

IMPROVEMENT OF TACTICS FOR THE MANAGEMENT CERVICITIS ASSOCIATED WITH PAPILLOMAVIRUS INFECTION IN WOMEN OF REPRODUCTIVE AGE

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ABSTRACT

Chronic cervicitis is diagnosed in 80% of women with cervical ectropion. Human papillomavirus (HPV) provokes cervical intraepithelial lesion and prevents normal course of cervical ectropion. High contagiousity provides the infection in 80% of cases even after single sexual act. In most patients, infection is transient, and HPV is spontaneously eliminated after 12 to 24 months. However, in 10% to 20% of women persistent infection increases the risk of severe cervical intraepithelial neoplasia which can progress to invasive cancer. The paper discusses cervix inflammation associated with papillomavirus and the role of cervical ectropion as a site of the realization of papillomavirus oncogenic potential. Indications to the medical treatment and surgical procedures for complicated ectropion are addressed. The authors analyze treatment outcomes of topical medications with glycyrrhizinic acid as monotherapy or in combination with cryodestruction. Recommendations on the management of cervical ectropion associated with papillomavirus infection in women of various ages are provided.

Keywords: *cervical ectropion, human papillomavirus (HPV), chronic cervicitis, neoplasia.*

Most women in the age group 18–30 years are susceptible to infection. The high contagiousness of the infection ensures transmission in 80% of cases even with a single sexual contact. In most cases, the infection is transient, and the virus is spontaneously eliminated over the next 12–24 months. [2], but in 10–20% of women persistent infection increases the risk of developing high-grade cervical epithelial neoplasia (HSIL), which in 30–40% of cases progresses to the stage of invasive cancer [3, 4]. HPV group high oncogenic risk is found in 99.7% of women with a histologically confirmed diagnosis of CC, which amounts to according to WHO, more than 500,000 women per year. Most cases of cervical cancer occur in the so-called transformation zone, which is connection between the proximal single-layer glandular epithelium and the distal stratified squamous epithelium. Today it is known that in an infected cell the virus can exist in two forms: episomal (productive) and integrative (transforming). In the first case, the DNA of the virus is in the nucleus host cells in the form of a stable isolated episome (DNA molecules, “silent” genetic elements capable of independent reproduction in the cytoplasm).

This form is considered benign because it does not cause pathological changes in cells and has a high probability of spontaneous regression. With integrative form, viral DNA is integrated into the genome of the host cell and replication of the already modified genome occurs. The cell of integrated viral DNA begins to actively synthesize viral oncoproteins E6 and E7, quickly exits from under the body’s immune control and avoiding apoptosis, over time, it can develop into a malignant state. The episomal form of PVI is histologically characterized as mild dysplasia, CIN 1–2 (LSIL), integrative - as moderate or severe dysplasia, CIN 3 (HSIL) [5].

Ectopia of the cervical epithelium as a risk zone of oncogenic activity of women with PVI

During puberty, physiological squamous metaplasia occurs, as a result of which the glandular columnar epithelium (CE) gradually turns into squamous epithelium. Cells representing this transformation is called metaplastic cells. The term "ectopia" refers to a condition where which is present and visualized on the ectocervix

simultaneously cylindrical and metaplastic epithelium. Over time, this transition zone moves to a more proximal position. So teenagers and young women have a larger area of ectopia compared to women of later reproductive age. However, the timing of this movement can vary significantly depending on the endocrine status, use of oral contraceptives, and the presence of concomitant diseases, chronic inflammatory processes, promiscuity and epigenetic factors [6].

The ectopic area is an area with a thin single-layer, good vascularized epithelium, where blood vessels are in close contact with the vaginal environment. This creates easy access to the circulatory and lymphatic systems, possibly reducing mucosal barriers to STI. Among women with ectopic CE, cervical cancer is significantly more common. Exo- and endocervicitis are diagnosed. Chronic cervicitis is diagnosed in 80% of women with ectopic cervix. Frequency of cervical inflammatory disease (N72, ICD-10) in women with ectopia it is 50–80% [7, 8].

