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Management of recurrent HPV-associated cervical intraepithelial neoplasias in women of perimenopausal age

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Aim: to increase the effectiveness of complex therapy of recurrence of cervical intraepithelial neoplasia (CIN) in women of perimenopausal age by optimizing management and postoperative rehabilitation.

Materials and methods. A prospective study of 60 Human papillomavirus (HPV) positive women of perimenopausal age with morphologically verified recurrent CIN II was carried out. Patients of the Group I (n=30) after radiowave conization of the cervix transvaginally used suppositories with ingredients of natural origin – centella asiatica, calendula, aloe, tea tree essential oil, hyaluronic acid, orally – a blend of extracts of herbs of Deschampsia caespitosa L., Calamagrostis epigejos, Echinacea purpurea. Patients of the Group II (n=30) received vaginal suppositories with methyluracil in the postoperative period.

Results. Cervical reepithelialization after the use of optimized management tactics was diagnosed in 100% of women, which occurred 1.3 times faster than in patients receiving traditional treatment. After 12 months from the start of treatment, the absence of multiple HPV infection and clinically significant viral load were determined, total elimination of the HPV in 96.7% of patients who received an optimized treatment complex.

Conclusions. Radiowave therapy in combination with a blend of plant extracts and ingredients of natural origin for topical use has anti-inflammatory, immunomodulatory, antiviral, and reparative effects, prevents the occurrence of postoperative complications, has adequate safety and tolerability.

The study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Local Ethics Committee of the participating institution. The informed consent was obtained from all patients.

No conflict of interests was declared by the authors.

Keywords: cervical intraepithelial neoplasia, human papillomavirus, perimenopausal age, radiowave conization, treatment, postoperative rehabilitation.

Менеджмент рецидивуючих ВПЛ-асоційованих цервікальних інтраепітеліальних неоплазій у жінок перименопаузального віку

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Мета: підвищити ефективність комплексної терапії рецидивів цервікальної інтраепітеліальної неоплазії (ЦІН) у жінок перименопаузального віку шляхом оптимізації менеджменту і післяопераційної реабілітації.

Матеріали та методи. Проведено проспективне дослідження комплексно пролікованих 60 жінок, позитивних до вірусу папіломи людини (ВПЛ) перименопаузального віку з морфологічно верифікованою рецидивною ЦІН II. Пацієнткам I групи (n=30) після проведення радіохвильової конізації шийки матки трансвагінально застосовували супозиторії з інгредієнтами натурального походження – щитолисника азійського (Centella asiatica), календули, алое, ефірної олії чайного дерева, гіалуронової кислоти, перорально – купаж екстрактів трав щучки дернистої, війника наземного, ехінацеї пурпурової. Пацієнтки II групи (n=30) у післяопераційному періоді отримували вагінальні супозиторії з метилурацилом.

Результати. Реепітелізацію шийки матки після застосування оптимізованого менеджменту і післяопераційної реабілітації діагностовано у 100% жінок, що трапилась у 1,3 раза швидше, ніж у пацієнток, які отримували традиційне лікування. Через 12 місяців після початку лікування встановлено відсутність множинного інфікування ВПЛ та клінічно значущого вірусного навантаження, повну елімінацію ВПЛ у 96,7% пацієнток, які отримували оптимізований лікувально-профілактичний комплекс.

Висновки. Радіохвильова терапія в комплексі з купажем рослинних екстрактів та інгредієнтів натурального походження для місцевого застосування чинить протизапальний, імуномодулюючий, противірусний та репаративний вплив, запобігає виникненню післяопераційних ускладнень, має адекватну безпеку і переносимість.

Дослідження проведено відповідно до принципів Гельсінської декларації. Протокол дослідження схвалено місцевим комітетом з етики закладу-учасника. На проведення досліджень отримано інформовану згоду пацієнток.

Автори заявляють про відсутність конфлікту інтересів.

Ключові слова: інтраепітеліальна неоплазія шийки матки, вірус папіломи людини, перименопаузальний вік, радіохвильова конізація, лікування, післяопераційна реабілітація.

Precancerous conditions and cervical cancer remain an urgent medical and social problem nowadays, causing significant morbidity and mortality among women around the world [26].

Despite extensive research efforts and advances in screening and prevention strategies, precancerous conditions and cervical cancer are still an unsolved problem for public health,

especially in low- and middle-income countries [5,9,32,33].

According to the World Health Organization and the European Research Organization on Genital Infection and Neoplasia, as well as the US National Institutes of Health, the main factor in the occurrence and progression of cervical intraepithelial neoplasia (CIN) is considered to be an infectious factor, and, first of all, highly oncogenic strains of the human papillomavirus (HPV) [23-25,35,36].

At present, the leading role of HPV in the etiopathogenesis of dysplastic and malignant diseases of the cervix has been proven.

The CIN or moderate to high cervical epithelial dysplasia associated with HPV of high oncogenic risk ranges from 9% to 21% [5,12,20,24,33].

This is an important medical and social problem in all economically developed countries. Scientists emphasize that in the complex and extensive problem of cervical cancer, three main areas have a key position: 1) pathogenetic substantiation of prevention methods, 2) early diagnosis, 3) improvement of methods of treatment of dysplasia and preinvasive cancer to prevent invasive cancer. These three areas should lead to the solution of a difficult but real task – to minimize the morbidity and mortality from cervical cancer [7,12,16,33].

There is no natural protection against HPV, the probability of transmitting it to a sexual partner is 65-80%. HPV can avoid a rapid response of the immune system, since during infection there is no viremia and local inflammation, local immunity is suppressed by the virus. The formation of a specific response to HPV infection is slow – the seroconversion period is about 12 months, and antibodies are produced in low titers, which is insufficient to eliminate the virus. That is why previously transferred HPV infection does not cause immunity that would protect against reinfection and the development of CIN, which is evidence of the integration of HPV into the cell genome of the epithelial cell. Attention is focused on the susceptibility of women to HPV at different age periods of life. Thus, there is an opinion that women of late reproductive age and in the perimenopausal period have a higher risk of HPV infection compared to women of reproductive age. This is due to a decrease in estrogen levels, which causes involution of the mucous membranes of the vagina and cervix, followed by the development of epithelial atrophy and lactobacilli deficiency (as a result, a lack of hydrogen peroxide, lactic acid, and bacteriocins), which creates a favorable environment for the reproduction of opportunistic flora, pathogens and damage to the epithelium of the cervix and vagina of HPV. The expediency of applying an integrated approach to the management of this contingent of patients and the appointment of pathogenetically based therapy is emphasized [2,3,6,13,18-20]. A feature of HPV is the tendency to long-term persistence, latent stay in the human body with an asymptomatic or atypical course of the infectious process, and the possibility of spontaneous progression, which requires optimal therapeutic and prophylactic management in the presence of precancerous conditions of the cervix associated with HPV infection.

