SCIENTIFICAL ARTICLE OF THEORETICAL PREDOMINANCE

Through the screening diagnosis is understood the testation of an asymptomatic population in the aim of establishing suspicions in the existence of the cervix cancer. This mass diagnosis supposes methodological and organizatorical methods and has to respect a certain diagnosis sequence. So, the algorithm of the examinations comprises: the clinical exam – cytologic exam – the colposcopic exam – biopsy recolitation (1).

In the organisatorical organisation of the precocious diagnosis of the cervix cancer are necessary few organizatorical shackles: a gynecologic cabinet centered on the pe problem of the precocious diagnosis of the cervix cancer, a laboratory of cytology and pathologic anatomy, also a hospital section specialized in the oncologic surgery, capable of solving the diagnosed pathology, also a service of specialised radiotherapy.

The superficial localisation of the pathological process in an easier accessible area to the clinical exam and the existence of a great sensibility diagnosis method (oncocytologic exam) make possible the precocious diagnosis of the cervix cancer. The cytologic examination fulfills all the necessary qualities of a method of screening diagnosis: simplicity, accessibility, accuracy (92-95%), resonable price.

The screening of the cervical cancer consists in periodical examination through cytologic exam of great feminine populational groups, that doesn’t present specific symptoms. The women that are selectionated as suspects are amenable then to a diagnosis process, to establish with for certain the disease presence and then treated correspondingly if the disease is confirmed.

The age limits of the examined feminine population are comprised between 30 and 65 years, to astound the risk group, and the optimal intervall between two cytologicaal examinations is appreciated at 2-3 years. This intervall has to be differentiated in accordance with the anterior cytologic result and age (women with dysplastic lesions have to be examined at small intervals, the same the women from the risk group, in exachange the aged women, after a period of negative frottage may be rarely examined).

A special attention has to be given to the psychological preparation of the women for this action and to the adequated popularisation of the action, so it may be assured a good degree of population cooperation. A participation of 75-80% of the female population is considered acceptable.

I. Cytologic screening

The cervix screening through the cytologic examination Papanicolau represents the most adequate actual method for the precocious diagnosis of the cervix lesions (1). The screening has to be initiated in 3 years after the beginning of the sexual activity, the intervall of repetition of the cytology has to be annually until the obtaining 3 results consecutives negative continued then at 3 years intervall.

The women that weren’t tested in the last 5 years re-enters in the annually screening programme. The cytologic screening Papanicolau continues until the age of 70 years if the history of the last decade is represented by negative tests.

The ideal method of recolitation of the Papanicolau test is represented by the liquid-based cytology technique– LBC that realises a uniform fixation of the artefacts and of the non-interpretable elements comparatively with the cytology realised through slide fixation (5).

The HPV infection produces an insufficient immunologic answer of the organism as to be detected through the antibodies determination. As a result, the diagnosis of the HPV infection is established through the detection of the ADN-HPV in the cervical cells from the level of the recolated cells through the LBC technique for the cytological examination or through a new recolitation. To determine the ADN-HPV is used either the hybridisation method, either the PCR technique (polymerase chaine reaction). At present the method that is more often used is of hybridisation (HC2-Hybri(di Capture2) with the use of enzymes linked to an imunoabsorbant support (ELISA technique) (6). An important role is attributed to the

**Keywords:** cervix cancer, screening, prevention

**Abstract:** This paper has as purpose the presentation of the methods of cervix cancer diagnosis, because the superficial localisation of thepathologic process in an easy accessible area to the clinical exam and the existence of a diagnosis method of great sensibility(oncocytologic exam) make possible the precocious diagnosis of the cervix cancer.

**Cuvinte cheie:** cancer de col uterin, screening, preventie

**Rezumat:** Lucrarea de faţă îşi propune să prezinte metodele de depistare a cancerului cervical, întrucât localizarea superficială a procesului patologic într-o zonă ușor accesibilă examenului clinic și existența unei metode de diagnostic de mare sensibilitate (examenul oncocitologic), fac posibilă depistarea precoce a cancerului cervical.

1Corresponding Author: Georgeta Din, Emergency Clinical County Hospital of Sibiu, 2-4, Bd Corneliu Coposu, Sibiu, Romania; e-mail: ginadin34@zahoo.com; tel +40-0723254897

Article received on 28.05.2011 and accepted for publication on 24.10.2011

ACTA MEDICA TRANSILVANICA December 2011; 2(4):304-307

AME, vol II, nr. 4, 2011, pag. 305
determination of the high risk HPV.

Motivated by the increased frequency of the HPV infection, especially in the young population and by the lack of specificity of the infection for the screening of the cervical cancer its emphasis is not indicated as an initial screening method. This method is recommended in the elucidation of the abnormal Papanicolau cytologic methods.

The emphasis of the HPV infection associated with the Papanicolau test has a sensitivity of 96-100% in the detection of the cervical intraepithelial neoplasia (CIN) and of the cervix cancer.

In a study on the mortality through uterine cancer, published in 1988, in the data that was assumed from OMS, was observed its growing in a certain number of countries among which România.

