

MANAGEMENT OF ABNORMAL PAP SMEARS

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Abstract: Screening programmes using the Pap test have significantly reduced the number of invasive cancer cases through early diagnosis and treatment of precancerous lesions. Starting from the main purpose of cervical cytological screening - preventing the development of invasive carcinoma –HPV testing really speeds up the diagnosis of CIN_{II-III} and allows immediate treatment.

Screening programmes using the Pap test have significantly reduced the number of invasive cancer cases through early diagnosis and treatment of precancerous lesions. When precancerous lesions are diagnosed before they develop into cancerous lesions and early and appropriate treatment is established for each grade, the survival rate can reach almost 100%. However, in the case of invasive cancer, prognosis depends on the time of diagnosis of precancerous lesion.

Introduction of the Pap test as a screening method for cervical cancer has reduced the mortality from this disease, but consecutively, the number of diagnoses of preinvasive lesions of the cervix has increased. Papanicolau cervical cytology screening is the most appropriate current method for the early detection of cervical lesions.(1,2)

Screening should be initiated 3 years after the start of sexual activity; rotation interval to repeat cytology must be annually until obtaining 3 consecutive negative results and then, every 3 years. Women who have not been tested in the past 5 years, re-enter in the annual screening programme. Pap smear screening continues until the age of 70 years if the last decade history registers negative tests.(1,2)

The ideal method to perform a Pap smear is represented by liquid-based cytology (LBC), which provides a uniform fixation of artefacts and of uninterpretable elements comparative with conventional cytology.

HPV infection causes an insufficient immunologic response from the body to be detected by antibody determination. As a result, the diagnosis of HPV infection is determined by detection of HPV-DNA in cervical cells from the cells harvested by cytological examination through LBC technique or by a new harvesting. To determine HPV-DNA, it is used either the hybridization technique or the polymerase chain reaction (PCR) method. Currently, the most commonly used method is the hybridization (HC2-Hybrid Capture 2) by using enzyme-linked immunosorbent assay (ELISA). An important role is assigned to determine the types of high-risk HPV strains.(3,4)

Motivated by the high frequency of HPV infection, especially in the young population and by the lack of specificity of infection for the cervical cancer screening, its highlighting is not indicated as initial screening method. This method is recommended to clarify abnormal Pap cytology methods.

Highlighting HPV infection associated with the Pap test has a sensitivity of 96-100% in detecting cervical

intraepithelial neoplasia (CIN) and cervical cancer.

Management of abnormal Pap smears

I. ASC-US – The term of ASC-US (Atypical squamous Cells of Undetermined Significance) is used by cytologists to define the cellular changes more noticeable than the reactive changes, but insufficient to diagnose a squamous intraepithelial lesion.(4)

Special circumstances occur in the presence of an infection or atrophy. In such cases, treatment of the infection is indicated and to repeat cytology at an interval of 4-6 months after treatment.

HPV testing can be used to triage patients with indication for colposcopy, this one having a much greater sensitivity than repeating cytology in the detection of possible squamous intraepithelial lesions.(5)

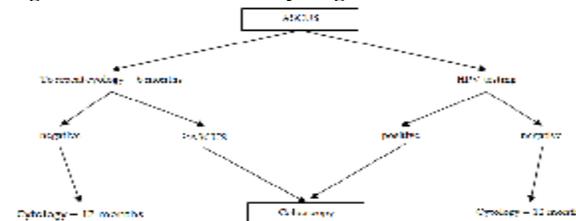
A positive test means a 15-27% risk for CIN 2/3 lesion and requires colposcopy with biopsy. A negative test is associated with a risk of CIN below 2%, but it may be also determined by an infection with HPV with lower titres or HPV types not included in the test. Repeating cytology is justified after 1 year.(1,2)

In HPV-positive women in whom biopsy does not indicate a CIN lesion, it is recommended to observe Pap test at 6 and 12 months with colposcopy and biopsy in case of persistent or worsening ASC-US lesion.

In the conditions in which HPV testing is not available, it is recommended to repeat Pap cytology every 6 months. Two negative Pap tests signify one negative HPV test and under these circumstances, patients' surveillance is achieved through annual screening programmes.

In the case of an abnormal smear result (ASC-US persistent or worsened), colposcopy or biopsy is necessary (figure no. 1).(6,7)

Figure no. 1. ASC-US cases cytologic exam



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2. *ASC-H (Atypical Squamous Cells: cannot exclude High-grade squamous intraepithelial lesion)* has a predictive value in detecting a possible CIN 2/3 lesions of about 48-56%, which requires colposcopy and biopsy.(4)

In case of a negative biopsy, it is indicated to repeat Pap test at 6 and 12 months respectively, associated with colposcopy in case of persistent or worsened lesion.(6,7)

3. *AGUS - Atypical Glandular Cells of Uncertain Significance* may be the expression of an inflammation, hyperplasia, dysplasia or endometrial or endocervical adenocarcinoma.(4)

Due to the risk of endocervical neoplasia or cervical dysplasia of high grade, it is required to perform endocervical biopsy from the junction area and complete biopsy with endometrial and endocervical curettage.