Modern methods of treating cervical pathology that have developed against the background of HPV infection include systemic and local immunocorrective therapy, as well as various methods for the destruction of the pathological focus [1,4,13-15,17,27,28]. The high frequency of combined gynecological pathology in patients with cervical dysplasia necessitates an integrated approach to the treatment of the problem, since, despite the variety of techniques used, the antiviral effect of therapy remains low, and the available schemes of treatment do not lead to a decrease in the incidence of cervical cancer. The most promising along with vaccination and screening programs is timely and adequate treatment of preinvasive cervical pathology [11]. The current tactics of treating patients with preinvasive cervical pathology do not reduce the incidence of invasive cancer. To increase the effectiveness of therapy, an integrated approach to treatment is necessary, taking into account the age of women and prognostic risk factors, and the formation of a treatment algorithm with rehabilitation [7,8,14,20-23].

Given the significant connection between CIN and the development of cervical cancer, the research and development of new methods for the diagnosis, treatment, and prevention of CIN is one of the priority areas of modern medical science [12,30-32].

When choosing treatment, the therapeutic spectrum of action of the drug on the immune system, in particular on the state of local immunity, should be taken into account. A clear understanding of the complex interaction between viral infection and the development of precancerous diseases and cervical cancer is crucial for the development and implementation of new treatment and prevention strategies. According to the recommendations of the National Consensus on the Management of Patients with CIN

caused by HPV infection (2017), in order to carry out anti-relapse therapy, it is advisable to prescribe drugs with direct antiviral action – flavonoids [34]. Scientifically based, available for practical use, and clinically effective for patients with HPV, the drug is presented as a blend of plant extracts from the grass of Deschampsia caespitosa, Calamagrostis epigeios, and the herb of Echinaceae purpureae – 116.4 mg. The extract of Deschampsia caespitosa grass contains flavonoids (quercetin and its derivatives), organic acids, vitamins, higher fatty acids, polysaccharides, extract of Calamagrostis epigeios herb – nitrogen-containing compounds, flavonoids, hydroxycinnamic and terpenic acids. Flavonoids, which are part of the extracts of Deschampsia caespitosa and Calamagrostis epigeios grass, inhibit the synthesis of DNA and RNA viruses in infected cells by inhibiting the activity of virus-specific enzymes RNA and DNA polymerases, thymidine kinase and reverse transcriptase, as a result of which viral replication becomes impossible, contribute to the synthesis of endogenous alpha and gamma interferons to a physiologically active level, increasing the body's nonspecific defense against viral and bacterial infections. At the same time, the immunostimulating activity of the extracts does not cause refractoriness of the immune system.

Deschampsia caespitosa extract has antioxidant activity, inhibits the course of free radical processes, thereby preventing the accumulation of lipid peroxidation products, and is also a modulator of apoptosis, contributing to the elimination of infected cells. Extract of the herb of Calamagrostis epigeios has anti-inflammatory, antiseptic, and diuretic effects Echinacea purpurea herb extract contains a number of biologically active compounds – phenolic acids, flavonoids, polyacetylenes, which have immunostimulating effects. Echinacea activates the phagocytic activity of neutrophils and macrophages, stimulates the production of interleukins, promotes the transformation of B-lymphocytes into plasma cells, improves the function of T-helpers, and activates the synthesis of interferons. Due to these properties, Echinacea purpurea helps to strengthen the body's defenses and reduces the duration of infectious diseases, prevents the recurrence of HPV and Herpes simplex virus.

The regimen for using the phytomixture involves ingestion of 1 capsule once a day before meals. The minimum course of treatment is 3 months [2,10].

To accelerate reparative processes, prevent vaginal dysbiosis, it is advisable to use topical agents, in particular, the issue of using vaginal suppositories for this purpose, the active ingredients of which are represented by a combination of natural plant substances with pronounced regenerative, antiseptic, anti-inflammatory and immunostimulating properties – Centella Asiatica seed extract – 20 mg; Calendula extract – 60 mg; Aloe extract – 60 mg; Tea tree essential oil – 2 mg; hyaluronic acid – 5 mg (daily for 20 days from the 3rd day of the postoperative period – 1 suppository/1 time per day).

Hyaluronic acid as a natural polysaccharide covers the vaginal mucosa, creates a protective barrier, promotes healing and elimination of the inflammatory reaction (reduces redness), strengthens the walls of the vagina and cervix after diathermocoagulation, laser therapy, and cryotherapy of the cervix or vagina, exhibits moisturizing properties in case of dryness of the vaginal mucosa.

Calendula extract promotes an anti-inflammatory effect, accelerates recovery processes, and exhibits antifungal, antimicrobial, protective, and immunostimulating properties.

Aloe extract helps to strengthen local immunity, and restore tissue metabolism, due to which it exhibits wound healing, antimicrobial and anti-inflammatory properties, eliminates inflammation and irritation, stimulates the restoration of the vaginal mucosa. Aloe contains vitamin C, which inhibits the growth of pathogenic bacteria, lowers the pH of the vagina, helps to restore optimal pH, and maintains normal vaginal microflora.

Tea tree essential oil exhibits powerful anti-inflammatory, antifungal, and bactericidal properties. The biologically active substances of tea tree moisturize the vaginal mucosa.

Centella asiatica seed extract (or oil) exhibits antioxidant, regenerative and antiseptic properties, stimulates collagen synthesis, promotes epithelialization and strengthening of the vaginal walls. Suppositories are used daily for 20 days from the 3rd day of the postoperative period in the mode of 1 suppository/1 time per day) [4].

Aim: to increase the effectiveness of complex therapy for recurrence of CIN in women of perimenopausal age by optimizing management and postoperative rehabilitation.

Materials and methods of the study

In a comprehensive prospective study that was conducted at the clinical bases of the Obstetrics and Gynecology Department No. 3 of the Bogomolets

National Medical University – Municipal Non-profit Enterprise «Kyiv City Maternity Hospital No. 3» and the Women's Health Center of the Clinical Hospital «Feofania» (Kyiv), 60 HPV-positive nulliparous women with recurrent CIN II of perimenopausal age, taking into account bioethical standards for conducting clinical trials involving patients, approved by the Commission on Bioethical Expertise and Ethics of Scientific Research at Bogomolets National Medical University (Protocol No. 151 of 25.10.2021).

The Control group consisted of 38 HPV-negative perimenopausal women without gynecological and severe somatic pathology.

