

INDIVIDUALIZED TREATMENT OF PREINVASIVE LESIONS OF THE CERVIX

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Abstract: The management of cervical preinvasive lesions in primary medical practice is characterized by a wide variety of attitudes, objectives and therapeutic decisions. The purpose of the study. To supply new landmarks referring to the preinvasive lesions of cervical cancer from the perspective of the clinician. Materials and methods. The study was made on a number of 16732 patients who were monitored comparatively in the Family Planning offices in the counties of Iași and Buzău, between 2007 and 2011. Results and discussions. The treatment was applied according to the type of the lesion. Conclusions. The individualized treatment of the preinvasive lesions of the cervix targeted the destruction of the pathogenic agent and the infected tissues and caused a fibroblast proliferation and re-epithelisation.

INTRODUCTION

If we want to have a correct conduct in the preinvasive lesions of the cervix we must have accordance between the colposcopic pictures, the cytologic reflection and the histopathologic substratum. We also need experiences specialists who are able to individualize treatment for every clinical form, to consider the risk factors, the way of communicating with the patient and the possibilities of monitoring her. It is preferable to have a more "aggressive" conduct with the patients who cannot come to a periodical consult, or with the ones having a precarious socioeconomic level. Without standardizing the conduct, we present therapeutic possibilities in different lesions of the cervix.

PURPOSE OF STUDY

The management of the preinvasive lesions of cervical cancer in primary medical practice is characterized by a wide variety of attitudes, objectives and therapeutic decisions. There is a tendency to use the paraclinical data excessively for establishing the diagnosis, and also to misuse the diagnosis methods in first-line therapy, and this imposes the re-analysis of an effective strategy, based on evidence, of diagnosis and treatment.

The present work wants to establish new landmarks referring to the preinvasive lesions of the cervical cancer from the perspective of a clinician; to facilitate the access to health services, including family planning, by using the primary care system – which is one of the main goals meant to improve the quality of life for all the people. We want to prove the effectiveness of the balance cost/benefit by introducing the preventive prophylactic conduct in Family planning offices.

MATERIAL AND METHODS

The study was performed on a number of 16732 patients that were monitored comparatively in Family Planning offices in the counties of Iași and Buzău, between 2007 and 2011. The medical treatment, which can be local and general, depending on the pathogenic agent identified, was established as it follows: after a case is accepted for study it is assessed, and a Papanicolaou test is performed, recommending a local trophic therapy and a medical check-up every 6-12 months, or minimally invasive surgical treatment: electrocautery or electrocoagulation with monopolar electrode, if the symptoms persist and the PAP test is changed. The purpose of these methods of treatment is to destroy the pathogenic agent and the infected tissues and to cause a fibroblastic proliferation and re-epithelisation.

RESULTS AND DISCUSSIONS

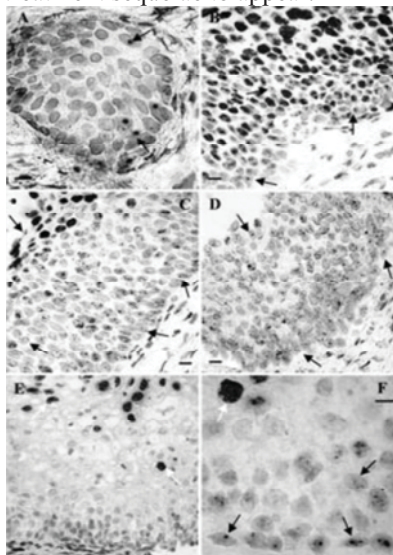
Depending on the type of the lesion identified we applied the following therapeutic schemes:

Lesions type CIN1 (cervical intraepithelial neoplasia)

Under the name LSIL/CIN1 (low grade squamous intraepithelial lesion) you can find: simple dysplasia and plan condiloma, which reflects a benign process, associated to the cervical infection with a heterogeneous group of HPV (1, 4, 5).

