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The diagnostic algorithm in pre-invasive cervical lesions

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ABSTRACT

The screening for pre-invasive cervical lesions has significantly decreased the incidence of cervical neoplasm. It is recommended to be performed starting with the age of 21 with a frequency of 3-5 years and it consists of pap smear testing and HPV genotyping, and, if required, it can be continued with colposcopy or biopsy followed by pathological assessment. The importance of the early diagnosis of pre-invasive cervical lesions has led to several studies on this topic. The paper analyzed the modern literature published on the PubMed and Scopus databases. Reference studies have found that most intraepithelial lesions are caused by the presence of HPV. Other commonly associated factors are immunosuppression, multiparity and other viral infections. HPV infection can be prevented by vaccination. It is recommended for people between 11 and 26 years old and also over 27 years old if they associate risk factors. A meta-analysis performed on patients diagnosed with CIN2 revealed a lower recurrence rate in vaccinated women than in unvaccinated women. Other studies have shown the transient nature of HPV infection and spontaneous regression of pre-invasive lesions. The early diagnosis of pre-invasive lesions is necessary for the initiation of therapeutic and follow-up behavior as soon as possible, with the aim of reducing the incidence of cervical cancer. This is possible and easy to access through national health programs.

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Introduction

The early diagnosis of pre-invasive cervical lesions has been a challenge since the twentieth century. National screening programs have been developed to reduce the incidence of cervical cancer, but this pathology remains a public health problem. In the United States, the incidence of malignant tumor pathology of the cervix has decreased since the 1970s, after the evolution of the first national screening programs [1,2].

Intraepithelial cervical lesions (CIN) are premalignant lesions of non-keratinized multilayered epithelial covering tissue [3]. The cervix consists of endocervix (cylindrical epithelium) and exocervix (squamous epithelium). The screening for pre-invasive and invasive cervical lesions includes Pap smear and HPV genotyping. Depending on the results, these investigations can be completed with colposcopic examination and pathological assessment [4,5].

In order to be able to diagnose these lesions at an early stage, every woman older than 21 years old has to undergo screening tests: Papanicolau smear (Pap smear) once every three years, or HPV genotyping together with Pap smear every 5 years [6,7].

Pap smear examines cervical cellularity, thus being able to diagnose malignant intraepithelial lesions, inflammation, atrophy, or other physiological and pathological changes in the cervical epithelium [8,9]. On the referral note of the cytological examination, one must specify the date of the last menstruation, the presence of intrauterine devices and pregnancy [10]. HPV genotyping seeks to multiply the HPV genome to identify viral strains [11].

For the diagnosis of intraepithelial cervical lesions, the colposcopic examination is also used, which analyzes the modifications of the external layer of the cervix and of the squamous-columnar junction. The investigation is indicated in case of unfavorable results at Pap smear

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examination or HPV genotyping [12]. During the colposcopic examination, a tissue fragment can be collected for the histopathological examination. This procedure does not require the hospitalization of the patient and it has few contraindications: cervicitis, hemorrhagic diathesis, vaginal bleeding, pregnancy and immunosuppression [13,14].

The next step in the diagnosis of the lesions is the pathological evaluation. Conization together with the diathermic loop electro resection and bioptome biopsy are reliable methods that provide tissue for the histopathological examination. Uterine curettage is not a routine indication if conization is performed. It is indicated only if there are glandular cell abnormalities on Pap smear or if they have risk factors for endometrial hyperplasia or endometrial adenocarcinoma [15].

The literature search was conducted in PubMed and Scopus databases using the terms “Cervical intraepithelial lesions”, “excisional procedures” and “screening and diagnostic for cervical lesions”. No date restriction was applied. Language was restricted to English and French. Additional studies from the reference list of the articles were searched.

Discussions

CIN occurs most frequently in the squamous-columnar junction, being secondary to the HPV infection. Most intraepithelial lesions are thought to be caused by HPV, but not all HPV infections cause CIN [16,17]. Besides the HPV infection, other risk factors are immunosuppression, diet, multiparity, first delivery before the age of 17 years, multiple sexual partners, lack of condom use, smoking, herpes virus infection. A study conducted by Anttila revealed that Chlamydia trachomatis has an implication in the development of pre-invasive lesions [18-21]. A study conducted by Aldieh revealed how a person living with HIV is affected by the co-infection with HPV. If left untreated, the HIV infection decreases the number of CD4 positive lymphocytes. On the other hand, an HIV positive undetectable person has a pro-inflammatory status [22]. Another important exponent is smoking, which releases nicotine-derived ketones that lead to decreased local immunity [23].