In order to verify the recurrence of CIN II that occurred after the previous destructive treatment of the cervix, before the appointment of surgical treatment, all HPV-positive patients (n=60) underwent a standard examination in accordance with the current protocols and guidelines. After the correction of immunological parameters and normalization of vaginal dysbiosis, depending on the chosen tactics of treatment of recurrent CIN II associated with HPV infection, the studied women were divided into two comparable clinical groups. The Clinical group I consisted of 30 patients who underwent radiowave conization of the cervix in order to optimize the management of recurrent CIN II. Postoperative rehabilitation was carried out by the use of vaginal suppositories, which combined ingredients with proven anti-inflammatory, regenerating, and moisturizing properties (Centella Asiatica, Calendula, Aloe, Tea Tree essential oil, hyaluronic acid) – 1 suppository per night from the 3rd day of the postoperative period for 20 days. Internally a blend of extracts of herbs of Deschampsia caespitosa, Calamagrostis epigeios, Echinacea purpurea with a certain immunomodulatory and antiviral effect 1 capsule daily orally for 3 months) was added to the therapeutic and prophylactic complex.

The Clinical group II included 30 HPV-positive patients with relapsed after surgical treatment of CIN II, who received standardized therapeutic and preventive measures regulated by the regulatory documents of the Ministry of Health of Ukraine (Order of the Ministry of Health of Ukraine of 02.04.2014, No 236 «On approval and implementation of medical and technological documents on the standardization of medical care for dysplasia and cervical cancer»). After cervical electroconization in patients of the Clinical group II (n=30), postoperative rehabilitation was carried out by using vaginal suppositories with methyluracil daily for 20 days from the 3rd day of the postoperative period 1 suppository transvaginally daily).

Immunological parameters were assessed by determining antibodies of Ig G, IgM, IgA class, levels of interleukin-1β (IL-1β), interferon-alpha (IFN-α), gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α) in blood serum and cervical mucus by the enzyme-linked immunosorbent method with sets of reagents of «Ukrmedservice» LLC on the automatic analyzer «Chemwell-2910» (Awareness Tech., USA). Determination of IgM, IgG, IgA in the blood serum of patients, and sIgA in cervical mucus by ELISA. The studied indicators were expressed in pc/ml, g/l, mg/l.

Studying the indicators of cellular immunity, the number of B-lymphocytes (CD-72+), T-lymphocytes (CD-3+), T-helpers (CD-4+), T-suppressors (CD-8+), immunoregulatory index (helper/suppressor ratio CD-4+/CD-8+) was determined, reflecting the cytotoxic potential of lymphocytes in the blood in the indirect variant of the immunofluorescence method using a monoclonal antibody panel (MCAB) to surface lymphocyte antigens.

The results of vaginal discharge microscopy were determined taking into account the Hay-Ison criteria. Polymerase chain reaction (PCR) studies with HPV genotyping were carried out using the real-time method and determining the viral load of cervical samples by the number of copies of HPV DNA per 100 thousand cells at <3 lg, 3-5 lg, >5 lg, respectively. Obtaining biological material for cytological examination was carried out in accordance with the standards for PAP tests with an assessment according to the Bethesda System (TBS) classification. Simple and extended colposcopy (according to the international classification International Federation for Cervical Pathology and Colposcopy, Rio de Janeiro, 2011) were performed on the colposcope «Leisegang» (Berlin, Germany).

The examination of women in the study groups was carried out 3, 6, and 12 months after the start of complex treatment of recurrent CIN II associated with HPV.

Statistical data processing was carried out using generally accepted parametric and nonparametric research methods. The statistical significance of the results was assessed using p-values with a critical threshold of $p<0.05$, where values below this threshold indicated statistically significant differences or effects.

Table 1

The state of cellular and humoral immunity in women with CIN II on the background of papillomavirus infection before treatment (M±m)

Indicators	Control group (n=38)	Clinical group I + Clinical group II (n=60)
CD3, %	51.2±2.31	44.08±0.38*
CD4, %	40.02±2.35	33.2±0.29*
CD8, %	21.91±1.06	27.01±0.87*
CD72, %	7.8±0.25	9.1±0.18*
CD4/CD8	1.82±0.52	1.22±0.17*
IgM, g/l	2.23±0.19	3.66±0.24
IgA, g/l	1.98±0.1	1.16±0.08
IgG, g/l	9.51±0.78	14.9±0.89*
sIg A, mg/l	46.3±0.98	25.6±1.2*

Note: * – the difference is significant with the indicators of the Control group (p<0.05).

Table 2

Features of interferon status of examined women before treatment, (pg/ml)

Indicator	IFN-α	IFN- λ	IL-1β	TNF-α
Clinical groups I + II (n=60)	51.43±3.1*	48.94±2.2*	79.4±3.7*	64.3±1.4*
Control group (n=38)	82.3±4.36	22.6±1.72	22.2±0.18	11.3±0.06

Note: *- the difference is significant with the indicators of the Control group (p<0.05).

Results of the study and discussion

A comprehensive examination of treated 60 HPV-positive patients aged 40 to 55 years (mean age 48.2±3.9 years) with verified recurrent CIN II that arose after destructive methods of cervical treatment was carried out.

The results obtained at the preliminary stage of the study indicate that in women with recurrent CIN II, in the case of the association of HPV infection with vaginal dysbiosis, a significant role in the development of the pathological process is played by changes in immunity at the systemic and local levels with impaired helper function of lymphocytes, a decrease in the immunoregulatory index (CD4/CD8) due to an increase in the percentage of cytotoxic lymphocytes against the background of a progressive decrease in natural killer cells (Table 1), a significant increase in the levels of pro-inflammatory cytokines in the blood serum (TNF-α – by 5.6 times, IL-1β – by 3.5 times) (Table 2).

The tension of the humoral link of the immune system was determined by an increase in the concentration of IgM, the level of IgG in cervical mucus by 1.6 times, and a decrease in the level of sIgA by 1.7 times. When assessing the indicators of local immunity in the specified contingent of patients, a significant decrease in IFN-α levels by 1.6 times and an increase in IFN-γ indicators by 2.2 times ($p<0.05$) relative to the Control group was determined. An increase in the concentration of TNF-α in cervical mucus by almost 6 times indicates long-term local immunosuppression in the integrative form of HPV, which can be considered a prognostic criterion for the severity of CIN.

During immunomodulatory therapy with the use of a blend with extracts of herbs of Deschampsia caespitosa, Calamagrostis epigeios, Echinacea purpurea for 3 months before surgical treatment, a significant decrease in the content of TNF-α – by 3.2 times, IL-1β – by 2.2 times in the blood serum and an increase in the content of sIgA by 1.5 times in the vaginal secretion ($p<0.05$) was observed. Compared to the indicators before the prescribed therapy, after 3 months of treatment, the level of IFN-α increased by 1.3 times with a decrease in the level of IFN-λ 1.6 times, the indicators of IgA, IgM, and IgG in the blood serum and vaginal secretions approached the reference values. The positive dynamics of immunological parameters reflected the effectiveness of the prescribed immunocorrection, which is due to the effect of biologically active com-

ponents of the plant mixture – phenolic acids, flavonoids, polyacetylenes, which have an immunostimulating effect, activate the phagocytic activity of neutrophils and macrophages, stimulate the production of interleukins, improve the function of T-helpers, increase the production of endogenous alpha and gamma-interferons to a physiologically active level, which increases the body's nonspecific resistance to viral and bacterial infection.