The precocious stadiums of the evolution of the cervical cancer are asymptomatic and the abnormal results obtained through the interpretation of the surface biopsy constitutes the first indication regarding the existence of a pathology in its preinvasive forms. CIN 3 and CIS may progress through the invasive cancer, the control programmes being orientated to their identification and their treatment. The prevalence of the precursor lesions is big in the young women. The CIS intervention is increased in the period of 30-40 years, and of the invasive disease in the interval of 40-50 years (6).

The analysis of the cases with invasive disease diagnosed at small intervals after negative cytologic tests doesn't conclude that those tumors could be enframed in a distinct ethiological subgroup. It is possible that in this situations the process has a rapid progression in the preinvasive stage, and the everyday screening doesn't emphasize the abnormal cells.

The faulty recollection isn't probable for the respective patients that had two or more previous tests with negative results. The Papanicolau test isn't a diagnosis method. Its performances could be improved through the method automatisation.

There were imagined techniques for the automatisation of the interpretation of the cervical surface biopsy (for example: Auto Pap 300 QC System) used in the screening for the re-evaluation of the surface biopsy labelled as normal and the identification of the false negative surface biopsy.

There are taken into consideration new methods, different from the conventional Papanicolau test (for example: the prelevations in liquidian medium), that would increase the possibility of detection of the anomalies of the epithelial cells comparatively with the cytologic surface biopsy. The inspection with an „open eye” was proposed as a method in the precocious detection of the cervical cancer, as an alternative of the surface biopsy, in the countries developing countries.

This mean is proposed for the area in which the programmes of cytologic screening aren't possible. The specificity of this method is of approximatively 55%. Generally, is considered that the inspection of the cervix isn't a very promising method for the screening (6).

The screening frequency

The death rate through the cervix cancer decreased scandalously after the screening programmes. Consensualized in 1987 between the American Cancer Society, National Cancer Institute, American Medical Association, American College of Obstetricians and Gynecologists and the American Academy of Family Practice recommended the effectuation of the surface biopsies in the females aged over 18 years that are or were active from the sexual point of view. After three negative annual exams, the screening's frequency is fixed in accordance with the risk category.

The reasoning of 1 year intervals or more in the test practicing is more difficult and is linked to the periodicity of the gynecologic control of the healthy women.

The population that present with an increased risk has to be examined annually, but the risk is hardly appreciated, and this practice would be justified by the compensation of the false negative results. The tracking out at intervals of 5 years offers, also, protection. The interval of screening realisation remains a debate subject.

Generally, is observed that the efficiency of the tracking down is appreciable, indifferently of the rhythm or on the debute age. The programmes of tracking down in Finland (surface biopsies effectuated at 5 years to the females aged between 30 and 55 years) and Down Countries (interval of 6 years, ages between 30 and 72 years) permitted the reduction of 3 times of the mortality through cervix cancer between 1962 and 1987.

2. The cervicography

Is a method used as adjuvant of the cytology with the purpose of growing the efficiency of the cervical screening. Adolf Sall (1981) is the colposcopist that imposed a photographic equivalent with the help of which are realised detailed images of the cervix and of the superioare part of the vagina after the badionation with acetic acid. There are realised two photographs (cervigrams) that may be framed in one of the following 4 categories: negative, atipical, pozitive or not realised from the technical point of view.

The combination of the cytology with the cervicography may increase the interval of the cervical screening. The cervicography is considered as having a higher sensibility than the cytology (1). Also, is considered superior to the tactic of cytology repetition in the purpose of tracking down the dysplasias in the cases with atypia.

3. Colposcopy

The colposcope was invented by Hans Hinselmann in 1925 and was continually perfected, at present there are several variants. It is a binocular surgical microscope adapted to the realization of the inspection of the epithelial surfaces of the inferior reproductive tract, to the investigation and treatment of the CIN. The best increasing for the cervix examination is of 10 to 16 times. The filters are usefull for the appreciation of the vascularization.

The main indication of the colposcopy is the analysis of the cases with abnormal surface biopsies. There are evaluated the following epithelium characteristics:

- The surface contour;
- Regular or irregular aspects of the vascular network;
- The blood vessels caliber, the intercapilar distance, the atypical blood vessels;
- ZT (the transition zone) vizualized as a whole.

There may be realized biopsies (colposcopic direction) and evaluations of the endocervical canal. The colposcopy examination has to be ended through a carrefull registration of the obtained data and of the indicated therapeutic protocole. The main purpose of the colposcopy method is the realisation of the differentiation between the preinvasive, noninvasive and invasive lesion.

The diagnosis is finalised using the data provided by cytology, colposcopy, biopsy conducted through colposcopy and the evaluation of the endocervical canal, the hystology being the last arbitrator.

