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COMBINATION THERAPY OF CERVICAL AND VAGINAL DYSPLASIA IN A SETTING OF HUMAN PAPILLOMAVIRUS INFECTION

КОМПЛЕКСНЕ ЛІКУВАННЯ ДИСПЛАЗІЇ ШИЙКИ МАТКИ ТА ПІХВИ НА ТЛІ ПАПІЛОМАВІРУСНОЇ ІНФЕКЦІЇ. У статті представлено результати обстеження та лікування 126 жінок з дисплазією шийки матки на тлі папіломавірусної інфекції генітальної локалізації. Доведена ефективність проведення конізації шийки матки апаратом радіохвильової хірургії з подальшою лазерною коагуляцією післяопераційної рани та уражених стінок піхви, з використанням противірусної та імуномодулювальної терапії.

КОМПЛЕКСНОЕ ЛЕЧЕНИЕ ДИСПЛАЗИИ ШЕЙКИ МАТКИ И ВЛАГАЛИЩА НА ФОНЕ ПАПИЛЛОМАВИРУСНОЙ ИНФЕКЦИИ. В статье представлены результаты обследования и лечения 126 женщин с дисплазией шейки матки на фоне папилломавирусной инфекции генитальной локализации. Доказана эффективность проведения конизации шейки матки аппаратом радиоволновой хирургии с последующей лазерной коагуляцией послеоперационной раны и пораженных стенок влагалища с использованием противовирусной и иммуномодулирующей терапии.

COMBINATION THERAPY OF CERVICAL AND VAGINAL DYSPLASIA IN A SETTING OF HUMAN PAPILLOMAVIRUS INFECTION. The article provides the findings of assessment and treatment of 126 women with cervical dysplasia in a setting ofgenital human papillomavirus infection. The authors have demonstrated the efficacy of cervical conization with a radiofrequency surgery device and subsequent laser coagulation of the postoperative wound and affected vaginal walls using antiviral and immunomodulatory therapy.

Ключові слова: дисплазія шийки матки, папіломавірусна інфекція, лазерна коагуляція, радіохірургічна конізація.

Ключевые слова: дисплазия шейки матки, папилломавирусная инфекция, лазерная коагуляция, радиохирургическая конизация.

Key words: cervical dysplasia, human papillomavirus infection, laser coagulation, radiofrequency conization.

INTRODUCTION. Among cancers of female genital organs, the incidence of cervical malignancies ranks second and is registered in 19 cases per 100,000 females in Ukraine, according to the National Cancer Registry [1]. Therefore, in the past, the present and well into the future, prevention of female genital cancer, especially of its visible forms, is a priority task for obstetricians and gynecologists.

In recent decades, as a result of migration and urbanization of the population, an increase in sexually transmitted diseases has been observed, among which human papillomavirus infection (HPVI) is one of the most common [2, 3]. Today, the number of infected patients has increased more than tenfold worldwide. The principal clinical manifestations of HPVI include anogenital warts and cervical lesions, which cause physical, psychological and sexual discomfort [4, 5]. The relevance of this disease is also attributable to the fact that it is a part of AIDS-associated set of symptoms [6, 7], which requires giving the patient more attention [8], as well as to the known oncogenicity of strain 16 and strain 18 viruses, which cause a significant portion of malignant cervical lesions [9-12]. Currently, among sexually active women (20-35 years of age) HPVI occurs in 30-50%, and cervical dysplasia - in 5%.

The term «dysplasia», coined by J. W. Reagan in 1956 and approved by the WHO Expert Committee in 1973, has been used to describe all pre-tumor cervical conditions for a long time. At present, there are many synonyms for dysplasia: atypia, atypical hyperplasia, basal cell hyperplasia, and cervical intraepithelial neoplasia (CIN). In 1988, cytologists have proposed the term SIL (Squamous Intraepithelial Lesion), which is currently the most common [13].

Cervical dysplasia is diagnosed in patients using cytological assessment of smears to detect cells with various degrees of atypia. The Pap test (Papanicolaou test) is one of the early most accurate methods for detection of minimal dysplastic changes in squamous cervical epithelium. It allows for effective detection of precancerous changes in the epithelium, such as cervical intraepithelial neoplasia of various severity. This assessment is mandatory for women diagnosed with areas of modified epithelium during colposcopic examination of the cervix. The Pap test is informative in 60-90% of cases, but it does not completely rule out the risk of cervical cancer. The final diagnosis is determined only by means of biopsy, the location of which is established by colposcopy [14, 15].

