

Recurrence of HPV Infection After Combination Therapy of Uterine Cervical Diseases

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Currently, diseases caused by human papillomavirus (HPV) are one of the most common sexually transmitted diseases. The problem of cervical intraepithelial neoplasia (CIN) management is actualized by increasing tendency of this disease frequency (HPV infection has increased more than 10 times over the last decade in the world), ability of some HPV types to initiate malignant transformation, as well as by the measures of primary prevention developed in the last decade, which, according to the conclusion of the World Health Organization, should completely prevent cervical cancer.

Aim: The aim of the study was to determine HPV infection recurrence incidence after combination therapy of uterine cervical diseases.

Material and Methods: 80 patients of reproductive age with uterine cervical diseases and with ≥ 3 years of persisting HPV infection were examined and received combination therapy (radio-wave conization of the cervix and 3 courses of Inosine pranobex).

Results: Administration of Inosine pranobex in therapy of benign uterine cervical diseases associated with persistent HPV infection, in combination with radio-wave destruction, allows to reduce the time of epithelization after destruction, to increase efficacy of therapy which was determined after 6 months according to data from colposcopy, cytology and the HPV DNA test, as well as minimize chance of recurrence in the next 3 years.

Keywords: HPV infection, recurrence, benign cervical diseases

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In the last decade, the dramatic increase in the incidence of human papillomavirus infection, (HPV) has been a prior medical and social issue due to its important contagiousness, poly-organic structure, and high oncogenic potential (6, 7).

Some questions about prevention and treatment of diseases related to HPV have no certain answers because of conflicting research results and because of the fact that there is no combined pathogenetic approach about these questions. Effects of changes in vaginal microbiota and immunity on HPV activity are still being discussed (9, 12). Most of these studies evaluate the microbiota and immunity without considering the phase of the process and there is no study on the definitive factors of transmission to real neoplasia vaginal microbiom or asymptomatic carriers in HPV's latent forms (4).

There are many treatment methods for genital HPV, however, recurrence rate of the disease is high and none of the suggested treatments are efficient and safe enough (5). In addition, even though the interest in HPV has increased, studies reflecting a comprehensive approach about HPV treatment are not enough up until today. Therefore, efficiency of the treatment is probably lower and the recurrence rates are high (8).

There is still no consensus about the treatment of the disease related to HPV: some authors do not see the latent forms of HPV as a disease and suggest passive tactics up to stop dynamic follow-up (1), others, on the contrary, request active treatment up to use of immunomodulators of virus carrying and even preventive devastating methods (11).

Currently, there is no specific medicine for HPV, therefore, attempts for curing the virus completely have been failed so far. According to some authors, when the infection goes to complete remission, replication and accumulation of HPV on epithelium surfaces stop, the virus goes to basal layer and spread of HPV stops. During the long term remission, it is not certain whether HPV is finally eliminated from the host organism or not, because, the contagiousness can continue even after the treatment [9].

According to different authors, efficiency of destructive treatment changes between 45% and 97, the recurrence rate goes up to 50% (10). In addition to various destruction techniques, as medical treatment methods, there are antiseptics, antibacterial and antiviral medicines to remove cervical and vaginal inflammation, accompanied by hormonal medicines and immunomodulators for ovary dysfunction. (14): Many data related to successful usage in the treatment of HPV infection showed up (interferon- α ve - β , interferon inducers, synthetic immunomodulators, immunoglobulins, etc.) [13].

For this reason, research of combination treatment in order to prevent the recurrence of cervical diseases related to HPV is hopeful.

Purpose of these researches is to determine the rate of recurrence of HPV infection after the combination treatment of cervical diseases.

Materials and Methods

We examined 80 women, who received the comprehensive treatment (cervical radio wave conization and 3 cure Inosine pranobex), who had persistent HPV infection for ≥ 3 years, who had cervical disease and who were in the reproductive age.

In order to define the degree of cervical epithelial lesions, we used Bethesda system, developed and suggested by National Cancer Institution (USA), according to this, changes related to dysplasia in cervix and preinvasive carcinoma are classified with the terms "SIL-squamous intraepithelial lesions low and high grade" - LSIL and HSIL. Evaluation of efficiency of the treatment and primal diagnosis includes various methods: diagnosis of urogenital infections and determining the dynamics of changes of HPV load by using colposcopic dynamic control of epithelial changes, cytological and bacteriologic examination, smear examination, polymerase chain reaction (PCR). Digene method has been used for qualitative and quantitative detection of HPV DNA.

After the treatment, recurrence of cervical disease related to HPV was evaluated 3 years later.