The modern colposcopy is characterised also through the introduction of a simplified terminology, approved in 1990 by the International Federation of Cervix Pathology and
Colposcopy. The colposcopy images have 3 characteristics: the epithelium colour, the surface character and the arrangement of the vascular bed. The new colposcopy terminology includes:

- Normal colposcopy images (epithelium squamous, columnar, ZT);
- The abnormal colposcopy images at the level of the ZT (white epithelium, punctuation, mosaic, leucoplasia, iodine-negative epithelium, atypical blood vessels) or outside the ZT;
- Invasive carcinoma;
- Non-concludent images (the squamo-columnar junction invisible, inflammations or severe atrophias);
- Different aspects (micropapillary surfaces, atrophias, ulcerations etc.).

The colposcopy and histologic examination constitutes the main elements in the orientation of the therapeutic attitude. The data amplification regarding the incidence of the HPV infection and the colposcopy modifications that are induced determined the creation of new sections in the colposcopy morphology.

The subclinical infection is more frequent than the condilomatosis and determines aspects that are similar to the ones observed in the CIN. The histologic exam is the final decisional factor in the diagnosis of the cervical lesions. An experimented colposcopist doesn't have to assume the histological diagnosis without passing it through its own filter.

4. HPV in the cervix screening programme

The tracking out of the ADN-HPV was possible, initially, through the Southern method (1975). Developing the ADN technology permitted the characterisation of the numerous types of HPV, approximatively 20 among them being identified at the level of the human genital tract. The significative correlation of the viral types characterised through increased risk, CIN 3 or the invasive cancers, suggest the fact that the screening of the ADN-HPV could be effectively in the cancer prevention (2).

The traditional methods of the nosologic diagnosis are less applicable in the case of the HPV infections. It is considered that to obtain fiable results is necessary the use of at least 3 method. „Southern blot” is the most fiable method, but, necessitates important quantities of biologic material and several realisation stages: the ADN extraction, the enzymatic digestion, electrophoresis, the transpher on the membrane, hybridisation. The in situ hybridisation is a simple method, but with reduced sensibility (3).

PCR (the chain reaction of polymerization) is the method in which after the extraction of the ADN is amplified (in vitro) a nucleotidic sequence with the help of polymerisation. It follows the transpher on the membrane and the hybridisation. Using the PCR method, the HPV 6 type was isolated in a great number of cases with CIN 1 and with a reduced risk of the progression. CIN 3 was dominated by the HPV 16 type, alone or in association with other types.

The main conclusion of the quoted study is the belief that a good discrimination may be realised combining the detection and the viral tipisation with the cytology. In different analyses, the lesion's progression was in relationship with the HPV detection or with the presence of the moderate or severe dysplasias (4). PCR may be used in the following of the treated cases evolution. The method is complementary to the cytologic screening, offering a great sensibility in detecting the cases that present the recurrence risks. It is hoped that the research of the factors that determine the viral persistence to contribute at the formulation of new principles for the prevention of the cervix cancer.

The prognosis signification of the HPV in the cervix tumors deserves considerations, although the data regarding the value of this test, as mentioned, are controverted. Despite the fact that the detection of the infections with HPV- major risk has the potential of prevention of the cervix cancer, this information isn't available for the diagnosis and treatment of the precursor lesions. A reason of this discordance is constituted by the lack of a detection kit of the HPV that allows the identification specific for each viral type.

Moreover, the validity of a certain screening system for the precursors of the cervix cancer is hard to define. Using the comercial detection systems of the HPV (for example: “hybrid capture assay”) is simpl and may be realised in laboratories with everyday activities. This technique is considered very useful in the identification of the CIN II and CIN III.

The epithelial anomalies induced by the HPV varies in intensity, manifestations, answer at treatment and risk of cancerization. So, there can not be formulated general treatment scheme. The cervix cytology is an instrument of screening (asymptomatic cases) conducted especially for the detection of the precursors. The positive test certifies the presence of the viral persistence.
risk, its degree being appreciated through the diagnosis methods(3).

Testing the presence of the HPV has the potential of selection of the patients with abnormal surface biopsy healed by those with recurrent or residual dysplasias. This aspect may be clinically important to avoid conisations in the cases with negative HPV test.

In conclusion, we may underline that the epidemiological studies or viral ones have as a common denominator for the appreciation of the cancerous potential of the cervical lesions the presence of the HPV types with a high risk. The morphologic aspects are less usefull in the appreciation of the progression to invasion. This conducts to the conclusion that the perspective case selection is based on the evaluation of the HPV. Using the colposcopy and the histologic exam is imposed by the selection through the ADN-HPV testing.

CONCLUSIONS

- The screening of the cervical carcinoma is based on the cytologic exam Babeş-Papanicolau (in the countries where it became accesible, the mortality was reduced with 40-80%).
- The cytologic exam is linked to the HPV tipisation (is recommended a cytologic exam, associated with the HPV testation once at 2 years in females over 20 years)
- Unfortunately, România is situated on the second place in Europe in the morbidity and on the first place in the mortality through cervical cancer
- The antiHPV vaccination comes as a partner in the screening programmes to reduce the incidence and the mortality through the cervical cancer and represents the main modality of primary profilaxis of the affection.
- A vaccine that aims at the relevant pathogenic types of HPV is expected to offer an important reduction of the incidence in the case of those diseases.

BIBLIOGRAPHY