REVIEW ARTICLE

CONTENTS

Cervical pathology: Diagnosis, treatment and management of patients with *Human Papillomavirus*

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ABSTRACT

Aim: The objective of this literature review was to identify current aspects of the diagnosis, treatment, and management of patients with human papillomavirus.
Materials and Methods: 15 articles published from 2018 to 2024 were analyzed using the keywords: cervix, *Papillomavirus*, precancerous cervical pathology, cervical cancer, cervical screening, cytological method, colposcopy, cervical biopsy, for which a review of the available literature was conducted. Pubmed, Google Scholar, Web of Science, and Scopus databases were used to search for materials on current aspects of the diagnosis, treatment and management of patients with *Human Papillomavirus*. Inclusion criteria were cervical pathology caused by human papillomavirus.
Conclusions: The goal of the screening program is to detect and treat high-grade precancer and prevent the development of cancer. Detection of LSIL (CIN1) is carried out by HPV testing and cervical screening, and the diagnosis is verified by histology. Most guidelines talk about surveillance from 18 years of age for 2 years for CIN 1. Diagnosis of persistent infection with HPV 16, 18, 31, 33 and others, and not the presence of CIN1, determines the risk of developing CIN 3.

KEY WORDS: papillomavirus, cervical cancer

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INTRODUCTION

Every year, cervical cancer is diagnosed in more than 600,000 women worldwide. In Ukraine, the disease is diagnosed annually in 7,500 women, of whom 2,500 die (including 500 of working age).

Since February 24, 2022, a war has been ongoing in Ukraine, which has a profound impact on the health of the population. The adverse consequences of armed conflicts include both combat injuries and stress, as well as chronic somatic diseases, including cancer. Diseases that emerged during armed conflicts are very persistent [1]. They continue even after the cessation of hostilities. According to statistics from some countries that have experienced armed conflicts, the incidence of cancer among military personnel and civilians increases by more than 100% over several years [2].

Along with carcinogens, important factors influencing the development of cancer during and after war are mass population movements, which increase the risk of transmission of oncogenic bacteria and viruses.

It is known that a surge in cervical cancer incidence of more than 260% was recorded after the end of the Vietnam War. Unfortunately, this trend can also be observed in Ukraine.

Considering the experience of countries that participated in previous military conflicts, we can conclude that the most important measures for reducing cancer morbidity and mortality may be state programs for prevention, screening, and early diagnosis of cancer.

AIM

The objective of this literature review was to identify current aspects of the diagnosis, treatment, and management of patients with *Human Papillomavirus*.

MATERIALS AND METHODS

15 articles published from 2018 to 2024 were analyzed using the keywords: cervix, papillomavirus, precancerous cervical pathology, cervical cancer, cervical screening, cytological method, colposcopy, cervical biopsy, for which a review of the available literature was conducted. Pubmed, Google Scholar, Web of Science,

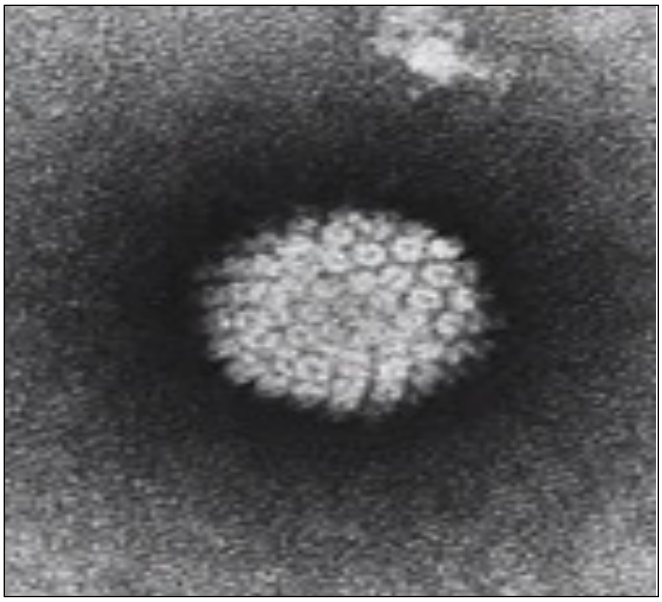

Fig. 1. *Human Papillomavirus*
Source: compiled by the authors based on [5]

and Scopus databases were used to search for materials on current aspects of the diagnosis, treatment and management of patients with human papillomavirus. Inclusion criteria were cervical pathology caused by human papillomavirus. EHTICS

All sources used in this literature review are publicly available

REVIEW AND DISCUSSION

Cervical pathology has an etiological factor that causes this pathology – it is the human papillomavirus. Cervical cancer is a completely infectious disease. Over the past 20 years, approaches to the diagnosis, treatment, and management of patients with *Human Papillomavirus* have completely changed. *Human Papillomavirus* is the most common sexually transmitted pathogen, one of the few that leads to cancer and oncological changes in the human body. Everything we know about the virus comes from its physiological properties.

In 1983, Harald zur Hausen and his colleagues isolated *Human Papillomavirus* type 16 (HPV-16), and in 1984, type 18 (HPV-18). He also examined a culture of Hela cells, which turned out to be infected with HPV-18. In 2008, Harald zur Hausen received the Nobel Prize in Medicine and Physiology for his discovery. Thus, an equal sign was drawn between the papilloma virus and cervical cancer. The whole world received the vaccine, and began vaccinating girls, older women who had already been exposed to the *Human Papillomavirus* and who already had precancerous conditions [3]. Today, there is experience from those countries that have begun to implement this. Currently, Australia, New Zealand, and some parts of America have already overcome the problem of cervical cancer (Fig. 1).

In 2023, a congress was held on the *Human Papillomavirus*, where work was published, studying cervical cancer microsamplings from women from different regions - Greece, Australia, New Zealand, America, Europe. Regardless of the region, the disease was caused by *Human Papillomavirus* type 16 (HPV-16).

In Ukraine, women do not accept the topic of cervical cancer vaccination for themselves and their children, but the war changed everything and many women ended up in other countries where they will not be asked whether they want to be vaccinated or not, children

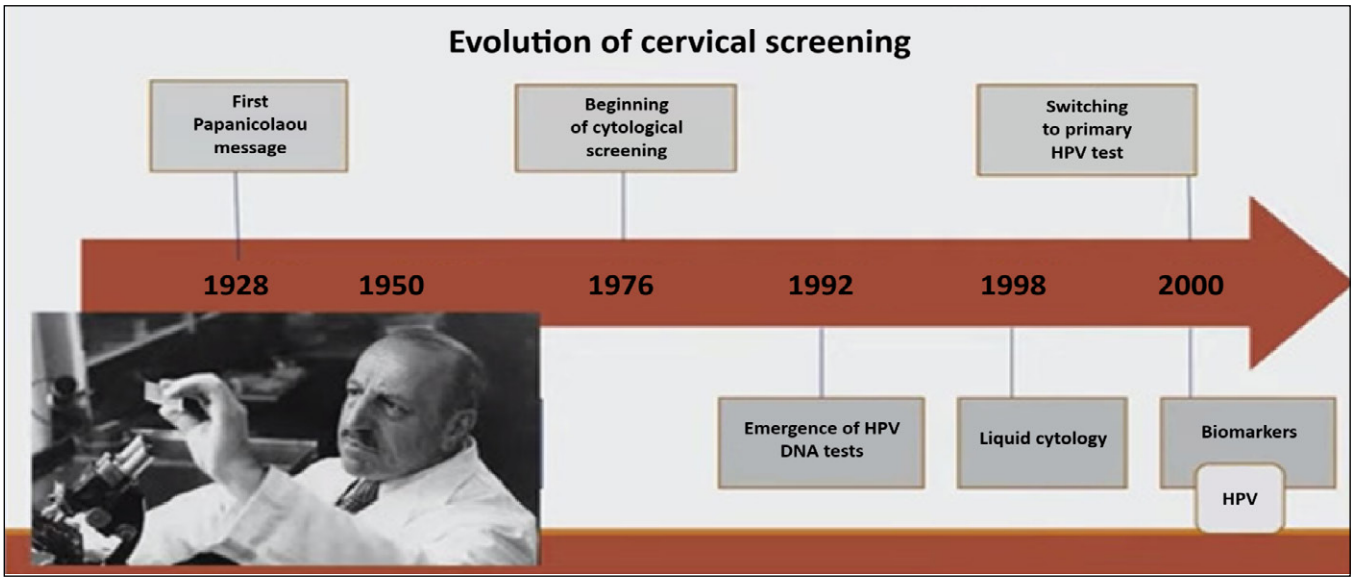

Fig. 2. The evolution of cervical screening
Source: compiled by the authors based on [1]