The antiviral effect of the prescribed herbal complex contributed to a decrease in the number of cases of detection of HPV highly oncogenic types and their multiplicity in 27 (26.6%) of the examined women but did not affect the distribution of viral load. The absence of positive changes in the regression of intraepithelial lesions of the cervix is due to the stability of viral particles that were integrated into dysplastic altered epithelial cells, the formation of a "progressive» immunophenotype according to the results of immunohistochemical examination, which contributed to the persistence of HPV infection with the integration of virus DNA into the genome of cervical epithelial cells. As a result of the studies, we came to the conclusion that the use of only conservative immunomodulatory and antiviral therapy in HPV-positive women of perimenopausal age with relapses of CIN II that occurred after destructive methods of treatment does not significantly affect the remodulation of the affected cells of the cervix, therefore, it is advisable to use this therapy in combination with excisional methods of treatment of the cervix before surgery and during the postoperative period rehabilitation in order to preserve vaginal normocenosis, effective cervical repair, increase HPV clearance and prevent recurrence of intraepithelial lesions of the cervix.

It should be noted that we observed the best result in terms of the effect of full-fledged epithelialization of the wound surface from the beginning of complex therapy in patients of the Clinical group I. As a result of the use of the proposed therapeutic and prophylactic complex, the period of epithelialization of the wound surface of the cervix of a high degree in women of the Clinical group I fell on 33.4± 1.9 days against 44.5±3.1 days in patients of the Clinical group II, that is, almost 1.3 times faster (11.1 days earlier), which proves the high clinical effectiveness of use in combination with radio wave treatment and immunocorrection of vaginal suppositories with regenerating, immunomodulatory, antiseptic and anti-inflammatory effects. Already at the end of the 3rd month of the postoperative period, complete cervical epithelialization was diagnosed in 100.0% of patients of the Clinical group I who received the proposed treatment and prophylactic complex, which was 13.3% higher than similar indicators in the Clinical group II of the study (86.7%) ($p<0,05$).

Indicators of vaginal normocenosis according to the Hay-Ison criteria during monitoring at the 3rd month of postoperative rehabilitation in patients of the Clinical group I were 23.3% higher than those in women of the Clinical group II, which was 83.3% (25 women) versus 60.0% (18 women), respectively. After 6 months of monitoring, normocenosis was diagnosed in 26 (86.3%) patients of the Clinical group I who received an optimized treatment and prophylactic complex, compared to women of the Clinical group II with standardized therapy, in which normalization of vaginal dysbiosis was stated 1.6 times less often, in 16 (53.3%) cases, respectively. According to the results of microscopy of vaginal discharge after 12 months of observation, the state of normocenosis was noted in 28 (93.3%) patients of the Clinical group I, which is 2.3 times more often than in patients of the Clinical group II – 12 (40.0%), which reliably reflects the positive antiseptic and anti-inflammatory effects of the proposed therapeutic and prophylactic complex ($p<0.05$).

During the dynamic observation of patients for a year after the complex treatment of neoplastic processes of the cervix, we were interested in complaints, the nature of the menstrual cycle, and possible cases of relapses of the underlying disease. Moderate discharge with an unpleasant odor from the genital tract was complained of by 7 (23.3%) patients in the Clinical group II, by 2 (6.7%) patients about pain during sexual intercourse, and by 1 (3.3%) patient in the Clinical group II about discomfort in the vaginal area. It should be noted that in all examined women, the nature of menstrual function did not undergo significant changes.

Extended colposcopy 3 months after surgical treatment of CIN II recurrence showed the normal colposcopic picture in the overwhelming majority of women in both Clinical groups and was characterized by the presence of stratified epithelium over the entire surface of the exocervix, an adequate vascular response to a 3% acetic acid solution and a positive Schiller test. Pathological colposcopic signs in patients of the Clinical group II were 2.8 times more common, which was 11 (36.7%) versus 4 (13.3%),

Table 3

Results of colposcopic examination in patients of the examined groups 3 and 6 months after treatment, abs. (%)

Indicators	Observation groups	
	I (n=30)	II (n=30)
3 months after complex treatment		
Normal colposcopic picture	26 (86.7)	19(63.3)*
Thin acetic white epithelium	2 (6.6)	4 (13.3)*
Fine mosaic	1 (3.3)	4 (13.3)*
Fine punctuation	0 (0.0)	2 (6.7)
Iodine-negative epithelium	0 (0.0)	3 (10.0)*
Signs of inflammation	1 (3.3%)	5(16.6)*
6 months after treatment		
Normal colposcopic picture	30 (100.0)	24 (80.0)*
Thin acetic white epithelium	0 (0.0)	0 (0.0)
Fine mosaic	0 (0.0)	0 (0.0)
Fine punctuation	0 (0.0)	0 (0.0)
Iodine-negative areas	0 (0.0)	2 (6.7)
Signs of inflammation	0 (0.0)	4 (13.3)*

Note: * – statistically significant differences with the Clinical group I indicators (p<0.05).

respectively (p<0.05). In patients of the Clinical group II of the study, abnormal colposcopic signs of the first degree in the form of acetic-white epithelium were determined 2 times more often, delicate mosaic – 4 times more often than in patients of the Clinical group I. Tender puncture was diagnosed in 2 (6.6%) cases only in the Clinical group II of subjects (p<0.05). Manifestations of vascular atypia during colposcopic examination 3 months after the start of therapy were not detected in any case in both Clinical groups of the study. After applying Lugol's solution to the cervix, iodine-negative areas were determined in 3 (10.0%) patients of the Clinical group II, which is a characteristic sign of immature metaplasia or atrophy of stratified squamous epithelium, especially characteristic of women of perimenopausal age against the background of hypoestrogenism. Colposcopic signs of inflammation in the form of uneven surface relief and local atrophy of stratified squamous epithelium, hyperemia in the area of the outer eye of the cervix occurred 5 times more often in patients of the Clinical group II who underwent standardized therapy, compared to patients of the Clinical group I who used the developed therapeutic and prophylactic complex (p<0.05) (Table 3).

For 6 months after treatment, the results of colposcopy indicated the absence of rough scarring on the cervix in patients of both Clinical groups, there was a significant increase in the number of cases of normal colposcopic pictures – in patients of the Clinical group I – 30 (100.0%) cases, in patients of the Clinical group II – 24 (80.0%). Abnormal colposcopic pictures in the form of iodine-negative areas were observed in 2 (6.7%) patients of the Clinical group II, and 4 cases (13.3%) of the inflammatory process of the cervix.