The HPV infection is a sexually transmitted infection, and 75-80% of sexually active people have had the infection. Its natural evolution has several stages: latent infection (minimal clinical, colposcopic and histopathological changes) is the most common form of HPV infection. Active infection, without genomic integration (the virus replicates intensely, cell nuclei become large, multinucleated and hyperchromatic with a halo around the nucleus) corresponds to low-grade lesions (L-SIL) on the cytological evaluation. The evolution at this stage depends on the host's immune system. Antibodies directed against viral particles are produced by CD4 + T lymphocytes and macrophages. Most people produce these antibodies efficiently, so the evolution is favorable.

The last stage in the evolution of the infection is the genomic integration, which corresponds to the malignant tumor pathology [24-28].

Clinical presentation

Intraepithelial lesions do not have a characteristic symptomatology, most often we encounter abnormal vaginal bleeding, changes in bowel movement, changes in bladder function, pelvic pain syndrome, dyspareunia, macroscopic lesions on the exocervix [29-31].

Paraclinical evaluations

The diagnosis of pre-invasive cervical lesions uses multiple paraclinical evaluations.

Pap smear

Pap smear examines cervical cellularity for abnormal cells. It is a screening method that must be done every three years. The appearance of a lesion on a properly performed screening is very small: 10-> 66 / 10,000. It is not recommended to be performed annually, as it does not decrease the risk of death from cervical cancer. A study conducted by Sawaya et al. covering patients aged 21 to 29 years revealed that the risk of death from cervical cancer is identical, regardless of whether the cytological evaluation is done at one, two or three years [6,10,32].

The evaluation is not done during menstruation. It is important not to touch the exocervix when inserting the vaginal speculum, as dysplastic cells can attach to the speculum. Although during menstruation it is recommended not to perform the examination, it should not be delayed in case of cervicorrhagia, metrorrhagia or abnormal secretion because they can be symptoms of a malignant pathology of the cervix.

On the referral note of the cytological examination, it is important to mention the date of the last menstruation, because the appearance of the vaginal and cervical epithelium varies with the ovarian cycle. Another thing to mention is pregnancy, exogenous hormone therapy, metrorrhagia, a history of dysplastic lesions, menopause, the use of intrauterine devices (IUD). In the case of IUD, it is recommended to take cells from the anterior vaginal wall as well, as these patients have an increased risk of developing vaginal cancer [33]. The Bethesda 2014 classification is used to provide the cytological result. Intraerpithelial lesions are subdivided into several groups. Squamous cell atypia-like lesions (AUC): lesions of determined significance (AUC-US) or lesions that cannot rule out a high-grade lesion (AUC-H). Low-grade lesions L-SIL include CIN 1, HPV infection, mild dysplasia. High-grade lesions: H-SIL include severe, moderate dysplasia, CIN2, CIN3, carcinoma in situ and the invasive lesion represents squamous cell carcinoma of the cervix [34,35].

The HPV genotyping can be done alone or together with Pap smear once every 5 years. The most common strains 16, 18 are routinely tested on the cytological examination. It is useful to do it alone in patients who do not have access to screening services [11,34,36].

Colposcopy

Colposcopy is used to evaluate the cervix. It is indicated in case of macroscopically visible genital tract lesions, abnormal cytological evaluation, positive HPV evaluation, intrauterine exposure to diethylstilbestrol, unexplained genital tract bleeding [12,33]. The examination can confirm if one has vulgar warts, cervicitis, pre-invasive lesions of the cervix, vagina or vulva.

It has few risks; it allows the biopsy to be performed. Among the risks that arise after tissue sampling are: bleeding, infection and pelvic pain syndrome. Pre-procedural training includes: no sexual intercourse 24-48 hours before, no intravaginal tampons should be used 1-2 days before, no intravaginal medication and no menstruation [37,38]. The examinations that are performed: the native macroscopic evaluation of the cervix, the examination with 3-5% acetic acid, which stains the aceto-white lesions, the Lahm-Schiller test using lugol. Normal cells have estrogen receptors; thus, those cells have glycerol in their cytoplasm. On the other hand, dysplastic cells lack these receptors and they have a lower quantity of glycerol. The last evaluation on colposcopy finds dysplastic cells using Lugol (an iodine solution). If the cells have glycerol, iodine will impregnate them. The last stage is omitted in the case of patients allergic to iodine or contrast agents. The results that suggest a cervical lesion are: acetone-white epithelium, mosaic, punctures and leukoplakia.

The study conducted by Sophia S. analyzed the incidence of malignant tumor subtypes located in the cervix, and as a result of the screening programs, the incidence of squamous cell carcinoma of the cervix is decreasing, but the lack of experience in endocervical cell evaluation has led to an increase of endocervical adenocarcinomas [12,33].

Conization

There are also invasive diagnostic methods: conization with the cold scalpel, conization with the electrocautery or excision with the diathermic loop.