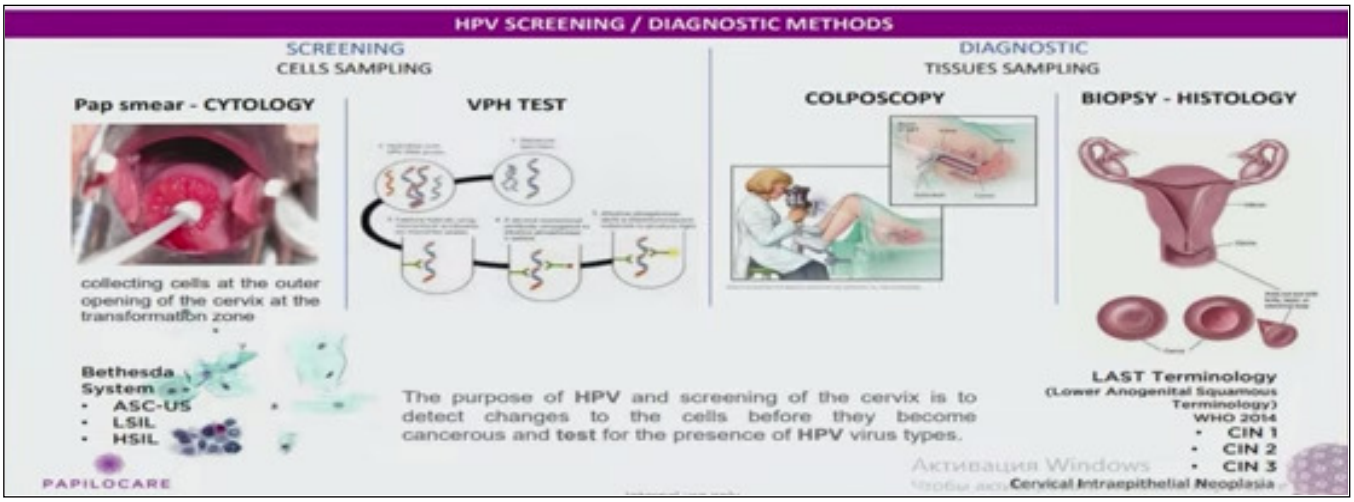

Fig. 3. Patient route depending on screening results
Source: compiled by the authors based on [2]

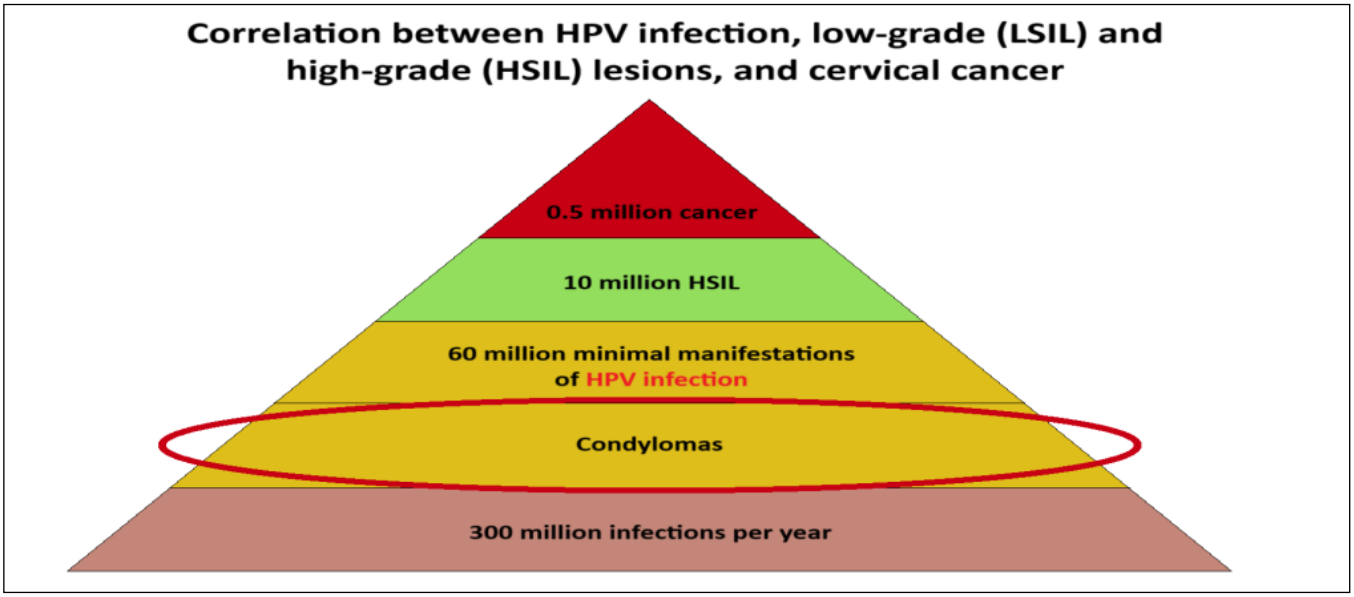

Fig. 4. Correlation between HPV infection, low-grade (LSIL) and high-grade (HSIL) lesions, and cervical cancer
Source: compiled by the authors based on [4]

are vaccinated and everyone understood what a good thing it is [4]. And in Ukraine, the approach to this issue is also changing, because every day we receive more and more evidence that the vaccine is not only prevention of infection, it is prevention of cervical cancer.

The vaccine has its present: the problem in the world is the shortage of vaccines. Many countries have lined up to get these doses of vaccines for their children, women, and men to protect their people from this disease. For example, Japan, which for a long time did not allow the HPV vaccine, but today they are standing in line.

As of 2022, 125 countries have included vaccination in their national vaccination program. The vaccine also has its future - it is the elimination of HPV in the population, and for this it is necessary to cover up to 90% of girls with vaccination, and this was introduced by the WHO. Currently, vaccination and screening are being carried out in age groups that are already carriers of the *Human Papillomavirus* (HPV-faster program). Girls who are past the age of vaccination and who have already been exposed to the *Human Papillomavirus*, currently under the age of 30, without gender equality, and boys should also be vaccinated. This is a late vaccination, but it is also protection.

Vaccination protects against disease, and screening protects those who were not helped by vaccination. That's why a screening program is important today. The first report of screening was in 1928, when the Papanicolaou test was introduced, and every year and every decade it has changed and evolved. Currently, there are tests for *Human Papillomavirus*, a more sensitive study

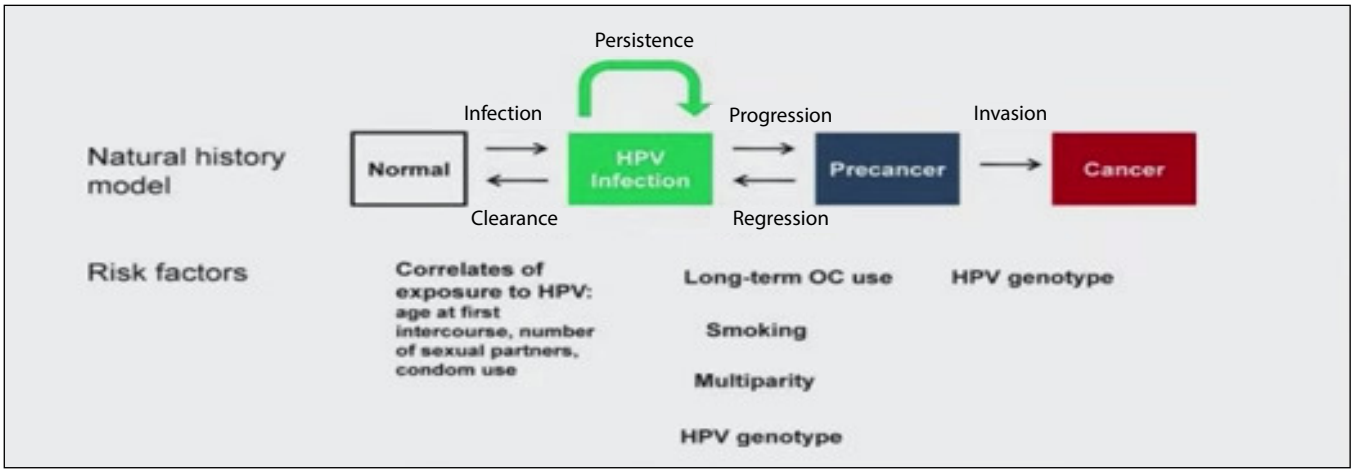

Fig. 5. The natural history of CIN and cervical cancer
Source: compiled by the authors based on [3]

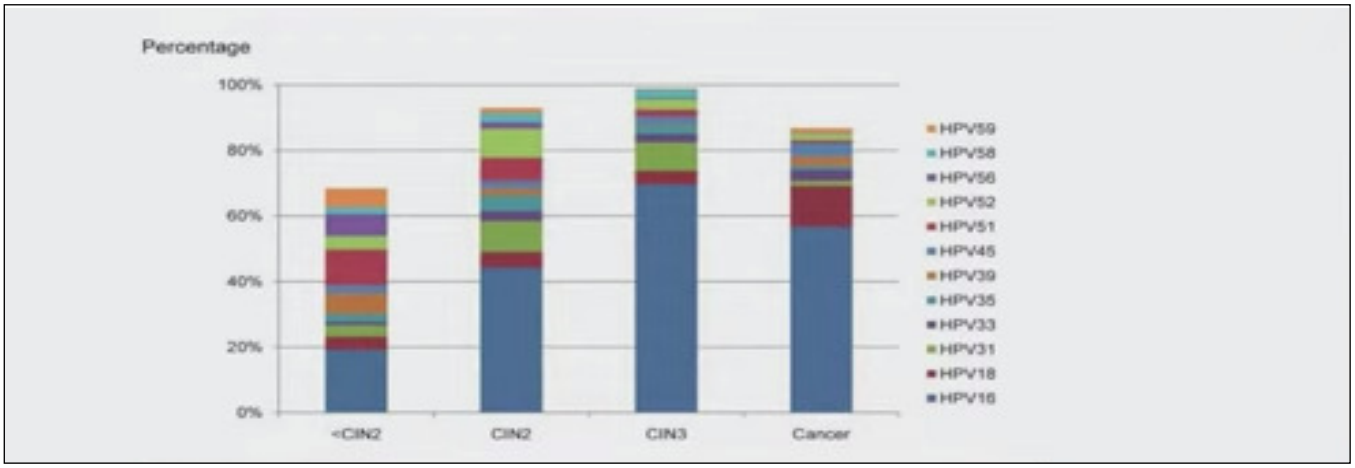

Fig. 6. HPV-16 is the most important viral factor in the development of cervical cancer
Source: compiled by the authors based on [7]

is being conducted, a risk group is identified that needs to be monitored, liquid cytology, and biomarkers have appeared (Fig. 2).