12 months after treatment, abnormal colposcopic changes occurred in 4 (13.3%) patients of the Clinical group II who received standardized therapy – 2 (6.7%) cases of iodine-negative areas and 2 (6.7%) with signs of inflammatory reaction, while in patients of the Clinical group I who used the proposed treatment and prevention complex, pathological colposcopic signs were not detected in any case. Our results confirm the feasibility of including in the complex therapy of HPV-associated forms of CIN II phyto-mixture with herbal extracts at the preparatory stage before the procedure of radio wave conization of the cervix and in the postoperative rehabilitation period in combination with suppositories based on ingredients of natural origin to increase the effectiveness of treatment and reduce the frequency of recurrence of PVI and precancerous conditions of the cervix.

Table 4

The state of cellular and humoral immunity in women with CIN II against the background of papillomavirus infection after 6 months of monitoring after surgical treatment, M±m

Indicator	Observation groups		
	Control group (n=38)	Clinical group I (n=30)	Clinical group II (n=30)
CD3, %	51.2±2.31	50.9±3.38	44.1±2.31*,**
CD4, %	40.02±2.35	39.8±2.96	33.7±1.3*,**
CD8, %	21.91±1.06	22.02±0.96	27.03±1.2*,**
CD72, %	7.8±0.25	7.9±0.16	8.2±0.67*,**
CD4/ CD8	1.82±0.52	1.81±0.15	1.24±0.79*,**
IgM, g/l	2.23±0.19	2.36±0.64	3.01±0.25*,**
IgA, g/l	1.98±0.1	1.91±0.08	1.61±0.08*,**
IgG, g/l	9.51±0.78	9.96±0.69	11.6±0.76*,**
sIgA, mg/L	46.3±2.98	47.6±2.31	38.7±1.1*,**

Notes: * – the difference is significant relative to the parameters of the Control group ($p<0.05$); ** – the difference is significant relative to the indicators of the Clinical group I ($p<0.05$).

Control cytological examination 6 months after the start of treatment in all examined women of the Clinical groups I and II demonstrated a statistically significant regression of high-grade CIN II (HSIL – high-grade squamous intraepithelial lesion): results of the category of the low-grade squamous intraepithelial lesion (LSIL) were obtained in 2 (6.7%) cases only in the Clinical group II of observation, atypical squamous cells of undetermined significance (AS-CUS) was diagnosed in 1 (3.3%) patient of the Clinical group I and in 4 (13.3%) patients of the Clinical group II of observation. After 12 months, cytological control against the background of the treatment demonstrated a total regression of HSIL (CIN II) in the Clinical group I of the study from 100.0% to 0.0%. In 2 (6.7%) patients of the Clinical group II, who received standardized therapy, LSIL results (CIN I) were diagnosed, in 3 (10.0%) – AS-CUS results of inflammatory origin, which required further observation and treatment ($p<0.05$).

Assessment of immunological parameters 6 months after the start of complex therapy reflects the effectiveness of the prescribed optimized therapeutic and prophylactic complex, which was marked by an increase in the number of lymphocytes, in particular CD3 cells by 1.2 times, CD4 cells by 1.3 times in relation to patients of Group II, with a decrease in the percentage of CD8 cells by 1.3 times, a significant increase in the immunoregulatory index (CD4/CD8) by 1.5 times, the values of which corresponded to the indicators in the Control group (Table 4).

If during immunomodulatory therapy with the use of phytomixture in order to stabilize the immunological status of HPV-positive women with CINI, at the stage of preoperative preparation, a significant decrease in the levels of IL-1β by 2.2 times, TNF-α by 3.2 times in peripheral blood and an increase in the level of sIgA in vaginal secretions by 1.5 times compared to patients in the Control group were observed, then after 6 months, in the case of the use of this phytomixture during the 3 months of the postoperative period, combined with vaginal suppositories based on biologically active natural ingredients in patients of the Clinical group I, a significant decrease in the levels of IL-1β by 3.4 times, TNF-α by 5.2 times in peripheral blood and an increase in the level of sIgA in vaginal secretions by 1.9 times, compared to indicators before immunocorrection in the preoperative period (Table 5).

The analysis of interferon status indicators showed that as a result of complex therapy in patients of the Clinical group I, the levels of IgA, IgM, IgG, and sIgA corresponded to the indicators of the Control group. It should be noted that in patients of the Clinical group II of observation, who received immunomodulatory therapy using the proposed blend of herbal extracts for 3 months only in the preoperative period, indicators of the levels of pro-inflammatory cytokines, immunoglobulins, alpha and gamma interferons in serum and cervical mucus did not statistically significantly differ from the previously obtained results (Table 5). The analysis of the

Table 5

Characteristics of interferon status of examined women with CIN II 6 and 12 months after therapy, pg/ml

Indicators	Observation groups				
	Clinical group I (n=30)		Clinical group II (n=30)		Control group (n=38)
	6 months	12 months	6 months	12 months	
IFN-α	80.2±4.1*	81.1±4.9*	64.15±3.2*,**	69.1±3.6*,**	82.3±4.36
IFN-γ	24.16±2.3	23.18±2.3*	31.16±2.31*,**	29.16±2.51*,**	22,6±1,72
IL-1β	23.2±2.6*	19.8±1.8*	36.12±2.68*,**	31.21±2.3*,**	22.2±0.18
FNP-α	12.4±1.3*	10.9±0.7*	19.2±1.03*,**	16.4±1.09*,**	11.3±0.06

Notes: * – statistically significant differences with the indicators of the Control group (p<0.05); **– statistically significant differences with indicators of the Clinical group I (p<0.05).

effect of combination therapy on the indicators of systemic and local immunity 6 and 12 months after the start of treatment indicates that the addition of immunocorrective therapy contributes to the normalization of cytokine indicators that regulate immune reactions.

Thus, the results of the studies indicate that the components of the phytomixture with herbal extracts contribute to the synthesis of endogenous alpha and gamma interferons to a physiologically active level, increasing the body's nonspecific defense against viral and bacterial infections. It should be emphasized that at the same time, the immunostimulating activity of the extracts does not cause refractoriness of the immune system, which is proven by the results of our studies during monitoring for 6 and 12 months.

HPV testing is a reliable criterion for the cure of HPV-associated CIN II, since the sensitivity of the HPV test in identifying residual or recurrent manifestations of CIN II in the context of predicting a negative result significantly exceeds cytological control. When comparing infection with highly carcinogenic genotypes of HPV among women of different age categories, this indicator was highest in women aged 45-50 years (64.1%), which is primarily due to low spontaneous elimination of the virus, prolonged persistence of HPV against the background of chronic recurrent inflammatory urogenital processes, with the simultaneous detection of several HPV genotypes and a high viral load.