Inclusion criteria: women in the reproductive age having benign cervical disease (age 19-47).

Exclusion criteria: pregnancy, cervix cancer.

Results and Discussion

When the age range of the examined women is examined, it has been seen that the age range of the patients with cervical diseases having persistent HPV infection is $27,6 \pm 3,9$.

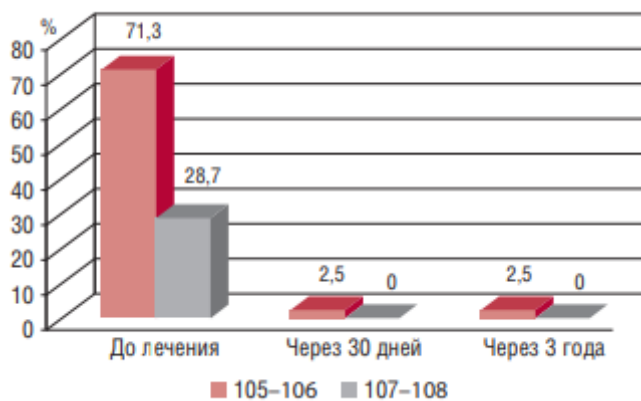
In 35 women (43,8%) of the examined 80 women, who had permanent HPV infection and benign cervical diseases, there was proliferative changes in endocervix and 20 of them

had cervicitis, 9 of 38 (23,7%) patients had leukoplakia, 4 of 18 patients (22,2%) had LSIL and 2 of 4 patients (50%) had HSIL.

Persistent diagnosis of HPV infection is based on typing: HPV type 16 - 32 were detected in (40%) women with benign disease in uterus, HPV type 31 and 33 - 27 were detected in (33,8%) women. When we come to HPV type 18, this type was detected in 15 (18,8%) women and HPV type 31 and 33 were detected in 6 (7,5%) women in combination. This way, HPV type 16 (one out of each 4 women) and type 18 (one out of each 3 women) have the highest frequency.

HPV quantitative load in all 80 patients having persistent HPV infection was evaluated by using Digene test method. The results were submitted with numeric values: 1 unit matched with 10^5 viral genomes per 1 ml. (Figure.1). To evaluate the persistence of HPV infection, we used 10^5 and 10^8 genome concentration per 1 ml. We detected that in 57 of the patients (71,3%) had HPV concentration clinically above the related level, 10^{5-6} , and in 23 (28,7%) of them 10^{7-8} genomes per 1 ml.

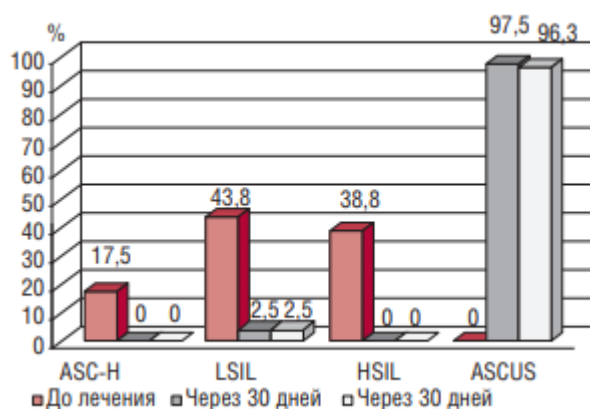
Figure 1. Results of evaluation of quantitative load of human papillomavirus by Digen-test



(Before the treatment - 30 days later - 3 years later)

Analysis of cytological examination results (Fig. 2): 14 of them (17,5%) had ASC-H symptoms (not value norm, but some atypia symptoms); 5 patients (43,8%) had LSIL (atypia showing low lesion level) and 31 (38,8%) patients HSIL (atypia showing the possible high lesion level).

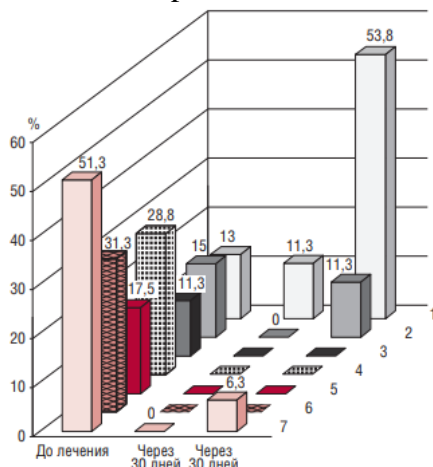
Figure 2. Cytological Examination Results



Before the treatment - 30 days later - 30 days later

In the colposcopic examination (Figure 3), colposcopic table was observed none of the patients. %78 of the examined women (97,5%), abnormal colposcopic table were observe: aceto-protein epithelial - 41 (51,3%), punctuation - 25 (31,3%), mosaic - 14 (17,5%), leukoplakia - 23 (28,8%) were dominant and atypical veins were - 9 (11,3%), these correspond to Class II lesions. 12 of the examined women (15%) iodine negative corresponding to specific symptoms of the abnormal colposcopic table.