However, it is important to remember that screening is a test that does not establish or exclude a diagnosis, but only identifies women in the population with a high probability of having the disease. Today, a Co-testing program has been developed, where cells are examined and tested for the presence of oncogenic strains of the *Human Papillomavirus*.

PURPOSE of cytological and HPV screening

- Detection and treatment of high-grade HSIL precancer and prevention of the development of squamous cell carcinoma of the cervix;
- Avoiding overtreatment of HSIL and its consequences (cervical stenosis and pregnancy complications).

The patient's route, depending on the screening results, is known (Fig. 3)

- Cytology
- ASC-US
- LSIL
- HSIL
- HPV test – virus detection
- Colposcopy
- Biopsy-histology

Every doctor who treats patients with *Human Papillomavirus* needs to know the following:

- Clearance
- Latency
- Persistence

Millions of people around the world are infected with the *Human Papillomavirus*. This can happen on the first or the hundredth sexual intercourse, but it still happens at some point [5]. The virus can leave the body of a woman or man, but it can also spread further (Fig. 4).

It is necessary to know the natural occurrence of dysplasia and cervical cancer (Fig. 5).

First, it matters which virus is causing the infection, because this is the most important factor.

Secondly, you need to know the woman's lifestyle. Studies show that if an infected couple uses condoms, the viral load

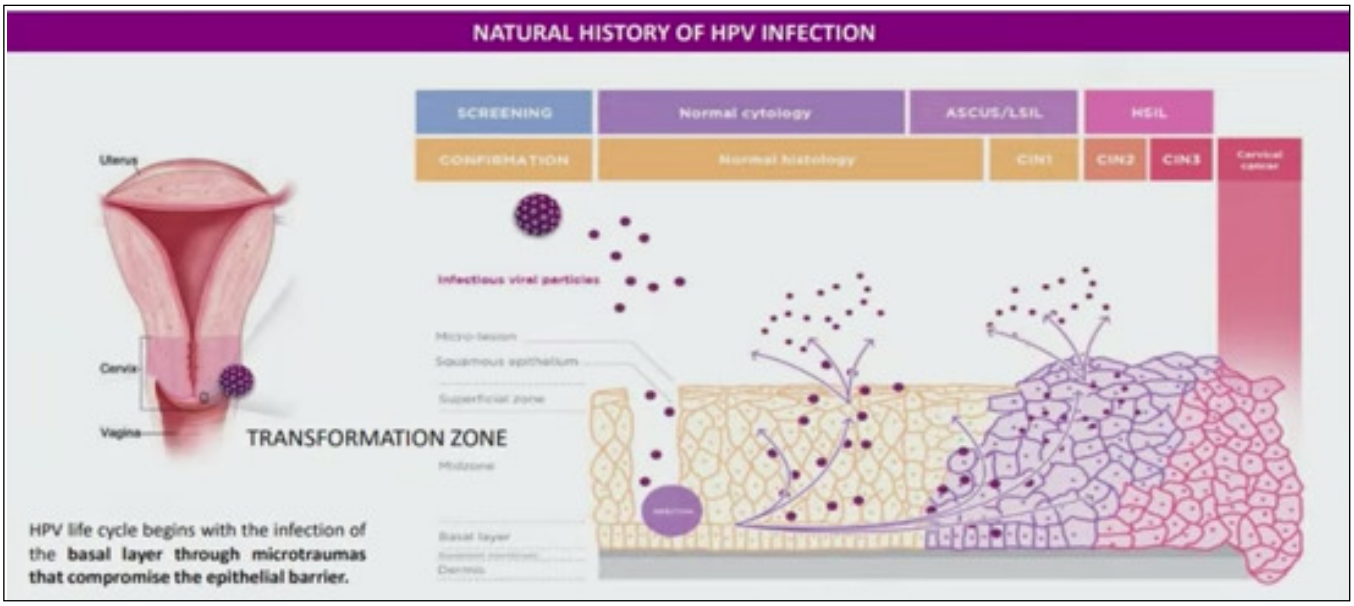

Fig. 7. The role of the transformation zone in the development of the cervical spine
Source: compiled by the authors based on [6]

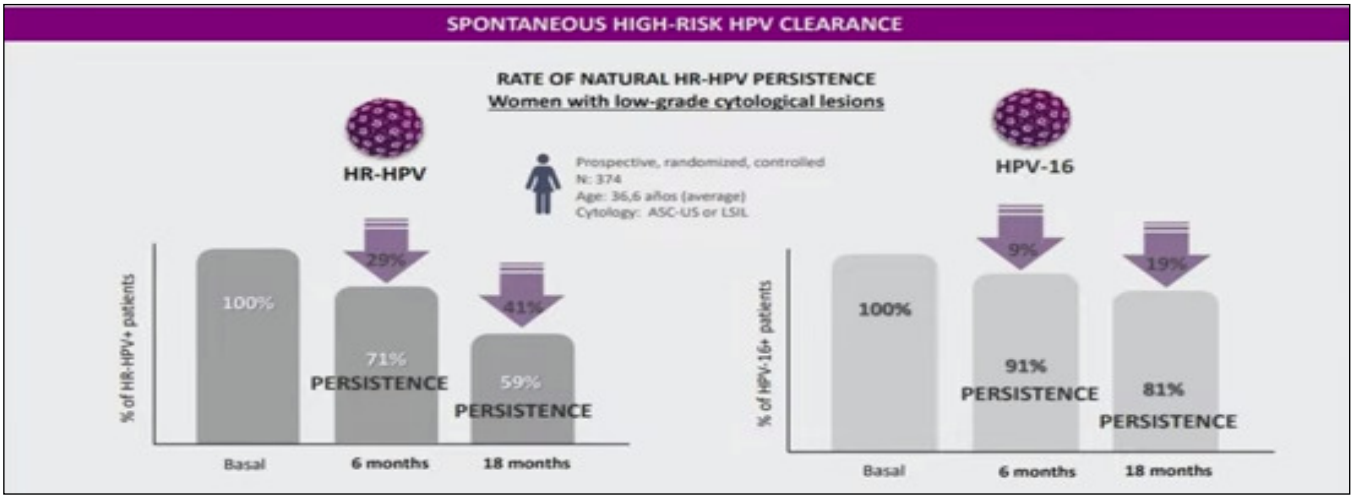

Fig. 8. HPV persistence
Source: compiled by the authors based on [9]

drops after a month. If a woman uses contraceptives, the amount of estrogen in the body decreases and due to this, lactobacteria also decrease, because it is estrogens that secrete them [6]. Women who take contraceptives reduce the protection in their body that occurs due to lactobacilli. Therefore, it is this mechanism that will affect women who use contraceptives for a long time. This is also something to keep in mind and to take courses of lactobacilli, etc.

Smoking is an important factor because smoking suppresses the very necessary P53 gene, which is responsible for apoptosis - one of the most important factors in the pathogenesis of the integration of *Human Papillomavirus* infection into the genome. Therefore, smoking is certainly a very important factor.

Thirdly, it is a type of *Human Papillomavirus*. Fig. 6 shows precancerous conditions and cervical cancer, where *Human Papillomavirus* type 16 is marked in blue. If we see that a woman has type 16 *Human Papillomavirus*, then special attention should be focused on her. *Human Papillomavirus* type 16 is the most virulent, fastest, and most common virus that causes the development of cervical cancer [7].