When monitoring HPV status in patients of the examined groups by the method of polymerase chain reaction (PCR) in real-time, 6 months after treatment, positive HPV status was confirmed in 14 (46.7%) patients of the Clinical group II, which is almost 1.8 times higher than in the Clinical group I of the study, in which this result was diagnosed in 8 (26.7%) subjects (p<0.05). The analysis of the frequency of highly carcinogenic genotypes HPV infection (as a percentage of the total number of women in the examined groups) revealed that after 6 months of monitoring, monoinfection accounted for 5 (16.7%) cases in the Clinical group I, which was 1.7 times higher than in the Clinical group II of the study – 3 (10.0%). Among the examined women, multi-infection with the association of two highly carcinogenic genotypes of HPV was reliably diagnosed only in 1 (3.3)% of cases in patients of the Clinical group I versus 10 (33.3%) in the Clinical group II (p<0.05), with three or more highly carcinogenic genotypes of HPV – only in 1 (3.3%) patient in the Clinical group II of the study. It can be assumed that infection with several types of HPV of high carcinogenic risk contributes to the persistent course of PVI and a less favorable prognosis for therapy (Table 6).

As a result of the study, 3, 6, and 12 months after the start of complex therapy, we found different predispositions of certain types of HPV to long-term persistence. It should be noted that among the long-term persistent types of HPV during the entire observation period, the HPV-16 genotype was significantly dominant, diagnosed in 11 (36.7%) women of the Clinical group II, which was detected almost 27% more often than in the Clinical group I – 3 (10.0%) women. Infection with HPV 18 and HPV 51 in patients of the Clinical group I occurred in 2 (6.7%) cases, while in the Clinical group II these indicators were 2.0 and 2.5 times higher (p<0, 05), which was 13.3% and 16.6%, respectively.

After 6 months from the start of therapy, it was possible to achieve a reduction in a larger number of HPV types in patients of both Clinical groups: genotypes HPV 26, HPV 45, HPV 58, HPV 53, HPV 56, HPV 58, HPV 68, HPV 69, HPV 73, HPV 82 were elimi-

Table 6

Estimation of the frequency of virus infection in HPV-positive women after 3.6 and 12 months of monitoring after complex treatment of CIN II, abs. (%)

Multiplicity infection	Clinical group I (=30)			Clinical group II (=30)		
	3 months	6 months	12 months	3 months	6 months	12 months
Monoinfection (with 1 HPV genotype)	21 (70.0)	5 (16.7)	2 (6.7)	9 (30.0)*	3 (10.0)*	3 (10.0)*
Persistence of 2 highly carcinogenic genotypes of HPV	9 (30.0)	3 (10.0)	0 (0.0)	19 (63.3)*	10 (33.3)*	3 (10.0)*
Persistence of 3 highly carcinogenic genotypes of HPV	0 (0.0)	0 (0.0)	0 (0.0)	2 (6.6)	1 (3.3)	0 (0.0)

Note: * – statistically significant differences with the Clinical group I indicators (p<0.05).

Table 7

Characteristics of the distribution of viral load in patients with HPV persistence at 3, 6 and 12 months from the start of treatment, abs./%

Examination parameters	Observation groups			
	I (n=30)		II (n=30)	
	Abs.	%	Abs.	%
3 months after complex therapy				
HPV DNA < 3 lg	24	80.0	16	53.3*
HPV DNA 3-5 lg	5	16.7	11	36.7*
HPV DNA >5 lg	1	3.3	3	10.0
6 months after complex therapy				
HPV DNA < 3 lg	7	23.3	11	36.7*
HPV DNA 3-5 lg	1	3.3	3	10.0
HPV DNA >5 lg	0	0.0	0	0.0
12 months after complex therapy				
HPV DNA < 3 lg	1	3.3	7	23.3*
HPV DNA 3-5 lg	0	0.0	1	3.3*
HPV DNA >5 lg	0	0.0	0	0.0

Note: * – statistically significant differences with the Clinical group I indicators (p<0.05).

nated in 100% of cases, while complete elimination of genotypes HPV 33, HPV 35, HPV 39, HPV 52, HPV 53, HPV 56, HPV 59, HPV 66 occurred only in patients of the Clinical group I. The number of cases of viral lesions in patients of the Clinical group I since the beginning of therapy decreased by 46.3% against 27.6% in the Clinical group II, which indicates that the university is 1.7 times more effective in the treatment and prophylactic complex proposed by us.

The analysis of the distribution of viral load among highly carcinogenic genotypes HPV-positive women with recurrent CIN II after antiviral and immunomodulatory therapy with the use of a herbal complex of herbal extracts at the preparatory preoperative stage demonstrated that among the studied contingent of women, patients with a low number of copies of HPV DNA predominated – 61.3% (38), which may indicate the absence of a direct correlation between the activity of the viral load and the degree of CIN in connection with the integration of the virus's DNA into the epitheliocyte chromosome when the virus loses its ability to reproduce.

The results of HPV DNA genotyping, which reflect the dynamics of viral load (the number of copies per 100 thousand epithelial cells) during 3, 6, and 12 months after complex therapy, are shown in Table 7.

After 3 months from the start of treatment, activity up to 3 lg prevailed in patients of the Clinical groups I and II of the study, however, the number of

cases of viral load below the threshold of clinical significance in women in the Clinical group I was 1.5 times higher than in the Clinical group II, which was 80.0% versus 53.5%, respectively ($p<0.05$). The opposite trend was noted in the case of a viral load of 3-5 lg – in women of the Clinical group I of the study, the number of cases of a clinically significant level of viral load was 2.2 times less than in the Clinical group II – 16.7% against 36.7%, respectively. Viral load above the clinically significant progression threshold (>5 lg) was diagnosed in 3 (10.0%) patients of the Clinical group II, which was detected 3 times more often than in the Clinical group I subjects.

After 6 months from the start of complex therapy, we found a positive trend in the level of viral load in patients of both Clinical groups: clinically significant viral load was diagnosed in 1 (3.3%) cases in the Clinical group I and in 3 (10.0%) in the Clinical group II, in the absence of viral load above the progression threshold ($p<0.05$).

After 6 months of follow-up during postoperative rehabilitation, HPV clearance was observed 1.6 times more often: in 22 (73.3%) patients of the Clinical group I who received treatment according to the recommended treatment and prophylactic complex, compared to women of the Clinical group II, in whom HPV elimination occurred in 14 (46.7%) cases ($p<0.05$).

After 12 months, according to the results of retesting, patients of the Clinical group I of the study had almost total elimination of HPV – in 29 (96.7%) due to the positive effects of radio wave conization in combination with the inhibitory effect of flavonoids of the plant complex on the synthesis of DNA and RNA viruses in infected cells, which makes it impossible for the virus to replicate, in contrast to patients with standardized therapy, in whom HPV-positive status was confirmed in 8 (26.7%) cases, which may indicate the persistence of HPV infection. The lack of a complete effect of HPV treatment may be due to the persistence of the virus near the lesion site in the unchanged epithelium of the cervix, which has not been removed during surgical treatment, or in case of reinfection.