The most characteristic morphological signs of dysplasia are as follows:

1) cellular atypia (nuclear polymorphism, hyperchromasia, stratification of nuclei and increased nuclear-cytoplasmic index);

2) impaired differentiation; reduction or cessation of mucus production by epithelial cells;

3) impaired architectonics of the mucous membrane (irregular structure of the scripts, proliferation and branching of the glands with formation of superficial and intraglandular papillary structures) [16-18].

Cervical dysplasia may affect various layers of squamous epithelial cells. There are 3 degrees of cervical dysplasia, depending on the depth of the abnormal process. The deeper epithelium is affected, the more severe the cervical dysplasia. Current international classification distinguishes between the following:

1. Mild cervical dysplasia (CIN 1, Grade I): changes in cellular structure are mild and are confined to the basal 1/3 of the stratified squamous epithelium.

2. Moderate cervical dysplasia (CIN 2, Grade II): changes in cellular structure are confined to the basal 2/3 of the squamous epithelium.

3. Severe cervical dysplasia or non-invasive carcinoma (CIN 3, Grade III): the abnormal changes occur throughout the entire epithelial cell layer, but do not extend to vessels, muscles, nerve endings, as in invasive cervical cancer, which affects these structures [13-15].

Before initiating treatment in a patient with dysplasia caused by HPVI, the clinician must assess the severity of changes and the age and reproductive plans of the patient. In 50-60% of cases, mild dysplasia may reverse spontaneously; other cases may include stable disease or progression. In mild cervical dysplasia with concomitant diagnosis of urogenital infections, follow-up and specific treatment are used. In moderate or severe dysplasia, cervical conization is performed (with electrical, laser and radiofrequency technique) [15, 16].

Research into the issues of diagnosis and treatment of cervical dysplasia in a setting of HPVI remains a standing current issue of female health [19-21]. This is due to the high incidence of malignant cervical lesions, which amounts to 65-85% of cases of genital cancerous transformations. Therefore, there is an undisputed need to manage cervical dysplasia in a setting of papillomavirus lesions, which would improve patients' quality of life and prevent malignant neoplasms [22, 23]. None of the modern treatments is able to secure complete cure or guarantee the absence of relapses [24, 25]. Timely and radical management of cervical dysplasia in a setting of HPVI is one of the fundamental ways to prevent cervical cancer [26]. Most of the employed modalities are essentially local and target external manifestations, rather than the pathogenetic mechanisms behind the disease [27]. Despite the widespread use of electrosurgical treatments, which have reduced the severity of this problem over the past 40 years, the issue of rational therapy remains extremely relevant [2, 28, 29]. The principle of radicality and health improvement in patients with cervical dysplasia involves the following: removal of the abnormal cervical area with cryosurgery and diathermoconization, destruction of dysplasias with high-energy lasers and excision with a scalpel [30, 32]. Besides the insufficient efficacy, endometriosis, substantial lymphorrhea, delayed epithelization and scar deformities of the cervix. Recurrent dysplasias in a setting of HPVI may also be observed [29, 33].

Individual literature reports are controversial [34-36]; there is virtually no data on progress of cervical dysplasia with time and on treatment in a setting of HPVI. At the same time, HPVI, being a trigger for cervical dysplasia, and inadequate immune response may trigger the recurrence of the disease [37, 38]. Systemic response in patients with cervical dysplasia to human papillomavirus primarily manifests with immunological changes, the latter still being insufficiently explored [39]. For this reason, this study is dedicated to assessment of cervical dysplasia and immune status in HPVI and efficacy assessment of therapeutic regimen combining both local and general agents (including pharmacological antiviral therapy and organ-sparing surgical procedures). To date, there is a large number of research studies confirming the effectiveness of using lasers in surgical treatment of a number of gynecological conditions [29, 32, 43, 13].