Fourth, the moment that will be of great importance in the development of precancerous conditions of the cervix is the transformation zone. The transformation zone can be several millimeters and can reach the vaginal vaults, and it is important to remember that the congenital transformation zone is centimeters on the mucous membrane. Sometimes doctors do not notice that there are such changes and believe that this is a type 3 transformation zone, which is actually not true. Infection can occur in any part of the zone, because

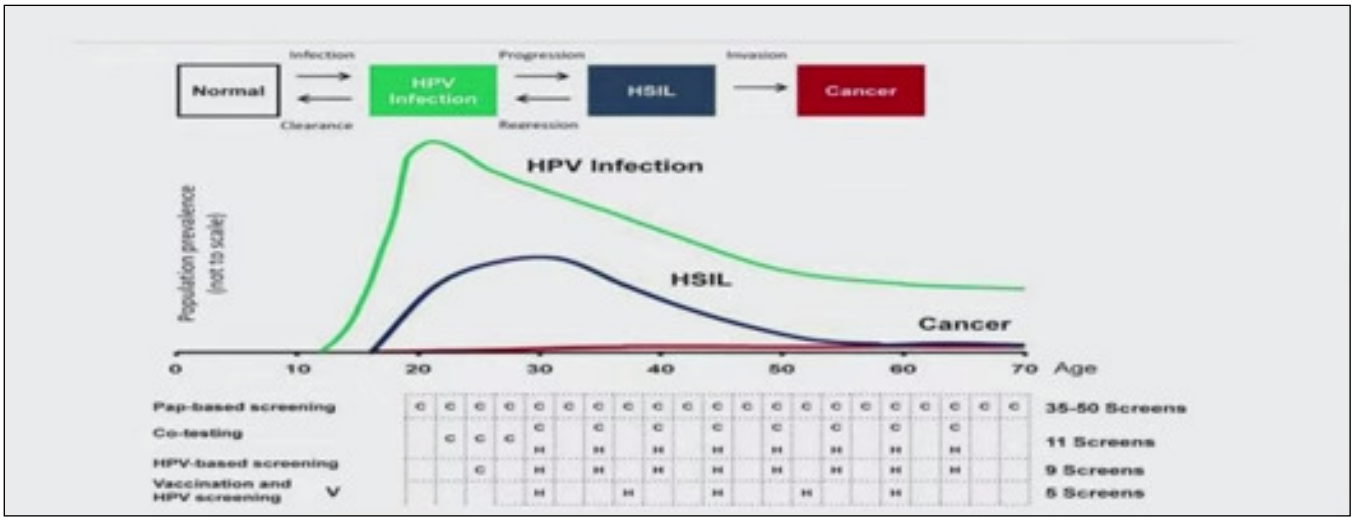

Fig. 9. Clinical perspective and history of CIN and cervical cancer
Source: compiled by the authors based on [8]

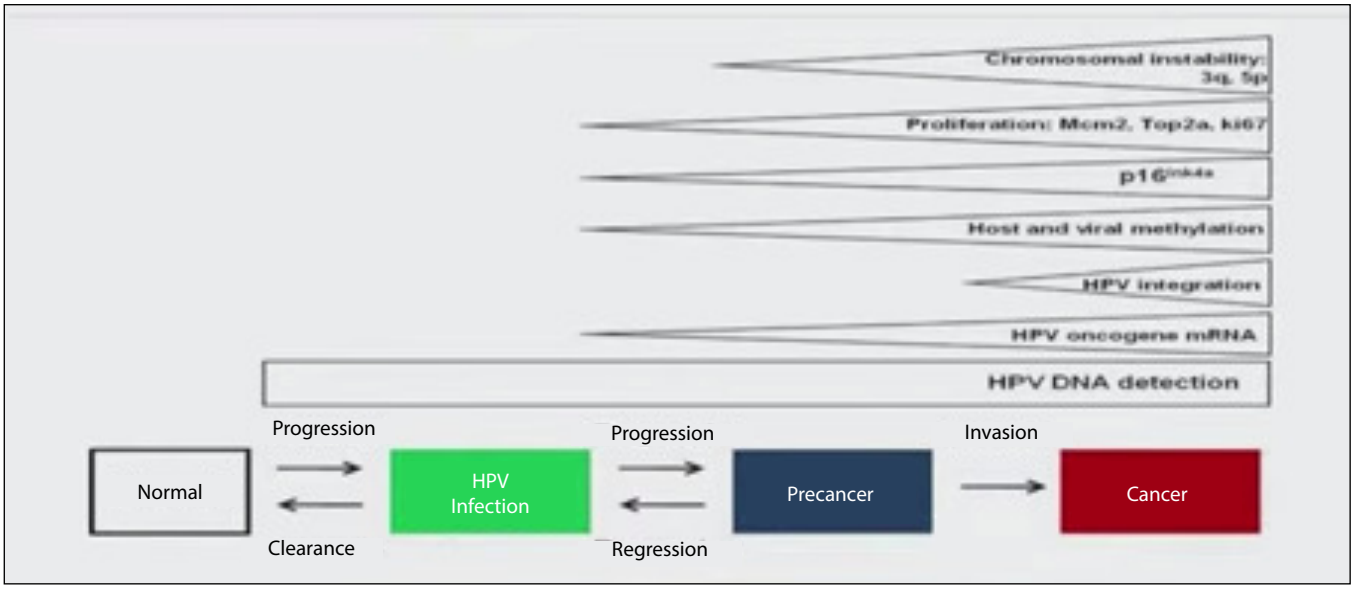

Fig. 10. Biomarkers for cervical cancer incidence categories
Source: compiled by the authors based on [11]

this metaplastic epithelium is an epithelium that has minimal immunological protection and foci of *Human Papillomavirus* interference can form in any area (Fig. 7).

Persistence is one of the main stages of finding the *Human Papillomavirus* for a fairly long time and in most cases, if there are more than one of those viruses, HPV-16, HPV-18, HPV-35, etc [8,9]. Therefore, we do HPV today, then observe in a year, repeat in a few years and thereby determine whether the virus persists or not (Fig. 8).

A woman becomes infected and by the age of 25-30 her future fate is determined, either the virus will leave the body, or there will be an acute intervention of the *Human Papillomavirus* and we have low-grade intraepithelial lesions (LSIL), which corresponds to CIN1, and all this will be eliminated and will be the norm, or there will be a severe precancerous condition, or there will be invasive cervical cancer [10,11]. This age is of great importance 25-30-35 years old. It is during this period that it is necessary to actively conduct screening. If it is a traditional PAP test, then it is annually, if it is Co-testing (liquid cytology + PCR of papillomavirus 28 types), then it can be in a year (Fig. 9).

After 2020, we will have data on biomarkers that help diagnose where there are weak lesions and where there are true precancerous conditions, and all of this will be reflected in the histological report. Cervical intraepithelial neoplasia CIN 1 (LSIL) is a premalignant squamous lesion of the cervix that is diagnosed by biopsy and histological examination. Cervical intraepithelial neoplasia CIN 1 (LSIL) is a premalignant squamous lesion of the cervix that is diagnosed by biopsy and histological ex-

Table 1. Results of revised biopsies with a primary diagnosis of CIN

Diagnosis of CIN1 confirmed	Reduced to normal	Increased to CIN 2.3
43%	41%	16%

Source: compiled by the authors of this study

Table 2. Terminology of cervical disease categories

Natural history model	Histology			Cytology	
	Dysplasia nomenclature	CIN nomenclature	LAST nomenclature	Papanicolaou classification	The Bethesda system
Infection	Negative	Negative		I	NILM
	Squamous atypia	Squamous atypia		II	ACS-US
Precancer	Mild dysplasia	CIN 1	LSIL		LSIL
	Moderate dysplasia	CIN2		III	
	Severe dysplasia Carcinoma in situ	CIN 3	HSIL	IV	HSIL
Cancer	Carcinoma	Carcinoma		V	Carcinoma

Source: compiled by the authors of this study

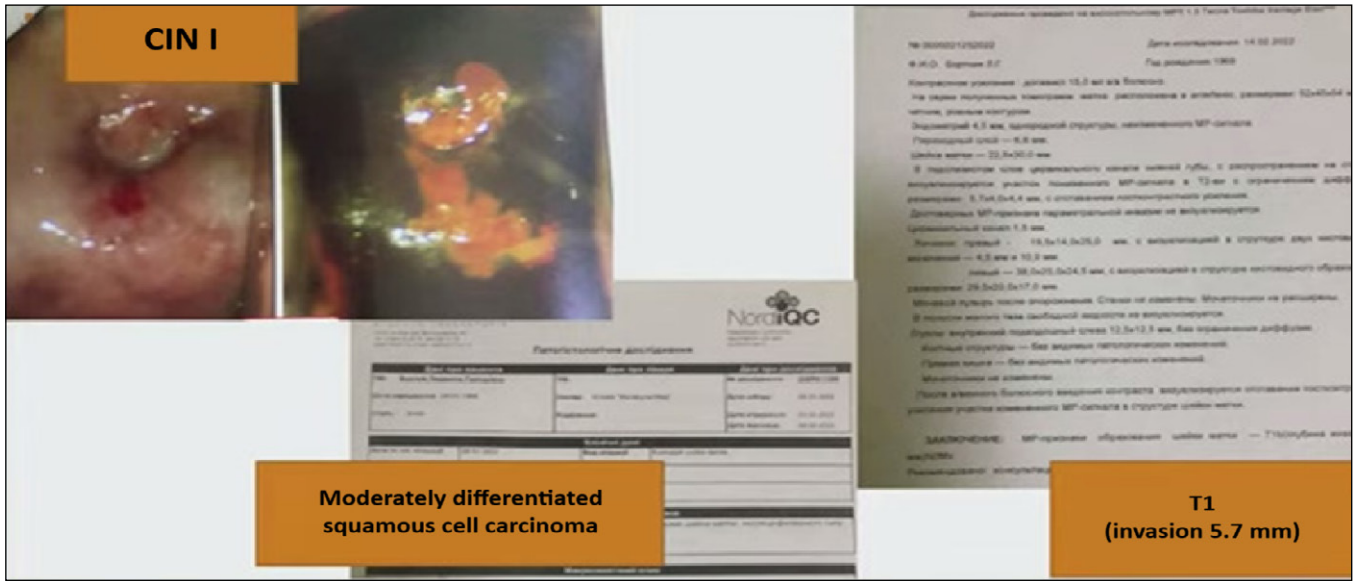

Fig. 11. CIN 1 – cytologically, colposcopically – metaplastic epithelium, histologically – moderately differentiated squamous cell carcinoma
Picture taken by the authors

amination. The diagnosis cannot be made by cytology and in any case must be confirmed by biopsy.