Conization with the cold scalpel offers a good piece for histopathological evaluation, it is simple, it requires general or local anesthesia, but it has a higher complication rate than other methods [39]. The patient is placed in a lithotomy position, the vaginal speculum is mounted, the colposcopic evaluation or Lugol can be used to observe the areas with lesions. Two sutures can be made at 3 and 9 o'clock to limit bleeding. Sometimes it is useful to inject vasopressors which lead to a decrease in the intraoperative bleeding, in the absence of contraindications (hypertension). A circumferential incision is made that goes as deep as possible, it is excised and the neck is restored with Strumdorf suture [33].

Conization with the electrocautery offers a good specimen, good hemostasis and it has a lower complication rate, but it is more difficult, it can cause thermal damage in the adjacent structures, it is difficult to make a small radius cone [39-41].

The loop electrosurgical excision procedure is easy, fast, has few complications and provides a good piece for histopathological examination, but it can cause thermal damage to adjacent tissues and it is difficult to perform for a large area of tissue. Lidocaine can be used for local anesthetic purposes, but also to limit bleeding. It penetrates the cervix with a loop and in a single movement a fragment of the cervix is excised and sent for the histopathological examination [33,39,42].

A study conducted by Hu X looked at the rate of HPV infection among medical staff practicing electrocautery or diathermic excision. Procedures that lead to smoke generation are dangerous for doctors and nurses because they expose them to HPV that will be found to the nasal epithelium (the incidence is 9-10% among doctors who treat people positive for HPV, compared to 2- 3%). If medical personnel use KN95 masks, the infection was 0%. [43].

All these methods provide enough tissue for the pathological evaluation. The histopathological result is classified into CIN1, 2 and 3. CIN1 is also called L-SIL: mild, moderate dysplasia, located in the basal third, HPV infection, with an increased regression rate. High-grade intraepithelial lesions (H-SIL) are subdivided into CIN2 and CIN3. CIN2: moderate dysplasia in two basal thirds, CIN3: severe dysplasia in two basal thirds, but can affect the entire epithelium, a situation called carcinoma in situ. [44].

A study led by Bansal, which included 680 patients, analyzed the evolution of CIN1 lesions. At 6 months after diagnosis: 49% regressed spontaneously, 35% had CIN1 lesions, and 7% had a negative outcome. Out of the patients with negative lesions at 6 months, at the one-year reassessment: 80% had no lesions, 16% had low-grade intraepithelial lesions, and 4% had an unfavorable evolution. In the case of patients with positive lesions at 6 months, at the one-year reassessment: 50% did not present lesions, 46% CIN1, and 4% evolved negatively [45,46].

The study conducted by Tainio K revealed that CIN2 lesions in half of the cases regress without treatment. This meta-analysis covering 36 studies and including 3,160 patients showed that at the two-year evaluation: 50% underwent regression of the lesion, 32% had persistent lesions, and 18% progressed to CIN3, carcinoma in situ, invasive cervical carcinoma [47].

CIN3 lesions may regress spontaneously in 32-47% of cases or may progress to invasive carcinoma in 12-40% of cases [48]. A study conducted by McCredie evaluated patients at 10 years and 30 years, comparing the patients' evolutions according to the treatment undergone. In the case of patients who opted for the expectant attitude, 20% developed invasive carcinoma at 10 years, and 31% developed malignant tumor pathology at 30 years. The patients who opted for the surgical treatment had an incidence of 0.3% at 10 years and 0.7% at 30 years [49].

HPV infection can be prevented by vaccination. It is recommended for all people between 11 and 26 years old and, in carefully selected cases, for people over 27 years old. It is recommended for women with a history of dysplasia and patients with vulgar warts. Vaccination has no therapeutic effects, but a decrease in the risk of recurrence has been observed. A meta-analysis performed by de Villiers EM et al. revealed that the recurrence in vaccinated patients is 1.9% compared to 5.9% in non-vaccinated patients with CIN2 [50].

Conclusions

Most pre-invasive cervical lesions are caused by the HPV infection, but not every infection causes the lesions, so it is not advisable to do it routinely among the young HPV genotypic population.

The diagnosis of pre-invasive cervical lesions is eminently made through paraclinical investigations.

Pap smear is an effective method of diagnosis and screening that must be performed every three years, performing it earlier does not reduce the risk of mortality from cervical cancer.

If there is an abnormal Pap smear result, colposcopy is indicated for a thorough assessment of the squamous-column transit area. Pathological lesions with pathological appearance are leukoplakia, mosaicism, punctures, aceto-white epithelium.

Invasive examinations provide the basis for the histopathological analysis, thus providing a careful assessment of the endocervix.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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