicitis, cervicitis, and leukoplakia, which are common in the population, compared to patients with neoplasia and intraepithelial cervical cancer.

The results of such comparative studies will allow us to evaluate the feasibility of screening these patients for human papillomavirus infection and subsequent treatment. This approach will, on the one hand, help prevent cervical intraepithelial neoplasia in these patients and, on the other, reduce the number of unnecessary surgical interventions in women of childbearing age.

**The aim of the study** was to improve the effectiveness of intraepithelial neoplasia prognosis and detection of preventive treatment for cervical epithelial infection with oncogenic types of human papillomavirus in patients with underlying cervical diseases.

### **Materials and methods**

To address the objectives of the study, 168 women aged 16 to 66 years were included in the study. Three clinical groups were formed based on the condition of the cervix of the examined women: Study Group I included 100 patients with underlying and precancerous cervical diseases; Study Group II included 18 patients with a newly diagnosed cervical cancer in situ. The control group consisted of 50 women currently free of pathological changes in the cervical epithelium, selected by a lottery based on the results of a preventive examination. Depending on the presence or absence of high-risk human papillomaviruses (HPVs) in the cervical canal of the examined women (16/18), all patients were divided into subgroups "A" (virus not detected) and "B" (virus detected).

The main study group 1, based on the nosological form of cervical disease, was represented by underlying cervical pathology (73.0%), including simple and proliferative endocervicitis (32.0%), endocervicitis (26.0%), leukoplakia (12.0%), glandular polyps (3.0%), and cervical epithelial dysplasia (27.0%). The clinical examination included a standardized survey, including a clinical, anamnestic, and laboratory-instrumental examination questionnaire for women. This questionnaire, developed by us during our work, recorded the results of a gynecological examination, as well as colposcopic, cytological, and morphological studies, as well as HPV typing using the polymerase chain reaction (PCR) method. Physical health was assessed through anamnesis collection and medical reports from related specialists. Cytological examination of cervical scrapings was assessed using the Bethesda system [2024], and the staining method was according to the Romanovsky-Giemsa method. General and extended colposcopy were performed using a Leisegang colposcope (Germany), providing 7x, 15x, and 30x magnification. In the International Evaluation of Colposcopic Classification of Pictures (updated, used by the International Association of Cervical Pathology and Colposcopy in Barcelona, 2023).

Histological specimens were prepared using a HistoEmbedder apparatus and stained with hematoxylin and eosin using the traditional method. The obtained results were processed using standard variation statistics. The significance of differences between mean parameter values was determined using Student's t-test and Fisher's exact test. For small group sizes, nonparametric statistics were used, including Spearman's rank correlation coefficient ( $p$ ).

### **Results and discussion**

The mean age between the study groups did not differ significantly. More than half of the patients (59.3%) were of active reproductive age (20-39 years). The qualitative and quantitative characteristics of extragenital and gynecological diseases did not differ significantly between the comparison subgroups. No statistically significant differences were found in the analysis of menstrual function. We assessed existing risk factors in the women examined to further determine their impact on the occurrence of infection with highly oncogenic types of human papillomavirus, which is of great importance for prognostication and preventive measures to prevent the development of neoplastic changes in the cervical epithelium. In women aged 20-29 years, the frequency of HPV detection significantly increased (25.4%) and continued to increase, reaching its maximum in the 30-39 age group (39.0%), although in

women over 40 years of age, the frequency of infection decreased slightly (23.8%), remaining significantly higher than in women under 20 years of age ( $p < 0.01$ ).

A burdened obstetric history was noted in 71.3% of patients in the study group, 66.7% in the study group, and 75.0% in the control group. The questionnaire results were used to examine the contraceptive methods used by women in the study groups. Intrauterine contraception was significantly more common among patients with newly diagnosed cervical cancer in situ (38.7%) compared to this method among patients with underlying cervical diseases (12.5%) ( $p < 0.05$ ). Patients with benign cervical diseases used all methods, with a non-significant predominance of COCs (28.4%). Healthy women significantly used COCs (44.4%) and barrier methods (28.9%) more often ( $p < 0.05$ ). We examined the relationship between the incidence of HPV types 16/18 and the contraceptive methods used. The use of intrauterine contraception (IUD) and no contraception were significantly more common among HPV-infected patients (14.3% and 38.8%) than among HPV-uninfected patients (1.7% and 24.6%) ( $p < 0.01$ ). Barrier methods of contraception were significantly more common among HPV-uninfected patients (28.9%) than among HPV-infected patients (14.2%) ( $p < 0.01$ ).

No statistically significant differences were found in the frequency of destructive treatments for cervical pathology and the qualitative and quantitative characteristics of patient complaints, depending on the type of human papillomavirus infection. When evaluating the results of the cytological examination, we used the Bethesda classification, the basis for which was the clinical, morphological and virological results of the study of cervical pathology.

In addition to koilocytic atypia, cytological examination reveals acanthosis, basal cell proliferation, metaplasia, and hyper-, para-, and dyskeratosis of the superficial epithelial layers.

Such smears and scrapings were found in 31.9% of patients with a positive HPV DNA test, which is significantly higher than the detection of identical cytological signs of papillomavirus infection in patients with cervical diseases and negative HPV testing (16.9%) ( $p < 0.01$ ).

It is believed that as cervical intraepithelial neoplasia progresses, the severity of koilocytic atypia decreases, and signs of malignancy, i.e., dyskaryosis, appear.

Cytological examination revealed changes associated with the inflammatory process: enlarged and pale nuclei, cytoplasmic vacuolization, multinucleation, numerous leukocytes, as well as histiocytes and lymphocytes. These changes were observed insignificantly more frequently in patients in subgroup "A" (47.7% of cases) compared to identical cytological changes in patients in subgroup "B" (38.9% of cases).

Thus, our cytological examination of cervical smears and scrapings demonstrates a significant predominance of signs of human papillomavirus infection, severe neoplasia, and cervical cancer in situ in the presence of high-oncogenic HPV infection, compared to a negative HPV DNA test ( $p < 0.01$ ).

Chronic cervicitis was diagnosed in 32.0% of cases in subgroup A, a histological finding significantly higher than the 8.5% rate in subgroup B ( $p < 0.01$ ). This is consistent with the clinical characteristics of cervical diseases depending on the presence or absence of HPV and suggests that HPV infection and persistence do not result in significant inflammatory changes, unlike other genital infections.

Thus, in patients with cervical pathology, infection with HPV types 16/18 is associated with a significant predominance of colposcopic and cytological factors for malignancy, with significantly less pronounced clinical and morphological inflammatory changes in the cervix.

### Conclusion

1. In patients with cervical pathology, the severity of colposcopic and cytological characteristics of intraepithelial neoplasia directly correlates with the frequency of cervical epithelial infection with human papillomavirus types 16 and 18.

2. Dynamic dispensary observation of all patients with identified high-oncogenic risk human papillomaviruses is mandatory: in the case of latent infection, once every 6 months; in the case of subclinical and clinical forms of papillomavirus infection, cervical intraepithelial neoplasia of mild and moderate severity, adequate etiopathogenetic therapy (antiviral, antioxidant).

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