In the late 1960s, Richard proposed the concept of intraepithelial neoplasia.

CIN 3 included severe dysplasia and carcinoma in situ.

CIN 2 was replaced by moderate dysplasia.

CIN 1 combined both cytological signs of HPV infection (koilocytic atypia) and mild dysplasia. CIN 1 is an acute infection with *Human Papillomavirus*, which can be influenced and which can progress to the normal stage.

The severity of the diagnosis is determined by the degree of replacement of normal stratified epithelium with mitotically active basal-like epithelium. (<1/3=CIN 1, <2/3=CIN 2, >2/3=CIN 3). CIN is seen as a stepwise progression with a high probability of transitioning from more minor to more aggressive precursors of cancer.

CHANGES IN VIEWS ON THE DIAGNOSIS, TREATMENT AND MANAGEMENT OF PATIENTS WITH *HUMAN PAPILLOMA VIRUS* (HPV)

After the 20s of the 21st century, we already have data on biomarkers that help establish a diagnosis, help identify where there are weak lesions, and where there are already true precancerous conditions. All this will be reproduced in the histological report (Fig. 10).

In 2012, the Lower Anogenital Cancer Classification (LAST) conference adopted the LAST nomenclature

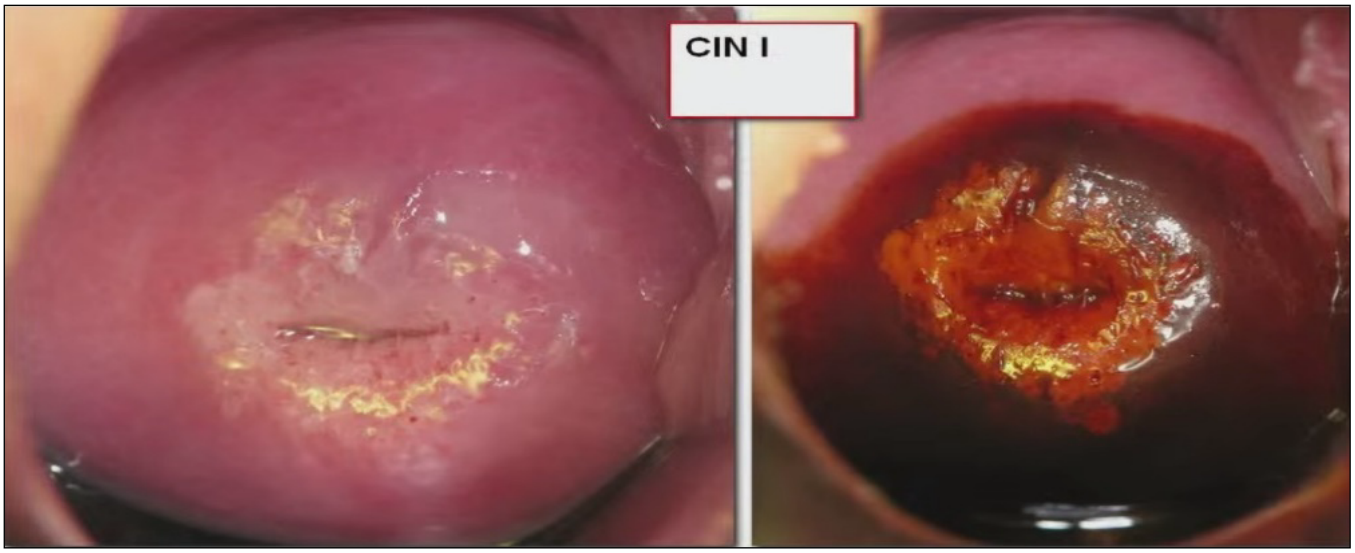

Fig. 12. CIN 1 Metaplastic epithelium, transformation zone
Picture taken by the authors

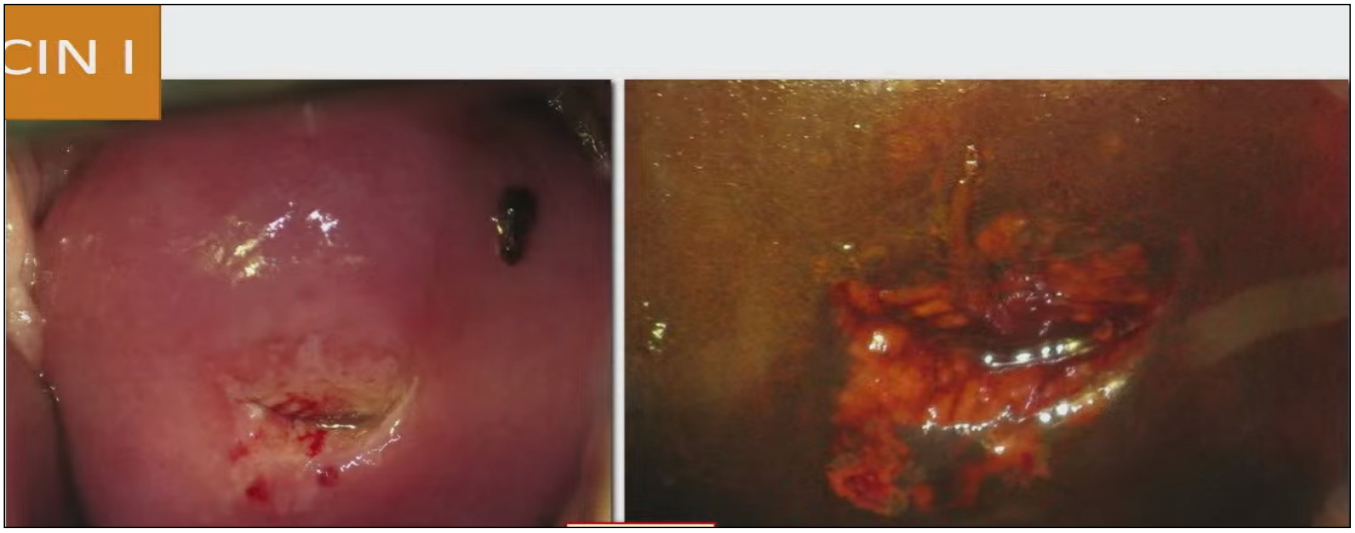

Fig. 13. CIN 1 Metaplastic epithelium
Picture taken by the authors

based on p16 staining for grading CIN 2; p16-positive combines with CIN 3 to form high-grade squamous intraepithelial lesion (HSIL), which is an immediate precursor to cervical cancer. CIN 2, negative for p16, combines with CIN1 to form low-grade squamous intraepithelial lesion (LSIL).

HPV studies have demonstrated the high prevalence and transient nature of most cervical HPV infections and it has become clear that there is no mandatory progression to CIN. Not all CIN will lead to cancer [12, 13].

CIN 1 has been found to be a poorly reproducible and insensitive histological diagnosis of an acute and generally transient infection.

When a number of histologists examined microscopy specimens from women diagnosed with CIN 1, some of them confirmed the diagnosis, some reduced it to normal, and some increased it to CIN 2 and CIN 3. Biopsies with a primary diagnosis of CIN 1 were reviewed by a panel of experts.

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Conclusions should be made based on the HPV test, cytological test, and sometimes using markers to establish the diagnosis, which is very important. Table 2 presents the compatibility of cytological and histological diagnoses.

Cytology does not diagnose dysplasia, it identifies those patients who need to be worked with, who need to be isolated, examined, and biopsied.

Fig. 11 shows CIN 1 - cytologically, colposcopically - a region of metaplastic epithelium, and histologically - moderately differentiated squamous cell carcinoma.