Back in the 19th century. German pathologist Rudolf Virchow drew attention to the fact that the appearance of a malignant tumor is often preceded by a chronic inflammation in a particular tissue. Research over the past decades has not only confirmed this observation, but also identified a number of immunocompetent cells and specific factors that can suppress growth tumors, and stimulate it due to the reprogramming of immune cells against the background of long-term inflammatory process [9, 10]. Thus, the ectopic epithelium of the cervix is a potential risk zone for the implementation of oncogenic activity of PVI.

Is it possible that the presence of PVI against the background of ectopia always leads to dysplastic changes in the cervix and requires active therapeutic tactics for such patients?

The prevalence of ectopia among women of reproductive age averages 40% and is most common in the age group under 30 years [7,11, 12]. The main complaints with ectopia and ectropion CMM may include heavy vaginal discharge (leukorrhea), pain in the pelvic area, and postcoital bleeding. But ectopia CE and ectropion cervix

can occur and completely asymptomatic. It was noted that productive PVI occurs in the basal cells of the metaplastic epithelium of the transformation zone and the adjacent ectocervix. For a transforming form, the weak point is transition zone and junction zone between multilayered squamous epithelium and single-layer CE of the cervix. There is data that the increased predisposition of this area to precancer and cervical cancer is associated with the maximum localization of reserve cells there, which have a high potential subsequent tumor transformation during infection with highly oncogenic HPV [13]. Ectopia also does epithelium more sensitive to STIs, for example those caused by *Chlamydia trachomatis* and *Neisseria gonorrhoeae*, against which PVI may develop a more malignant course [6, 14]. A larger area of ectopic epithelium and a high infectious index were noted against the background chlamydial infection even if asymptomatic ectopia [15, 16]. Thus, in the management plan for women with ectopic cerebrovascular disease it is necessary to include examination for STIs even if the patient has no complaints. Frequency of intraepithelial lesions of the cervix in women with ectopia, CE ranges, according to various sources, from 17 to 40%, at the same time, dysplasia is more common at the age of 23 years mild (CIN 1), and most cases are moderate and severe dysplasia (CIN 2–3) occur between the ages of 25 and up to 35 years [7, 12].

There was a higher prevalence of HPV in ectopia, as well as the frequency of CIN in the background PVI [18]. In a study conducted among female students under the age of 30, it was found that the inflammatory type of smear was the leading one in the structure of cytological conclusions in the group with cervical ectopia, regardless of the presence HPV. However, the incidence of CIN was significantly higher (43.6%) against the background of PVI than in HPV-negative patients (17.5%). Adolescents are of particular concern because they usually have a wide area of ectopia. Interesting data were obtained in a cohort study HIV-infected adolescents aged 12–20 years in 13 cities USA. In the work of L.I. Maltseva a correlation was found between low levels of estrogen metabolite ratios, a positive p16ink4a reaction and the presence of long-term persistent PVI. It has been shown

that assessing the expression of p16ink4a protein and the degree of disruption of estrogen metabolites 2-ONE1/16a-ONE1 allows a differentiated approach to the treatment of HPV-associated cervicitis.

CHOICE OF MANAGEMENT TACTICS

Despite the fact that ectopia is a normal physiological process and does not require treatment, there are several arguments in favor of treating this condition. The best known fact is that chronic Cervicitis (CC) against the background of ectopic CE serves as a powerful cofactor for the persistence of HPV and the occurrence of intraepithelial lesions [14]. As mentioned earlier, there is a relationship between squamous metaplasia and induction of squamous cell cancer and cells undergoing metaplasia are more susceptible to carcinogens. Theoretically, if, by removing ectopia, the process of epithelialisation it is possible to accelerate and reduce the size of metaplasia, this creates unfavorable conditions for HPV persistence and reduces the risk of developing intraepithelial lesions, and therefore cervical cancer [23, 24]. Constant heavy discharge (leukorrhea), pain sensations and postcoital bleeding cause significant discomfort in women and may be an indication for the treatment of cervical cervical ectopia. In the 2017 Clinical Guidelines for the Prevention of CC of the Ministry of Health of Russia, active management of women with CIN 1 is recommended in the following cases: unsatisfactory colposcopy findings, extensive lesions, duration of CIN 1 more than 18 months, age older 35 years old, impossibility of further observation (the woman's reluctance to visit a doctor). In young women with LSIL (CIN 1, CIN 2, p-16 negative), proven in a biopsy, and a satisfactory result of colposcopy, it is preferable to use immunomodulatory drugs with cytological studies after 6, 12, 24 months. In case of progression through 12 months destructive or excisional treatment is indicated. Watchful waiting with cytological monitoring and colposcopy for CIN 2 and 3 is acceptable for pregnant women and very young patients with CIN.