The unique properties of the laser beam helped modern medicine achieve impressive success in management of many diseases. Over the recent decades, the introduction of Lika-Khirurh semiconductor lasers has become a turning point in clinical practice in Ukraine; their use has many advantages over traditional methods of treatment used in cervical, vaginal, and vulvar conditions, such as diathermo- and cryodestruction, chemical and conservative methods:

- laser effect is used under colposcopic guidance, allowing for complete removal of the affected area;
- laser crust develops, which prevents bleeding with exfoliation;
- a thin film covers the surface of the wound, which provides barrier and protective properties, thereby improving the postoperative period and reducing the risk of postoperative complications;
- reliable control of vaporization depth and of the amount of removed tissue;
- minimal damage to the tissues underneath the tissue subject to vaporization or coagulation;
- bloodless surgery;
- absence of gross postoperative scarring, which is especially important for cervical procedures in women of reproductive age, including nulliparous women;
- high levels of regeneration and absence of stenosis and injury to cervical glands [40, 41].

The effectiveness of laser technology is attributed to a number of advantages over alternative surgical methods.

Most notably, surgical lasers made it possible to deliver accurately targeted local impacts, since the tissue-cutting laser beam will simultaneously coagulate blood on the walls of the incision. This results in lower blood loss. Thus, the use of lasers virtually fulfils the surgeons' long-nurtured dream, that is, the ability to operate on a dry surgical site. Carefully metered exposure

to laser radiation ensures minimal tissue damage and improves the capacity to perform organ-sparing operations. Laser coagulation necrosis is qualitatively different from the necrosis caused by electrocoagulation or cryodestruction in that its area is much smaller [43].

In our opinion, the most promising technique is to perform cervical conization with a radiofrequency surgery device followed by laser coagulation of the postoperative wound and the affected vaginal walls with Lika-Khirurh laser (940 nm) with a power range of 10-25 W (depending on the type and location of the abnormal lesion). The device does not cause deep tissue damage; it produces atraumatic incisions and facilitates tissue coagulation, thereby ensuring absence of postoperative edema and pain. This method of treatment is particularly effective in lesions of the walls and the anterior, posterior and lateral vaginal vaults with papillomatous hyperplasia, as well as in cervical dysplasia spreading to the lateral vaults.

The objective of this study is to increase the efficacy of diagnosis and treatment for cervical dysplasia in a setting of human papillomavirus infection by developing adequate and pathogenetically valid methods of treatment for cervical dysplasia.

MATERIALS AND METHODS. Clinical assessments were performed at the Obstetrics and Gynecology Department of the I.Ya. Horbachevsky Ternopil State Medical University of the Ministry of Health of Ukraine SHEI and at the premises of the Professor S. Khmil Clinic Medical Center.

Study assessments involved 126 women; 30 of study subjects were found healthy and made up the control group, and the remaining 96 women had cervical dysplasia in a setting of genital HPVI.

The patients were divided into 3 treatment groups.

The first group included 29 women with cervical dysplasia in a setting of HPVI, who underwent cervical conization with a radiofrequency surgery device followed by laser coagulation of the postoperative wound and the affected vaginal walls with the Lika-Khirurh laser (940 nm, power range of 10-25 W) (depending on the type and location of the abnormal process).

The second group included 32 women with cervical dysplasia in a setting of HPVI, who underwent cervical conization with a radiofrequency surgery device followed by laser coagulation of the postoperative wound and the affected vaginal walls with the Lika-Khirurh laser (940 nm, power range of 10-25 W) and received treatment with Proteflazid.

The third group included 35 women with cervical dysplasia in a setting of HPVI, who underwent cervical conization with a radiofrequency surgery device followed by laser coagulation of the postoperative wound and the affected vaginal walls with the Lika-Khirurh laser (940 nm, power range of 10-25 W) and received treatment with Proteflazid and Laferon.

The procedures were performed on Day 3-7 of the menstrual cycle (in order to create optimal conditions for tissue regeneration and to prevent cervical endometriosis). Anesthesia was performed preoperatively with paracervical administration of one (1) ampoule of Ubistesin Forte (4% - 1.7 mL); in addition, vaginal walls were anesthetized with Lidocaine 10% anesthetic spray and with Emla anesthetic cream.

The procedure was performed as follows:

1. The cervix was exposed using a Sims' vaginal speculum.

2. The cervix and the vaginal walls were treated with an antiseptic solution, wiped off with a dry sterile cotton swab, and then treated with Lugol's iodine solution. Iodine has the ability to stain glycogen-rich cells in brown. Abnormally changed glycogen-poor cells are not stained by iodine and look like white spots. In this manner, the sites of prospective conization and laser vaporization were identified.