It should be emphasized that when using the proposed therapeutic and prophylactic complex, most of the study participants were satisfied and tolerated the treatment well, not a single patient had individual intolerance or allergic reactions.

Thus, when evaluating pathogenetic mechanisms of healing after cervical surgery in patients with PVI, therapeutic measures were carried out against the background of the integration of the virus into the cellular genome during its transition from the episomal stage of development to the integrative one. With a compromised cell cycle control system, there is a slowdown in the differentiation of epitheliocytes, and the persistence of cells with impaired replication in the proliferation phase. Prolonged persistence can lead to the virus slipping out of immune control, which makes spontaneous remission impossible and reduces the effectiveness of therapeutic measures. However, the use of radio wave conization with the inclusion of a blend of plant extracts and vaginal suppositories based on ingredients of natural origin with proven immunostimulating, antiviral, antiseptic, anti-inflammatory, antiseptic, anti-inflammatory, and regenerative effects demonstrated high clinical efficacy of HPV infection therapy, adequate safety, and tolerability, and contributed to reducing stress levels in case of recurrent CIN II in women of perimenopausal age.

The data obtained by us prove the feasibility of including recurrent CIN II in the treatment regimen of HPV-associated forms at the preparatory stage before the procedure of radio wave conization of the cervix and during postoperative rehabilitation of a blend of plant extracts in combination with vaginal suppositories with ingredients of natural origin to increase the effectiveness of treatment and reduce the frequency of recurrence of HPV infection and precancerous conditions of the cervix.

Conclusions

1. Radiowave therapy in combination with a blend of plant extracts and ingredients of natural origin for topical use has anti-inflammatory, immunomodulatory, antiviral, and reparative effects, prevents the occurrence of postoperative complications, provides a high level of subjective feeling of comfort, has adequate safety and tolerability, which proves the expediency of use proposed complex in the treatment and postoperative rehabilitation of women with recurrent CIN II.

2. The effectiveness and safety of the optimized therapeutic and prophylactic complex were proven by the complete absence of multiple highly carcinogenic genotypes of HPV infection, clinically significant and above the threshold of viral load progression, total elimination of the HPV, which was carried out in 96.7% of patients with the proposed complex, in contrast to 73.3% of women treated in a standardized manner.

3. Cervical reepithelialization after the use of optimized postoperative rehabilitation management was diagnosed in 100% of women with total cytological regression of HSIL (CIN II), which occurred 1.3 times faster, compared to 86.7% of patients receiving conventional treatments.

4. The inclusion of immunocorrective agents in the therapeutic and prophylactic complex leads to the stabilization of cytokines and antibodies that ensure the regulation of immune systems by a significant decrease in the levels of IL-1 by 3.4 times, TNF- by 5.2 times in peripheral blood and an increase in the level of sIgA in vaginal secretions by 1.9 times, compared to the indicators before immunocorrection in the preoperative period.

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References/Література

1. Banerjee D et al. (2020). A Prospective Randomized Trial to Compare Safety, Acceptability and Efficacy of Thermal Ablation and Cryotherapy in a Screening and Treat Setting. Asian Pac. J. Cancer Prev. 21: 1391-1398. doi: 10.31557/APJCP.2020.21.5.1391.
2. Beniuk VO, Hinzburh VH, Honcharenko VM, Nykoniuk TR, Laskava TH et al. (2024). Farmakolohichna korektsiia imunolohichnykh porushen u zhinok perymenopauzalnoho viku z retsydyvnoiu tservikalnoiu intraepitelialnoiu neoplaziieiu, asotsiiovanoiu z papiloavirusnoiu infektsiieiu. Women's Reprod Health. 3(74): 68-76.
3. Beniuk VO, Honcharenko VM, Usevych IA, Korniiets NH, Oleshko VF, Momot AA et al. (2022). Peculiarities of colposis and vaginal biocenosis in menopausal women with atrophic vaginitis. Women's Reprod Health. 6(61): 65-70.
4. Beniuk VO, Kurochka VV, Oleshko VF, Momot AA. (2022). Suchasnyi kompleksnyi pidkhid u likuvanni atrofychnoho vahinitu u zhinok menopauzalnoho viku. Reproduktyvne zdorovia zhinky. 5(66): 51-56.
5. Berger L, Wolf-Breitinger M, Weiß C et al. (2023). Prevalence of higher-grade dysplasia in persistently high-risk human papillomavirus positive, cytology negative women after introduction of the new cervical cancer screening in Germany. Cancer Causes Control. 34: 469-477 https://doi.org/10.1007/s10552-023-01677-z.
6. Berggrund M, Gustavsson I, Aarnio R, Lindberg JH, Sanner K, Wikström I et al. (2020). Temporal changes in the vaginal microbiota in self-samples and its association with persistent HPV16 infection and CIN2. Virol J. 17(1): 147. doi: 10.1186/s12985-020-01420-z.
7. Bosch XF, Broker TR, David F. (2018). Comprehensive Control of Human Papillomavirus Infections and Related Diseases. Vaccine. 31: 1-31.
8. Broutet N, Dangou J-M, Fadhil I, Lazdane G et al. (2014). WHO Guidelines for Treatment of Cervical Intraepithelial Neoplasia 2–3 and Adenocarcinoma in situ: Cryotherapy, Large Loop Excision of the Transformation Zone, and Cold Knife Conization. World Health Organization.
9. Castle PE, Kinney WK, Xue X et al. (2019). Role of Screening History in Clinical Meaning and Optimal Management of Positive Cervical Screening Results. J Natl Cancer Inst. 111(8): 820-827.
10. Chistyk T. (2023). Improved formula for etiopathogenetic support of women with urogenital viral diseases. News Med Pharmacy. 782(1): 1-5.
11. Dahoud W, Michael CW, Gokozan H, Nakanishi AK, Harbhajanka A. (2019). Association of Bacterial Vaginosis and Human Papilloma Virus Infection with Cervical Squamous Intraepithelial Lesions. Am J Clin Pathol. 152(2): 185-189. doi: 10.1093/ajcp/aqz021.
12. Derzhavnyi Ekspertnyi Tsentr Ministerstva okhorony zdorov'ia Ukrainy. (2024). Standart medychnoi dopomohy «Skryninh raku shyiky matky. Vedennia patsiientok z anomalnymy rezultatamy skryninhu ta peredrakovymy stanamy shyiky matky». Nakaz MOZ Ukrainy vid 18 chervnia 2024 No.1057. [Державний Експертний Центр Міністерства охорони здоров'я України. (2024). Стандарт медичної допомоги «Скринінг раку шийки матки. Ведення пацієнток з аномальними результатами скринінгу та передраковими станами шийки матки». Наказ МОЗ України від 18 червня 2024 №1057].
13. Diakova MV, Potapov VO, Sukhanova AA, Shponka IS, Akulina OO. (2019). VPL-asotsiiovna patoloiia shyiky matky: suchasna stratehiia diahnostyky, likuvannia ta profilaktyky. Hinekolohiia. Akusherstvo. Reproduktolohiia. 2(34).
14. Dyndar OA, Nykoniuk TR, Neimark OS, Polovynka VA. (2020). Risk factors of pre-cancer cervical diseases in women of reproductive age. Medical Science of Ukraine. 16; 1: 17-20.
15. Dyndar OA, Nykoniuk TR, Neimark OS. (2020). Vykorystannia ultrazvukovoi kavitatsii dlia likuvannia tservikalnoi intraepitelialnoi neoplazii na tli henialnoi papilomavirusnoi infektsii asotsiiovanoi z trykhomoniazom. Zbirnyk naukovykh prats Asotsiatsii akusherivhinekolohiv Ukrainy. Rivne. 2(46): 41-48.
16. Fedorenko Z, Michailovich Y, Goulak L. (2022). Cancer in Ukraine, 2020-2021. Bull Nat Cancer Registry Ukr. 23: 44-44.
17. Gungorduk K, Ozdemir A, Shahin O. (2021). The optimal time of the loop electrosurgical excision procedure according to different phases of the menstrual cycle. J. Gynecol. Obstet. Hum Reprod. 50: 101888. doi: 10.1016/j.jogoh.2020.101888.
18. Hinchytska LV, Lasytchuk OM, Zhurakivskyi VM, Basiuha IO, Kurtash NI, Pakharenko LV. (2021). Restoration and preservation of the vaginal ecosystem in postmenopausal women. Women's Reprod Health. 6(51): 77-82.
19. Khyts A. (2022). Suchasni aspekty terapii henitourynarnoho menopauzalnoho syndromu. Zdorov'ia Ukrainy – Health-ua. 5. [Хиць А. (2022). Сучасні аспекти терапії генітоуринарного менопаузального синдрому. Здоров'я України – Health-ua. 5]. URL: https://health-ua.com/akusherstvoginekologiya/menopauza/71683-suchasn-aspekti-terap-gentourinarnogo-menopauzalnogo-sindromu
20. Kondratiuk VK, Horban NYe, Nikitina IM, Kondratiuk KO. (2023). Urazhennia shyiky matky na tli infikuvannia virusom papilomy liudyny: aspekty profilaktyky, diahnostyky ita likuvannia. Reproduktyvne zdorovia zhinky. 6(69): 68-75.
21. Lasytchuk OM, Bazhan OI, Pakharenko LV, Zhurakivskyi VM, Basiuha IO et al. (2022). Improvement of cervical epithelium recovery and prevention of complications after electrosurgical treatment. Art Med. 22(2): 48-52. doi: 10.21802/ artm.2022.2.22.48.
22. Manzhura OP, Maievska IO. (2023). Likuvannia ta reabilitatsiia patsiientok iz tservikalnoiu intraepitelialnoiu neoplazvieiu tiazhkoho stupenia. Reproduktvne zdorovia zhinky. 8(71): 7-14.
23. Mirabello L, Schiffman M, Ghosh A et al. (2018). Elevated methylation of HPV16 DNA is associated with the development of high grade cervical intraepithelial neoplasia. Int J Cancer. 132: 1412-1422.