Figure 3. Colposcopic findings: 1 - inflammation; 2 – iodine negative space; 3 - atypical veins; 4 - leukoplakia; 5 - mosaic; 6 – punctuation; 7 - aceto-white epithelial



Before the treatment - 30 days later - 30 days later

Choosing of the combination treatment method is based on the algorithm developed by us. The combination therapy includes:

1. Antiviral treatment of HPV infection. Inosine pranobex was given in standard dose: 1 tablet (500 mg) for per 10 kg of the patient's body weight, normal daily dose - 6-8 tablets, divided into 3 doses for 10 days and 14 days break after that. Total 3 cures, one of which coincides with the surgical treatment of the cervix. If the cervical dysplasia is associated with HPV, a special dosage regime was used. In this combination, 2 tablets 3 times a day for 10 days were given and 2-3 similar cures followed that 10-14 days apart.

2. Curing with radiology. We think that using radio wave technique in 5-9th days of menstrual cycle has the main importance, considering the below advantages:

- onco-safety: all the excised mass is examined as histological;
- economic: pre-biopsy is not required;
- efficiency: a spindle shaped cervical canal is formed, in which the mucus plug is preserved;
- there is no burnt or necrosis in the tissues under the uterus.

3. Treatment for curing conditional pathogenic microflora, yeast-like fungi and other microorganisms.

4. Vaginal biocenosis restoration

The patients were examined after the treatment, in 8th and 45th days. The recovery was under the fibrin layer. Rejection time of the scab and fibrin film varied significantly and it was

significantly shorter (8 days) in the patients cured with radiotherapy and antiviral treatment. On 45th day, after radio wave treatment and 3 cures of antiviral treatment, epithelialisation process in 75 (93,8%) patients was completed.

Result and efficiency of treatment of cervical lesions related to persistent HPV infection were evaluated 30 days later according to the below criteria: according to colposcopy, PAP test and Digene test, full effect in 78 (97,5%) women and missing effect in 2 (2,5%) women were observed after the combination therapy. In the missing effect, HPV DNA detected at clinically significant concentration.

3 years later, many follow-up examinations, including Digene test, colposcopy and cytology, were done to all the treated patients. It is detected only in 2 (2,5%) patients that the HPV concentration (Digene-test) was clinically below the related level, which is 10^5 genomes per 1ml. Analysis of cytological examination results: 77 of them (96,3%) had ASCUS (not value norm, but no atypia symptom) and 3 of them (3,8%) had LSIL (atypia meaning low lesion level) findings.

In the examination, 23 (28,8%) patients showed normal colposcopic chart. In 57 (71,3%) of the examined women, abnormal colposcopic chart was seen: inflammation - 43 (53,8%), acetate white epithelial - 5 (6,3%) and iodine negative transformation area was dominant 9 (11,3%).

This way, we evaluated the treatment quality of benign cervical diseases with Inosine pranobex for 3 years in women who had persistent HPV infection. Results of the study confirms that with complete remission of the infection, HPV replication and accumulation in the superficial layers of the epithelium (in 2 patients, HPV concentration was clinically below the related level, which was 10^5 genome per 1ml), as well as the transfer of the virus to the basal layer (a second radio wave conisation was done to 2 patients, who had LSIL and 10^5 genome HPV concentration per 1ml, 3 years later). In other words, after the combination therapy, recurrence rate of HPV infection was 97,5%.

Conclusion

Understanding the features of HPV persistence in cervical epithelia and the related development process of benign diseases of this area determines the treatment methods of cervical lesions related to HPV. One of the systemic immunomodulators, which was tested in the most comprehensive way and has a direct antiviral effect in practice both in our country and in the world, is Inosine pranobex (Isoprinosine, Teva Company).

Our choice of immunomodulator is based on the clinical experience related to the use of Inosin pranobex, which has shown that the medicine has a broad range of antiviral activity. When it is used together with radio wave destruction in the treatment of benign cervical diseases related to the persistent HPV infection, it reduces the epithelialization time after the destruction, increases the efficiency of the treatment determined 6 months later according to colposcopy, cytology and HPV DNA detection and reduces the recurrence rate within the next 3 years (97,5%).

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