3. The cervix was fixed with a vulsellum.

4. Cervical conization was performed with a radiofrequency method followed by coagulation of the postoperative wound using the Lika-Khirurh device. In cases when cervical dysplasia spread to the anterior, posterior, and lateral vaults, as well as in cases of papillomatous hyperplasia on vaginal walls, local anesthesia was performed with Emla anesthetic cream, after which, laser vaporization was performed in 3-4 minutes with the Lika-Khirurh device. The laser beam was conducted to the abnormal tissue using a quartz diffuse light fiber optic (at a distance of 0.1-0.2 mm to the object). No cases of bleeding have been registered in our clinic over the period of using the Lika-Khirurh device for the treatment of cervical and vaginal lesions.

In the postoperative period, patients with cervical disease were prescribed vaginal lavage with antiseptic solutions (chlorhexidine, Betadine, Miramistin) for 9-11 days, and vaginal suppositories with methyl uracil to improve regeneration.

Despite the high informational value of modern assessment methods used in HPVI and cervical disease, review of patient history is an integral part of the multicomponent patient assessment; to this end, we have developed a case record questionnaire to be filled with data on menstrual and generative functions, history of somatic and gynecological disease, time of detection of cervical disease, and the quality/efficacy of previous treatments. As a part of comprehensive patient assessment, attention was paid to inflammatory conditions of the appendages, vulva and cervix, as well as to such complaints as contact hemorrhagic vaginal discharge, burning sensation, pain, and vesicular rash. Particular attention was paid to the visual inspection of external genitals and detection of papillomavirus hyperplasia in the vulva and in the genital area. The inspection was conducted using vaginal speculums to identify papillomatous hyperplasia in the area of the vaginal opening and vaginal walls; the shape and size of the cervix, polyps (if any), areas of vulvar leukoplakia, macular changes of mucous membranes, old ruptures, and variously shaped erosions were also documented. Smears for bacteriological and bacterioscopic tests were taken from the cervical canal and the vagina. The polymerase chain reaction method was used to detect the highly carcinogenic types of HPVI [23, 25, 38, 40, 42].

Diagnosis of dysplasia and papillomavirus infection was performed with colposcopy (per L.M. Vasilevskaya's

technique) using the Scanner-200 video colposcope with regular light filters, 8-12-20X magnification range, and 210-240 mm frontal distance to the object. Location and nature of the abnormal process were determined in course of cervical colposcopy. For a more detailed colposcopic presentation, extended colposcopy was performed using 3% acetic acid solution and Lugol's solution (Schiller's test). This test allowed for a more effective identification of abnormal sites and for a more precise subsequent laser destruction. Colposcopy was also used to assess the color of cervical mucosa, the vascular pattern, the surface and level of the stratified squamous epithelium, the tissue junction between stratified squamous and columnar epithelium (location and nature), the presence and shape of glands, and the type of epithelium. Particular attention was paid to papillomatous structures located in various sections of the cervix and the vagina.

We performed a cytological assessment of smears obtained in patients with 1st-2nd relative degree of microbial contamination of vaginal contents. Biopsy samples of cervical tissue were obtained under video colposcopic guidance (from at least two sites) in patients with papillomatous changes and iodine-negative cervical areas, where cytological and colposcopic testing diagnosed cervical dysplasia and signs of viral lesions.

The patients were prescribed pharmacological therapy: Proteflazid, an antiviral medicinal product supplied as drops, was prescribed for local and systemic use under an appropriate regimen. Twenty (20) mL of isotonic sodium chloride solution was used to dilute 2 mL of Proteflazid; then soaking therapy was applied to papillomas, and tampons soaked with the preparation were inserted into vagina 2-3 times a day for 20 days. Simultaneously with external use, the medicinal product Proteflazid was administered orally as drops (10 drops three times a day for 30 days).

The medicinal product Laferon was used locally, as circular low-depth injections around the cervix, 3,000,000 IU 2 times a week (10 procedures per course).

A microbiome assessment smear was taken using a conventional technique to determine the numbers of epithelial cells, leukocytes and specific microbiota (Döderlein bacilli, pathogenic biota, gram-negative bacteria, cocci, Chlamydia, clue cells, fungi and Trichomonas vaginalis), as well as to test the pH of vaginal contents.