24. National Cancer Institute. (2023). HPV and Pap Test Results: Next Steps after an Abnormal Cervical Cancer Screening Test. URL: https://www.cancer.gov/types/cervical/screening/abnormal-hpv-pap-testresults.
25. Ogilvie GS, Krajden M, van Niekerk D. (2017). HPV for cervical cancer screening (HPV FOCAL): complete round 1 results of a randomized trial comparing HPV-based primary screening to liquid-based cytology for cervical cancer. Int J Cancer. 140(2): 440-448.
26. Okunade KS. (2020). Human papilloma- virus and cervical cancer. J. Obstet. Gynaecol. 40(5): 602-608. doi: 10.1080/01443615.2019.1634030.
27. Riera M, Ruperez B, Lazaro I. (2020). Effect of a multi-ingredient vaginal gel on clearance and/or cytology normalization in high-risk HPV positive patients. J Low Genit Tract Dis. 24: 16.
28. Russomano F, Tristao MAP, Côrtes R, de Camargo MJ. (2015). A comparison between type 3 excision of the transformation zone by straight wire excision of the transformation zone (SWETZ) and large loop excision of the transformation zone (LLETZ): A randomized study. BMC Womens. Health. 15: 12. doi: 10.1186/s12905-015-0174-5.
29. Stepanenko TA. (2018). Features of psychological adaptation of women with early menopause. Health of woman. 9(135): 103-106. [Степаненко ТО. (2018). Особливості психологічної адаптації жінок з ранньою менопаузою. Здоров'я жінки. 9(135): 103-106].
30. Sukhanova AA. (2023). Efektyvnist mistsevoho likuvannia VPL-asotsiiovanoi patolohii shyiky matky u zhinok za dopomohoiu vahinalnoho heliu na osnovi Coriolus versicolor. Reproduktyvne zdorovia zhinky. 3(66): 29-35.
31. Sukhanova AA, Sokolova YeI. (2019). Comparative characteristics of local destructive methods of treatment of precancerous pathology of the cervix. Zbirnyk naukovykh prats spivrobitnykiv NMAPO imeni P.L. Shupyka. 36: 98-103.
32. Svintsitsky VS, Priymak VV, Renkas OP. (2020). Modern approaches to the diagnosis and treatment of cervical cancer. Ukrainian medical journal. 3 (137): Vol. 2(V/VI):1-7. doi: 10.32471/umj.1680-3051.137.178064. [Свінціцький В.С., Приймак В.В., Ренкас О.П. (2020). Сучасні підходи до діагностики та лікування раку шийки матки. УКР. МЕД. ЧАСОПИС, 3 (137), Т. 2 – V/VI 2020:1-7]
33. Tsentr hromadskoho zdorov'ia MOZ Ukrainy. (2022). Skryninh raku shyiky matky ta rannie vyiavlennia khvoroby. [Центр громадського здоров'я МОЗ України. (2022). Скринінг раку шийки матки та раннє виявлення хвороби]. URL: https://www.phc.org.ua/news/skrining-raku-shiyki-matki-ta-ranne-viyavlennya-khvorobi.
34. Volodko NA, Vinnytska AB, Kaminsky VV. (2018). Ukrainian national consensus on ex- amination and treatment of women after primary cervical screening. Reprod Endocrinol. 43(5): 8-14.
35. World Health Organization Comprehensive Cervical Cancer Control (2021). Explanatory notes for 2021 cervical cancer profiles. URL: https://cdn.who.int/media/docs/default-source/ncds/ncd.
36. World Health Organization. (2020). Global Strategy Towards Eliminating Cervical Cancer as a Public Health Problem [Internet]. Geneva: WHO: 56. URL: https://www.who.int/publications/i/ item/9789240014107.

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