In case of a negative biopsy, it is indicated to follow Pap cytology for 2 years every 6 months for the diagnosis of a possible lesion previously undetected. If the result of Pap test does not return to normal, more aggressive assessment of the case is required, with no consensus in this situation, conisation is usually required in this situation.(8)

4. *L-SIL - Low Grade Squamous Intraepithelial Lesion* requires careful monitoring and compliance to Pap examination every 6 months. The persistence of abnormal Pap smear requires performing colposcopy with biopsy, in these circumstances determining HPV infection does not bring additional benefits, about 83% of these women being HPV positive.

The exception to this conduct is represented by the cases of L-SIL lesions that occur in adolescents, mostly representing the expression of a HPV infection with self-limiting evolution, frequently followed by spontaneous regression of the lesion.(9) In this situation, cytology examination will be repeated at 6 and 12 months, colposcopy being necessary only if obtaining a new abnormal Pap result.(9,10)

In case of a negative biopsy, it is recommended to repeat cytology at 6, respectively at 12 months completed with colposcopy and biopsy in case of abnormal Pap result.(8)

5. *H-SIL - High Grade Squamous Intraepithelial Lesion* gathers the moderate and severe dysplasia of the cervix and carcinoma in situ. Standard practice requires colposcopy with biopsy, subsequent management being determined by its outcome. In case of a negative biopsy, it is recommended the excisional diagnostic method, that is conisation.

Endocervical curettage must be performed, if at colposcopy, transformation area is not visible in women with altered Pap smear changed that is with atypical glandular cells (AGC) and in women with abnormal cytology of high – grade type (H-SIL), particularly for those more than 45 years old. The recommendation is: the patient's age can influence management, age being correlated with lesion regression or persistence of infection.(11)

The algorithm in the case of H-SIL persistence in teen girls: Frequently, this type of lesion is spontaneously regressive, cytologic and colposcopic follow-up at 4-6 months can be recommended, so as to avoid the complications of an excisional treatment, with possible repercussions on the reproductive prognosis and obstetrical future. If after this period, H-SIL cervical cytology persists, the teen girl will be a candidate for an excisional biopsy.(12)

H-SIL presence in the particular context of pregnancy requires the following management:

- a colposcopy should be carried out and if the result is not satisfactory, it should be repeated 6-12 weeks later. Target biopsy is aimed at if the lesion has an evolutionary character and possibly invasive. If the H-SIL cytology is

revealed in the third quarter of pregnancy, cytological and colposcopic reassessment is recommended at 6 weeks postpartum. (12)

Conclusions:

- Pap test is one of the easiest medical investigations, is cheap, fast, but very effective in detecting cervical cancer. However, too few women are periodically tested. The proof is the sad top place that Romania has in Europe regarding cervical cancer mortality.
- Without minimizing the undeniable progress concerning the etiology, the diagnostic and therapeutic means and the ways of prevention and early detection, I believe that modern medicine owes in this area, where stronger actions should be taken in order to improve the incidence and treatment in curable stages of the disease.
- When Pap test is regularly performed, it can early detect abnormal cells in the cervix, before they turn into cancer cells.
- The main conclusion is the belief that a good discrimination can be achieved by combining the detection and viral typing with cytology. In different analyses, lesion progression was correlated to HPV detection or with the presence of moderate or severe dysplasia.
- Screening of cervical carcinoma is based on Pap smear (in countries that it became available, mortality was reduced by 40-80%).
- Cytology is closely related to HPV typing (cytology is recommended in association with HPV testing every two years in women over 20 years old).
- Endocervical curettage will be performed if at colposcopy, the transformation area is not visible in women with altered Pap smear, that is with atypical glandular cells (AGC) and in women with abnormal cytology of high – grade type (H-SIL), particularly above 45 years old. The recommendation is: the patient's age can influence the diagnostic algorithm.
- Women aged 30 years and over (in whom frequently, HPV infection is persistent) who as a result of phenotyping, presence of HPV strains - HR (high-risk) is noticed in the context of an unchanged cytology, cyto-oncologic examination will be repeated 12 months later at the same time with a colposcopy.
- Abnormal cervical cytology management in the context of pregnancy with the presence of abnormal cytology of ASC-US or LSIL type will require repeating the cyto-oncologic examination 3 months postpartum. Pregnant women with H-SIL, ASC-H or AGC Pap result will benefit from colposcopic evaluation. Pregnant women in whom CIN 2 or CIN 3 is suspected or is histologically confirmed presence will benefit from colposcopic reassessment and treatment 8-12 weeks postpartum. Endocervical curettage is prohibited during pregnancy.
- Statistics rank Romania first in Europe in terms of mortality from cervical cancer and third, regarding the incidence. The increasing incidence of the disease in the recent years, especially in people of young age, requires raising the health education level of the population and the establishment of effective screening programmes to include all female population at risk.

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