USING GLYCYRRHIZIN DRUGS ACIDS IN THE TREATMENT OF DISEASES

In recent years, many studies have been conducted regarding the inhibitory effects of natural materials on cancer. Search for compounds that are non-toxic for humans and without side effects, attracts the attention of many researchers. Thus, it has been established that compounds derived from licorice root, such as glycyrrhizin, have anti-inflammatory activity, and 18- β -glycyrrhizic acid (GA), which is a triterpenoid compound obtained as a result of the hydrolysis of glycyrrhizin, has not only anti-inflammatory, but also antitumor effects [27].

GK also increases the production of viral cyclin, which causes selective death of those infected with the virus cells, and stimulates the production of interleukin-12 in macrophages, which facilitates the development of T-helper lymphocytes in cell-mediated immune response, inhibits phosphorylation of the viral protein, mediated by cellular kinases, and modifies post-translational signals. Thanks to these properties, HA has found wide use in the treatment of diseases associated with viral infections, including PVI. A number of foreign studies have shown the effectiveness of HA-based drugs in the treatment of cervical cancer pathology against the background of PVI, both in combination with destructive methods and as monotherapy.

In two other studies a twofold reduction in the number of relapses of PVI was obtained against the background of isolated treatment with a local drug actions (Epigen Intim) based on HA on preclinical stages of HPV infection and a significant increase in frequency cures of dysplasia with a combination of cryotherapy and subsequent local GC therapy. In a study where 40% of HPV-infected patients initially had LSIL (CIN 1 and 2) in cytological smears after 12 weeks combined use of the drug GC(oral and intravaginal) regression of clinical manifestations of PVI according to the results of colposcopy and Pap test was observed in the majority of patients (74%) ($P < 0.001$). Then in at least 27.7% of patients from the general group, LSIL, and only one has cervical intraepithelial neoplasia progressed from CIN 1 to CIN 2. However, the researchers concluded that with intraepithelial lesions may require

longer treatment and monitoring for up to a year. Also higher the effectiveness of the GC drug in combination with an immunomodulator has been shown against anogenital warts compared to podophyllin.

Experience with the use of GCs in young women with persistent PVI for a year showed a decrease in the number of patients with clinical manifestations of CC by 2 times, improvement of PAP test indicators to normal in 29% of women, reduction in the number of atypical changes during colposcopy from 40 to 16%. Elimination of HPV within 6 months. In the treatment group was 40%, in the control group without treatment - 29% [17]. Thus, drugs based on HA, which has the ability to treat HPV-associated cervicitis in young women, promote faster regeneration of the mucous membrane CMM after destructive treatment and can be recommended for long-term use, including in pregnant women with signs of intraepithelial lesions of CMM anti-inflammatory, immunostimulating, regenerating effects, are the optimal choice for the prize.

Ectopia CE SM is a functional state and does not require special treatment. Moreover, gross intervention in the process of metaplasia can lead to undesirable obstetric complications. However gentle CE is a vulnerable zone and a comfortable nutritional zone environment for transmissible bacterial and viral infections, which promotes the development of CC and prevents normal epithelialization of the cervix. In case of joining PVI there is a high probability of developing intraepithelial lesions. Nevertheless, in general the prognosis for this condition is favorable. HPV-infected patients with ectopic CE require a differentiated approach to management depending on age, medical history and clinical manifestations. For young women under the age of 25, conservative treatment and dynamic observations with cytological control. The age group of 25–35 years requires active tactics in the transforming form of PVI: moderate cytological changes in combination with a high viral load and or the production of oncoproteins. In the older age group at 35 years of age, physiological ectopia of cervical cerebrospinal fluid is rare. Tactics are determined according to general clinical recommendations for the management of women with intraepithelial

lesions of the cervix. An important point is identification and modification of cofactors, because they can have significant influence on the modulation of persistent infections and progression of PVI to neoplasia.

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