CIN 1 is presented in Fig. 12, Fig. 13, where metaplastic epithelium is visible, the transformation zone of type 1, can be regarded as acetowhite epithelium, but without

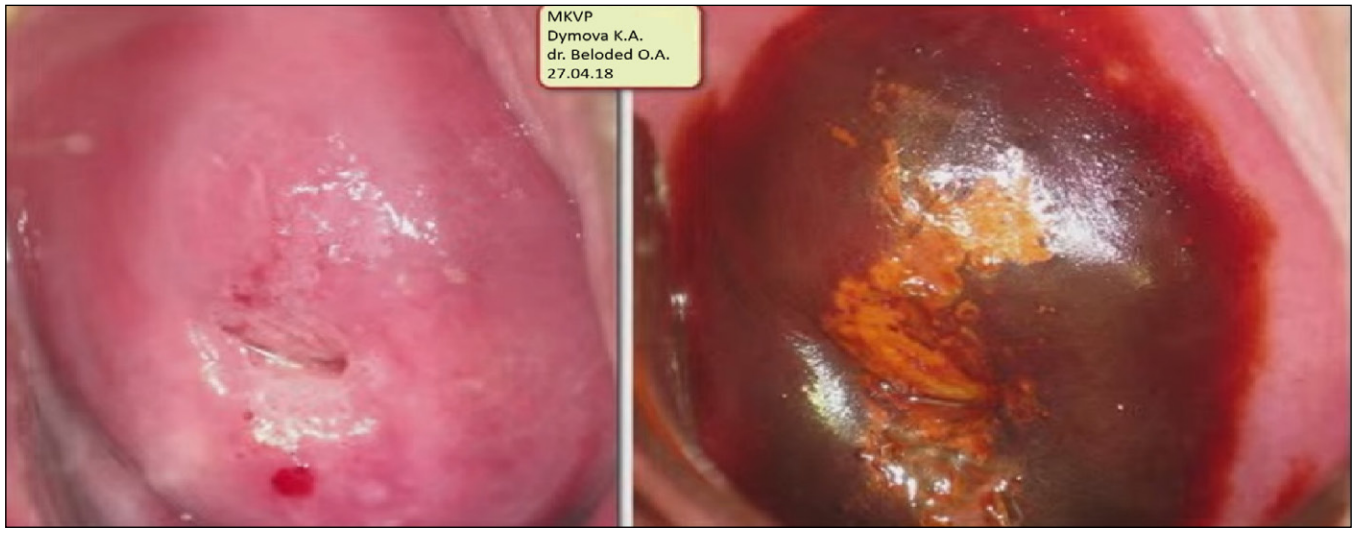

Fig. 14. Acute inflammation, reactive changes with atypia

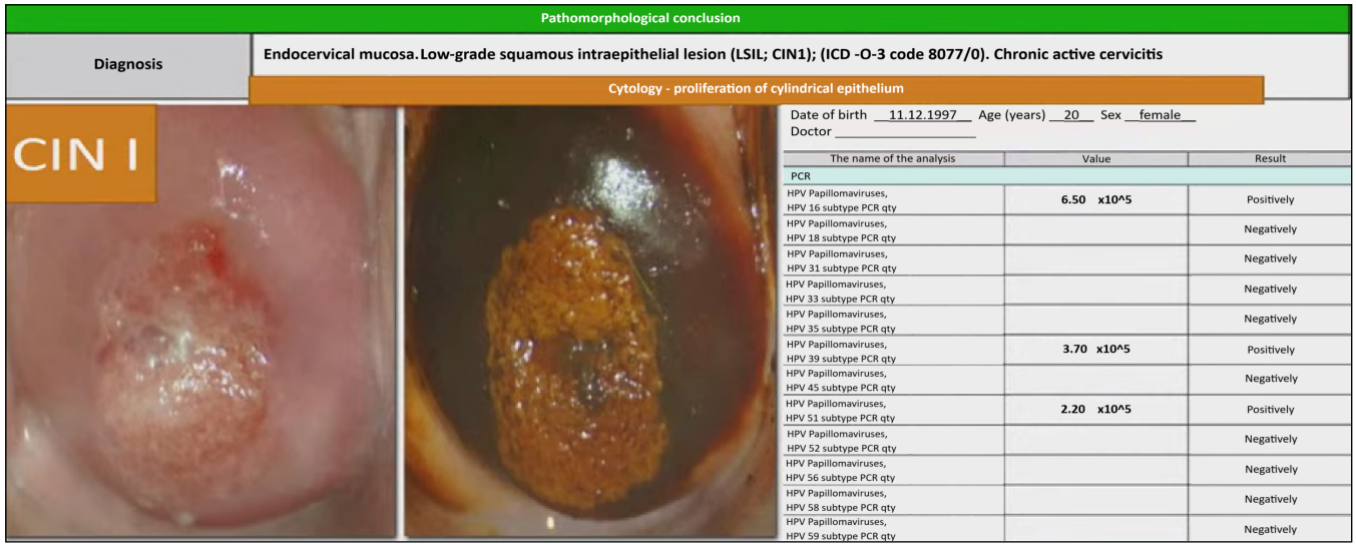

Fig. 15. Ectopia of the cervix of a woman whose biopsy revealed CIN 1
Picture taken by the authors

a biopsy we cannot say for sure what this will be in true manifestation.

Fig. 14 shows acute inflammation, no changes were detected cytologically, bacterial vaginosis, reactive changes with atypia of epithelial cells are present, because the epithelium suffers from an inflammatory reaction.

Fig. 15 shows a long-term ectopia in a woman with altered hormonal background, PCOS, unstable hormones, with a high viral load, in whom CIN 1 was detected during biopsy.

MODERN LSIL TREATMENT ALGORITHMS

Currently, the following issues are problematic:

- There is no true verification of the diagnosis. Treatment is planned and carried out based on screening.
- "Quick" treatment is carried out, sometimes almost without examining HPV status.
- Treatment is dominated by surgical and ablative methods, the infectious state is not taken into account.
- The median observation time for HPV clearance is not tracked.

CIN 1 – persistent HPV has:

- Viral cytopathic effect
- Damage to 1/3 of the epithelium
- Detection as a result of (HPV and cytological) screening programs
- Diagnosis = biopsy

CIN 1 regresses in 60-80% of cases within 2-5 years, very often regresses due to pregnancy, so there is no need to endlessly cut off pieces on the cervix in women planning pregnancy. There are studies that show that CIN 1 becomes normal due to pregnancy.

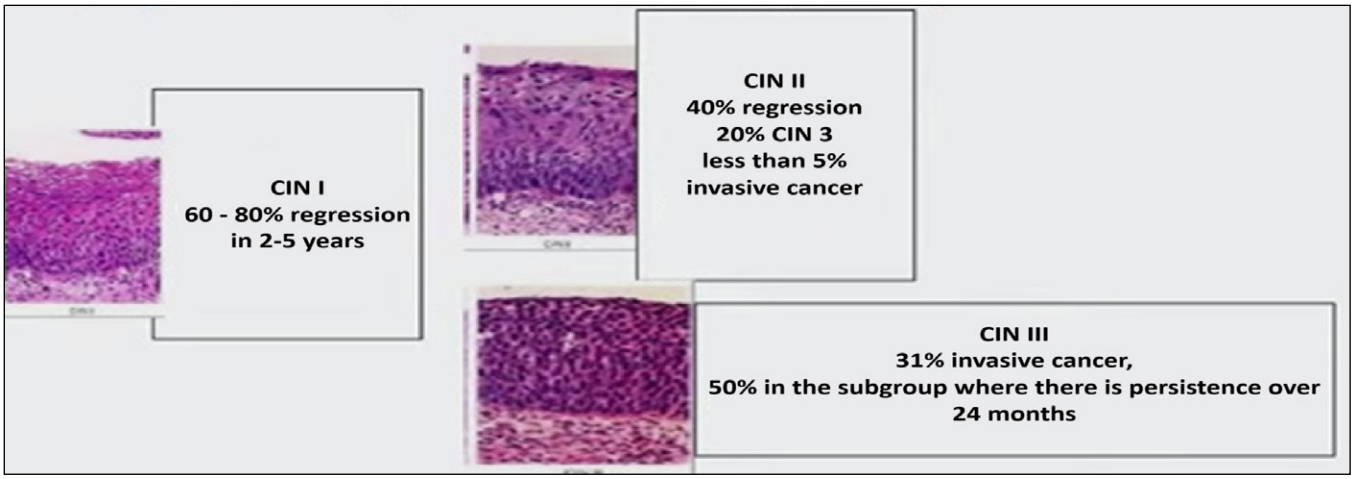

Fig. 16. CIN risk assessment
Source: compiled by the authors based on [12]

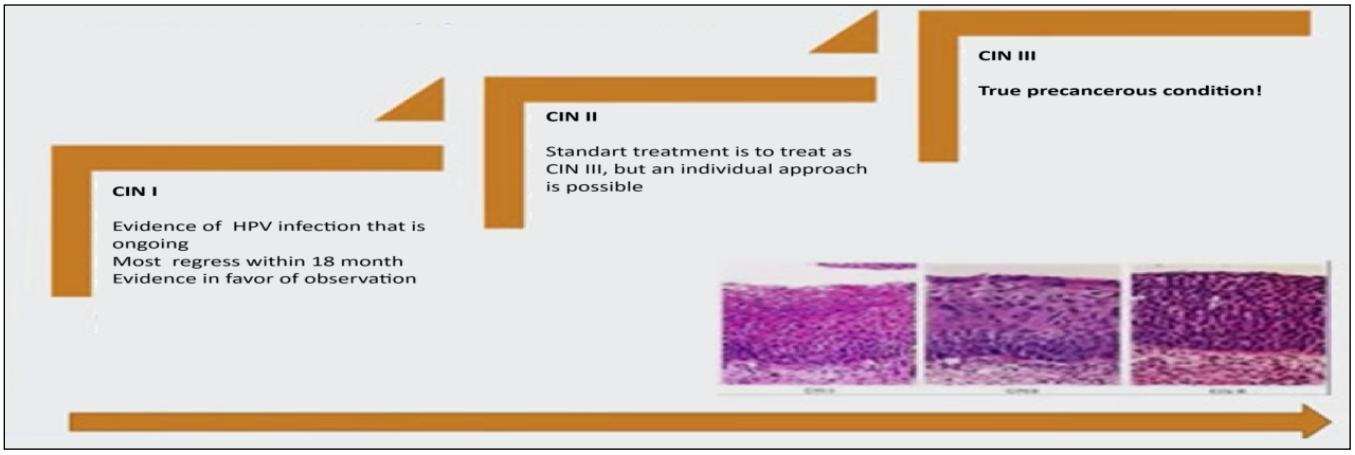

Fig. 17. CIN Management
Source: compiled by the authors based on [13]

CIN 2 40% regress, but 20% definitely transform into invasive cancer, but without having HPV-16 in this diagnosis, regression can be observed.