All subjects were assessed for systemic immunity parameters, such as B- and T-lymphocytes and their fractions and immunoglobulins. This assay was performed using indirect surface immunofluorescence reaction with IKO monoclonal antibodies (Mab): Mab IKO-90 against CD3 antigen of T-cells of peripheral blood; Mab IKO-86 against the CD4 antigen of T-helper cell subpopulation; Mab IKO-31 against the CD8 antigen of T-suppressor cell subpopulation and Mab IKO-12 against the CD22 antigen found on the surface of B-lymphocytes. Clinical and laboratory tests were performed before and after treatment.

STUDY RESULTS AND DISCUSSION. Patient distribution by age and diagnosis showed that most study subjects were women 18 to 45 years of age. Given the role of sexual activity as a risk factor of HPVI, we described the patterns of sexual activity in study subjects. In a significant proportion of women, the onset of sexual activity was at the age of 15-17 years. Female sexual activity is characterized not only by the age of onset of sexual activity, but also by the number of sexual partners. It was not possible to obtain reliable data on sexual life in all cases. The resulting findings of the assessment show that early-onset sexual activity and uncontrolled sexual behavior, as well as frequently changed sexual partners are conducive to sexually transmitted infections and frequently cause infection with human papillomavirus.

We compared complaints reported by study subjects. More than half of the patients (80%) complained of profuse discharge. The second most frequent clinical symptom was itching and burning sensations in the vagina (52%). Absence of complaints was observed in 16% of the patients.

During analysis of clinical manifestations in various abnormal vaginal conditions associated with HPVI, no disease-specific symptoms have been detected. According to our data, the symptoms of sexually transmitted genital disease are prominent. HPVI duration ranged from 4 months to 10 years. However, these findings are relative, since routine gynecological surveillance of these patients has been sporadic in most cases.

Patient history informs that 70% of the study subjects were treated using different methods. The range of therapeutic interventions was very wide. Both conservative methods and therapeutic destruction were used. Among others, the most frequently used methods included diathermocoagulation and destruction of papillomas with Collomak and Solcoderm. The resulting findings confirm that the methods used to remove morphological signs of HPVI do not eliminate papilloma virus from the tissues of mucous membranes and from the body in general. Therefore, it is recommended to conduct pre-treatment assessment of the patients for human papillomavirus DNA due to the risk of malignant transformations (depending on the type of the virus). Detecting viral type and appropriate routine antiviral therapy should significantly increase the effectiveness of destructive treatments and reduce the incidence of dysplastic cervical/vaginal disease and recurrent colpitis.

Summing up the above, it should be emphasized that HPVI primarily affects young women of active reproductive age. Most of the patients had an early onset of sexual activity, large numbers of sexual partners and sexually transmitted disease; smoking and use of intrauterine and hormonal contraceptives has also been common. All these factors are of a theoretical and practical interest, making it possible to use certain preventive measures in order to limit the prevalence of HPVI, which will contribute to significant reductions in vulvar and cervical cancers.

During analysis of systemic reactions in patients with cervical dysplasia in a setting of HPVI, signs of immunosuppression were found, mainly due to affected cellular component of the immune system (Table 1).

As shown in Table 1, there was a significant decrease in total lymphocyte counts; analysis of lymphocytic subclasses has shown that this was caused by a decreased CD4 cell count, while the reduction of CD8 cell count was not significant. The helper cell malfunction was manifested by a decrease in the immunoregulatory index (which, however, was not significant).

Parameters of humoral immunity were indicative of its activation, as the counts of CD72 cells and immunoglobulins of all classes were increased. The increase in IgG levels was the most prominent, while the levels of other immunoglobulin types did not increase significantly.

The clinical efficacy of HPVI treatment was 68.96% in Group I (20 subjects), with somewhat better results in Group II (78.12% or 25 subjects); the highest treatment efficacy was obtained in Group III, reaching 94.29% (33 subjects).

Concerning immune system parameters, the positive changes were similar (Table 2). Thus, in Group I, which included women receiving local treatment alone, the changes of the parameters with time were minor, and the observed changes were statistically insignificant, although the total T-cell count (CD3) was close to the values in the control group.

The changes in Group II were more pronounced, especially in relation to humoral immunity. There was a significant decrease in Ig G levels compared to pre-treatment values; the remaining parameters did not differ significantly from the values in the control group.