CIN 3 has a very small percentage of spontaneous recovery – less than 5%, and this occurs when the woman's viral aggression disappears.

CIN 3 progresses to invasive cancer in 31%, 50% in the subgroup where there is persistence for 24 months (Fig. 16).

CIN management is presented in Fig. 17.

DIFFICULTIES IN DIAGNOSIS AND TREATMENT

The following problematic issues very often arise (Fig. 18):

- this is a positive HPV test and normal cytology or colposcopic changes are detected, a biopsy is taken, a diagnosis is made, etc.
- is a positive HPV test and cytological changes to LSIL →refer for colposcopy →biopsy →observe →treat
- this is a positive HPV test, LSIL, CIN 1 diagnosis, quantitative viral load should be taken into account
- whether the place that causes changes in histology was correctly found colposcopically
- age: women who are 30-35 years old and older and may have already been infected with the *Human Papillomavirus* during their sexual life

CIN 1+high-risk HPV

– Most guidelines suggest treatment or continued observation for CIN 1 (LSIL) if the changes persist for at least 2 years
– Regression is defined as a CIN 1 lesion that returns to normal cytology (70-80%)
– Persistence is defined as CIN 1 lesions demonstrated cytologically after 2 years (5-20%)
– Progression is defined as histologically confirmed CIN2+ (various studies 1.5– 4% to 10% in one study)
– Менш, ніж 1 % призведе до інвазивного раку
– Less than 1% will lead to invasive cancer
– Both progression and persistence are correlated with HPV infection

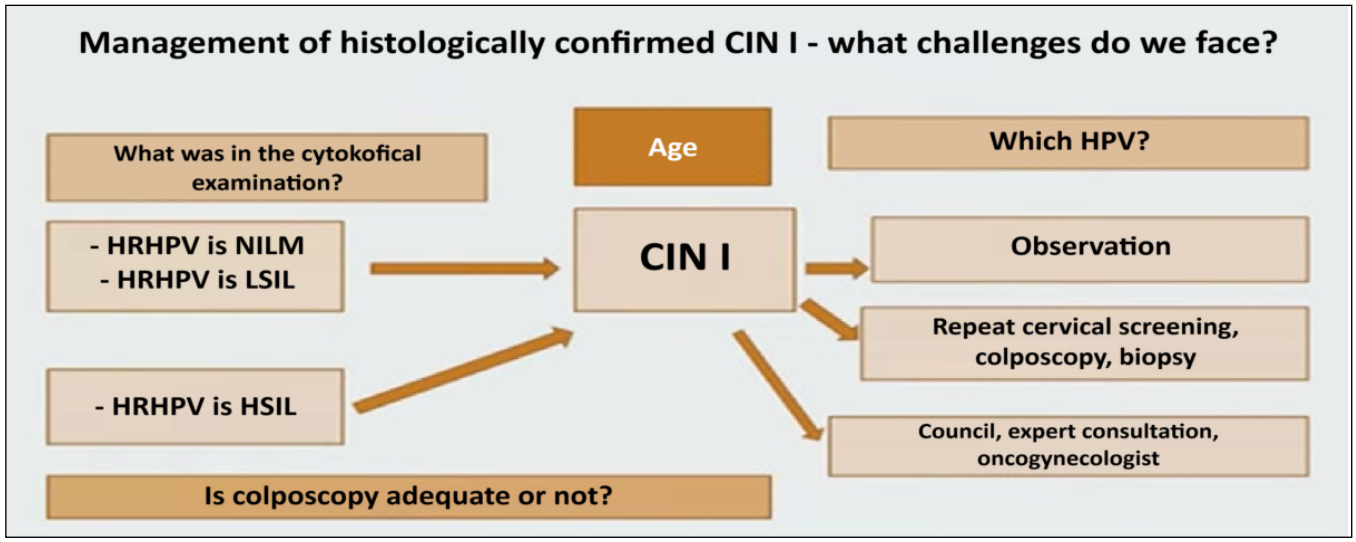

Fig. 18. Management of histologically confirmed CIN 1
Source: compiled by the authors based on [14]

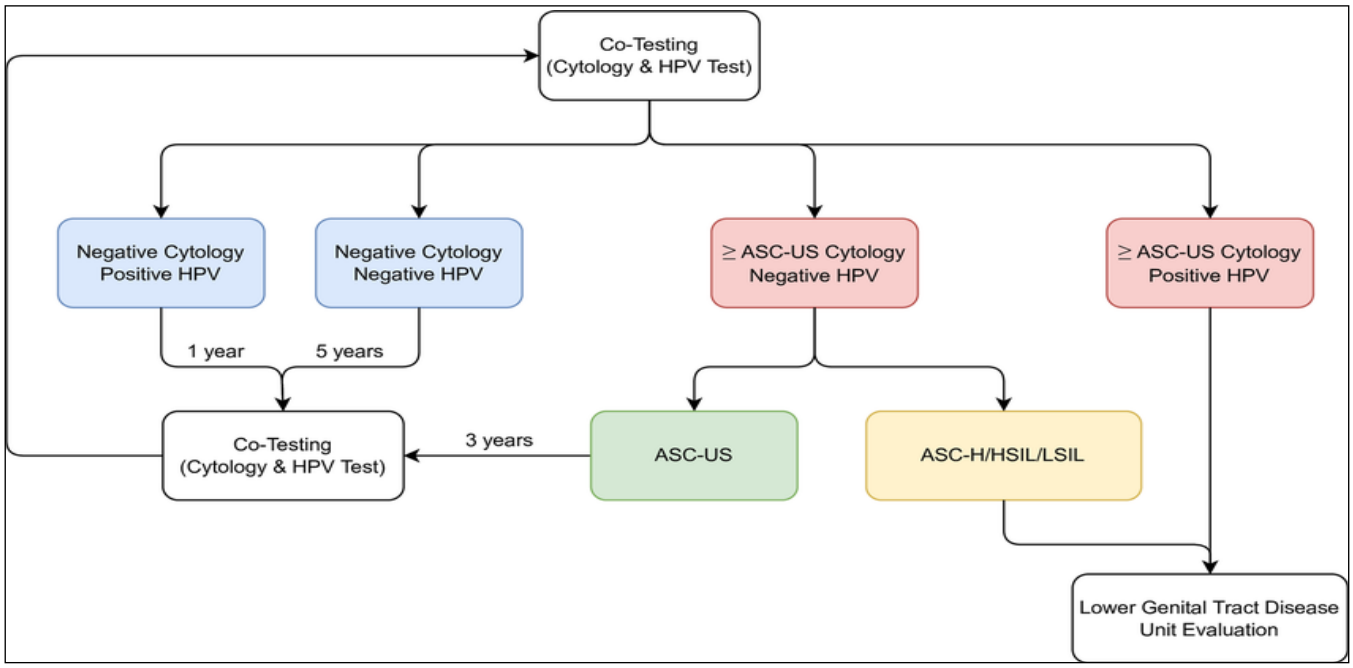

Fig. 19. Cervical cancer screening algorithm via co-testing
Source: compiled by the authors based on [14]

Progression
– CIN 3 may occur *de novo*, rather than being the result of progression of CIN 1 (infection with a different viral genotype PARK, Quint, Litjens studies)
– It is not the presence of CIN 1 that determines the risk of developing CIN 3, but the diagnosis of persistent HPV infection 16,18,31,33, etc. (Patricia, Viviant, and others).

The goal of treatment
– Recognition of occult CIN 3
– Treatment of low-risk abnormal cells
– Return to normal cytology
– Patient support

HPV
– Clearance
– Latency
– Persistence

The algorithm for screening for cervical cancer is presented in Fig. 19.

The main question of the congress on *Human Papillomavirus*, held in Washington in 2023, is whether HPV can leave the body forever? The world must answer this question. But today there is a tool that, within 2 years, has changed the perception of cervical cancer treatment. Today, they don't treat something, they don't cut something out, they treat the virus, and this process is called the elimination of the

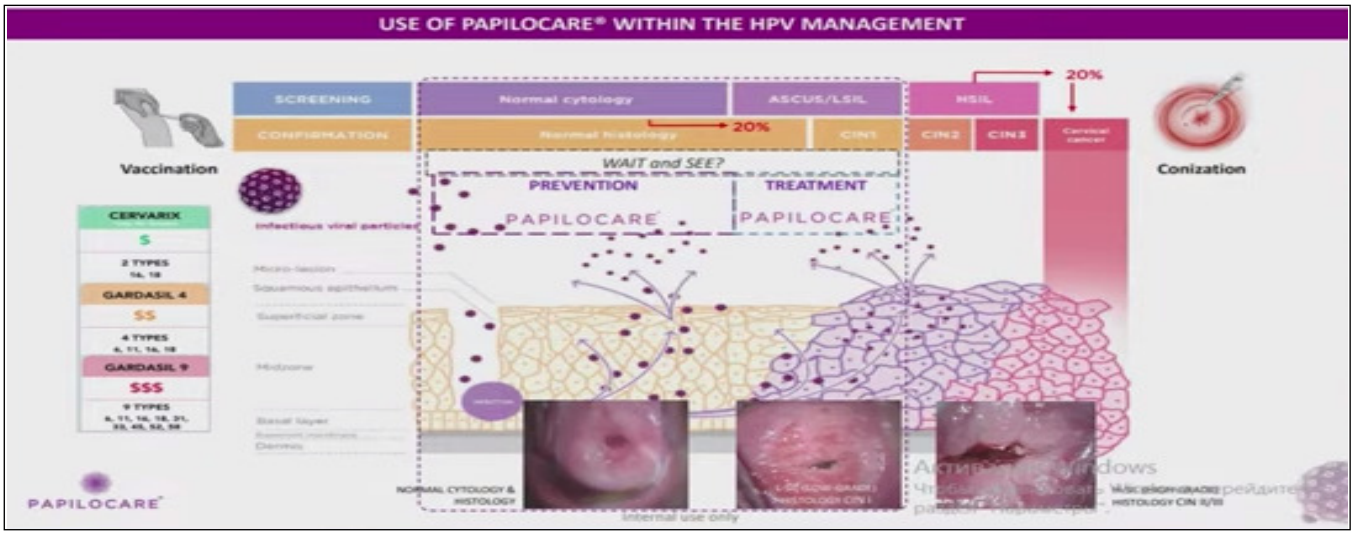

Fig. 20. The path of Papilocare gel in the human body
Source: compiled by the authors based on [15]

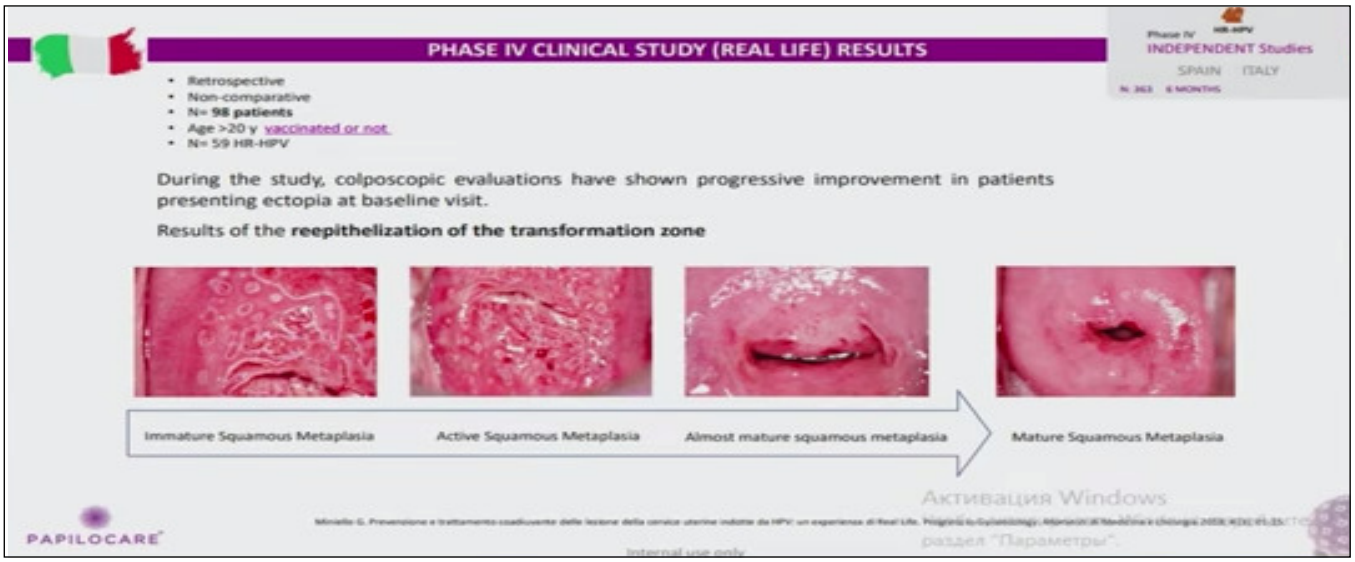

Fig. 21. Incomplete epithelialization with Papilocare gel
Source: compiled by the authors based on [12]

Human Papillomavirus pathogen. This is something that the body couldn't handle, something that lactobacteria should have handled. Interferon α should strengthen the immune system, it should clear on its own. But this did not happen and the process continued. The virus began to infect the epithelium and divide cells similar to itself, so there is a means of eliminating the human papillomavirus – papilocare.

– A medical product that combines ingredients of natural origin
– Vaginal gel that forms a protective and healing barrier in the "transformation zone"of the cervix.

Papilocare gel follows the same path as the human papillomavirus, cleansing layer by layer of stratified squamous epithelium. The entire epithelium has 5 layers. 1 superficial – exfoliates and definitely the human papillomavirus affects all layers from below, all layers are cleaned, 5 months of cleaning are required for 5 layers. After two years of administration, excellent results in eliminating the pathogen have been observed (Fig. 20).

Indications for use of Papilocare gel:

– Monitoring and assisting in the reepithelialization of the cervical transformation zone to prevent the risk of HPV-induced lesions (LSIL)
– Use as an adjunctive treatment for intraepithelial lesions caused by HPV
– Restoration and assistance in re-epithelialization of lesions of the cervical mucosa
– Treatment of dryness of the cervical and vaginal mucosa
– Restoring the balance of vaginal microbiota
– Improving the overall condition of the vagina
– Creating conditions for rapid healing of scratches caused by inflammation or itching

– Formation of a protective film that quickly reduces irritation, creating the right conditions to promote the natural healing process.

The action of Papilocare gel is explained by the fact that it is a very small molecule in structure, like the human papillomavirus, therefore, starting layer by layer, the cleansing process takes place. The main component of Papilocare gel is Coriolus versicolor, an antitumor fungus that has the property of restoring apoptosis.

Coriolus versicolor

– Induction of anti-inflammatory cytokines, interferon-γ, effects on NK cells
– Expression of tumor necrosis factor – stimulation of apoptosis

To date, 50% to 70% of patients have HPV clearance after 6 months in 4 studies. An example of incomplete epithelialization using Papilocare gel is shown in Fig. 21.

Who can use Papilocare gel:

– It is recommended for women over 18 years of age infected with human papillomavirus, regardless of whether they have lesions caused by the virus (LSIL) with appropriate colposcopy results.
– Women whose histological results are: CIN 1 or who do not require surgical treatment of CIN2.
– Duration of treatment is 5-6 months, administered every day for 21 days, and then every other day for 2,3,4 months for 21 days.
– Control tests after 6 months.

Treatment options depend on:

– Vasibility of the junction of the squamous and columnar epithelium (how adequate was the colposcopy)
– Age (greater caution in reproductive age)
– Ablation (cryo and thermal ablation)
– Excision
– Hysterectomy only in the presence of concomitant gynecological diseases

PREVENTION

Vaccination is not currently considered a purely preventive measure. Currently, vaccination is one of the parallel ways to eliminate the *Human Papillomavirus*, to protect women from cervical cancer and subsequently their healthy cells, as a means of preventing the recurrence of severe precancerous conditions.

Today, vaccination is mandatory after each treatment for severe cervical dysplasia, especially if it concerns the viruses that caused the dysplasia. Research into vaccinating infected women is ongoing.

In the UK and Europe, women receive preventive vaccines at the time of conization or other treatment and are re-examined 6 months later [14]. In 2021, at the XVII Congress, which was held in India, there was a report by Dr. Eva Lois from the Department of Oncology and Gynecology from New Zealand, who reported that the population practically does not have HPV-16, they may have other precancerous conditions, condylomas, but they are not caused by HPV-16, HPV-18, because due to the vaccination introduced in the country, HPV-16 has almost completely disappeared from the human population and due to this, the incidence of cancer has decreased [15]. New Zealand is a country that currently has a cervical cancer incidence rate of 5 cases per 100,000, which is almost the rate that the WHO calls for - 4 cases per 100,000.

CONCLUSIONS

1. Detection of LSIL (CIN1) is carried out by HPV testing and cervical screening, and the diagnosis is verified by histology.
2. The goal of the screening program is to detect and treat high-grade precancer and prevent the development of cancer.
3. Avoiding overtreatment and its consequences (cervical stenosis and pregnancy complications).
4. It is not the presence of CIN 1 that determines the risk of developing CIN3, but the diagnosis of persistent HPV infection 16, 18, 31,33, and others.
5. Most guidelines talk about surveillance from 18 years of age for 2 years for CIN 1.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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