The best treatment effect has been documented in Group III (that is, in women with cervical dysplasia in a setting of HPVI, who underwent cervical conization with a radiofrequency surgery device followed by laser coagulation of the postoperative wound and the affected vaginal walls with the Lika-Khirurh laser [940 nm, power range of 10-25 W] and also received treatment with Proteflazid and Laferon). This group of patients had significant changes in all of the major immunological parameters, both cellular and humoral.

Thus, the CD3 and CD4 cell counts increased, while the counts of all immunoglobulin classes decreased. None of the parameters differed from those in the control group.

Our data show that the use of antivirals alone may influence the pathogenetic mechanisms of the disease, producing a better clinical effect at the same time. Local treatment does not improve the status of the immune system and only reduces local manifestations.

Table 1. **Immunological parameters in women with cervical dysplasia in a setting of HPVI**

Parameter	Control group (n=30)	Treatment group (n=96)
CD3, %	52.5+1.34	48.06±0.44*
CD4, %	35.71±0.89	32.41±0.28*
CD8, %	16.79+0.71	15.65±0.22
CD72, %	8.6±0.25	9.42±0.19*
CD4/CD8	2.12±0.32	2.07±0.25
Ig G, g/L	9.18±0.89	12.11+0.18*
Ig A, g/L	1.57+0.16	1.9±0.08
Ig M, g/L	2.89±0.36	3.51+0.13

Note. *- the inter-parameter difference is significant, p<0.05.

Table 2. **The effect of different treatment regimens on the parameters in women with cervical dysplasia in a setting of HPVI**

Parameter	Control group (n=30)	Before treatment (n=96)	After treatment		
			Group I (n=29)	Group II (n=32)	Group III (n=35)
CD3, %	52.5+1.34	48.06±0.44*	49.12+1.22	50.11+1.18	51.78+1.14*
CD4, %	35.71 ±0.89	32.41±0.28*	32.89±0.78*	33.54±0.68	34.87±0.62**
CD8, %	16.79+0.71	15.65±0.22	16.23±0.65	16.57+0.61	16.91+79
CD72, %	8.6±0.25	9.42±0.19*	9.11+0.65	8.99±0.59	8.69±0.41
CD4/CD8	2.12±0.82	2.07±0.25	2.03±0.12	2.02+0.11	2.06±0.09
Ig G, g/L	9.18±0.89	12.11+0.18*	11.54+0.56*	10.87±0.49**	9.54±0.47**
Ig A, g/L	1.57+0.16	1.9±0.08	1.81 ±0.09	1.74±0.08	1.63±0.07**
Ig M, g/L	2.89±0.36	3.51+0.13	3.34±0.28	3.09±0.21	3.04±0.14**

Notes:
1. * - the difference vs. control is significant, p<0.05.
2. ** - the difference vs. pre-treatment parameters is significant, p<0.05.

CONCLUSIONS.

1. Cervical dysplasia in a setting of HPVI is accompanied by changes in the immune system, which are characterized by inhibition of the cellular component and activation of the humoral component.

2. The use of the radiofrequency method for cervical conization with subsequent laser coagulation of the postoperative wound and the vaginal walls affected by papilloma and dysplasia with a Lika-Khirurh diode laser does not affect the parameters of systemic immunity.

3. The recommended treatment for cervical dysplasia in a setting of HPVI includes combination of the following: the use of the radiofrequency surgery device followed by laser coagulation of the postoperative wound and the vaginal walls affected by papillomatous hyperplasia and dysplasia with the Lika-Khirurh diode laser and drug therapy with Proteflazid (drops for topical and oral administration, 10 drops three times a day for 30 days) and Laferon for circular low-depth paracervical injections, 3,000,000 IU 2 times a week/10 procedures per course.

4. Laser coagulation of the postoperative wound and the vaginal walls affected by papillomatous hyperplasia and fields of dysplasia (using the Lika-Khirurh laser) provides the following benefits: performing minimalistic organ-sparing procedures, pronounced hemostatic effect and accelerated tissue repair and regeneration.

5. Using a comprehensive therapeutic approach in patients with cervical disease in a setting of HPVI substantially improves treatment outcomes.

PROSPECTS FOR FUTURE RESEARCH. Future studies into the particularities of comprehensive treatment of cervical dysplasia with vaginal wall lesions in a setting of papillomavirus infection will allow developing more effective treatment methods and reducing recurrence rates of precancerous conditions and cervical cancer.

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