The main data that must be considered when choosing the therapeutic alternatives are (7):

- the degree of uncertainty of the diagnosis;
- the biologic potential of spontaneous regression without treatment and a decreased rate of progression towards neoplasia;
- the absence of a certain method for identifying the CIN lesions, which will regress spontaneously, persist or progress;
- the quality of the cooperation with the patient for a systematic surveillance;
- the possibility to develop a cervical lesion after regression; the risk is appreciated to be 23 times higher when compared with patients without cervical lesions;
- the age of the patient and the size of the lesion;
- the patient' s anxiety and the medical responsibility;
- the possibility for post treatment sequelae to appear.



Picture 1. Perinuclear cytoplasmic vascularisation, cytoplasmic membrane thickening, presence of nuclear atypia (big nucleus, increased nucleo-cytoplasmic ratio, hyperchromasia, irregular nuclear membrane, anisocytosis, koilocytosis) (personal collection – Dr. Dorin Neacsu)

Conduct

There are two options: supervision of the patients with treatment or without treatment.

A. Supervision of the patients without treatment.

It is an option that must be supported by a complete clinical and cyto-colpo-histologic balance sheet, in relation with the clinician' s experience and the patient' s anxiety from diagnosis, the lesional prognosis.

Supervision of the patient and treatment timing:

- Avoids the useless treatment;
- Consists of repeated cytologic and colposcopic examinations;
- Does not confer prognostic safety for the patients;
- You can recommend the biopsy to be repeated after 6 months.

The classic protocol of surveillance consists of cytologic surveillance every 6-12 months and an associated cytology-colposcopy also every 6-12 months and determining the ADN-HPV after 12 months from the CIN1 biopsy.

The supervision is recommended to last for 2 years, in which interval there is a spontaneous regression or the lesion progresses to CIN2 or CIN3 (6).

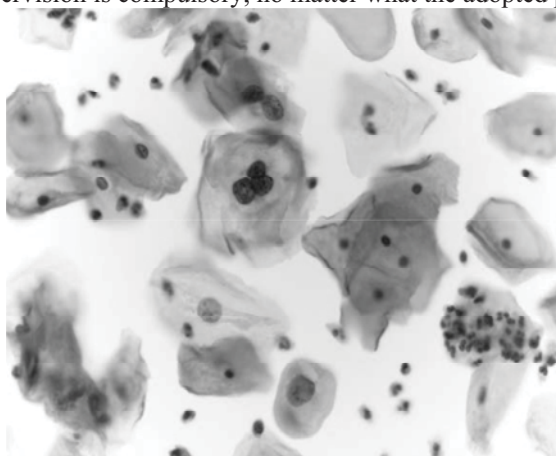
B. Curative treatment

It has as purpose to make sure there is a high rate of long term healing, to reduce the risk of progression of a lesion and also to protect the patient's psychic.

This treatment recommends the destructive methods: electrocautery, cryotherapy, laser vaporization, excisional procedures like cone biopsy.

Cone biopsy has a more restricted indication in CIN1 type lesions, but in the cases where there are differences among the cytologic, colposcopic and biopsic diagnosis, most authors recommend exeres, and the histopathologic diagnosis to be repeated (5,7). The same conduct is recommended if CIN1 lesions persist after applying another local treatment or if there are any recurrences.

Postoperative supervision is compulsory, no matter what the adopted protocol is.



Picture 2. Lesions CIN2 and CIN3 type (5, 7)

Altered stratification with the loss of cell polarity; alteration of architecture in the whole thickness of the epithelium; basophilia and alteration of the cytoplasmatic difference; hyperchrome and hypertrophic nuclei; ratio nucleus/cytoplasm in favour of the nucleus; frequent mitoses in the deep and intermediate layers; integrity of the basal membrane.

CIN2 and CIN3 type lesions are also called high degree lesions; they group the moderate and severe dysplasia. These lesions have the highest degree of progression to an invasive cancer. Their frequency increased significantly for the age group 20-29 years old when compared to the age group over 40; it is also unanimously accepted that HPV positivity is over 76%, 8 oncogenic types being incriminated: HPV-16, 18, 31, 33, 35, 45, 52, 58, the most frequent being HPV-16 (2,10).

Cytology can identify smears like: ASCUS (Atypical squamous cells of undetermined significance), LSIL (Low grade squamous intraepithelial lesion), but the most frequent is HSIL (High-grade Squamous Intraepithelial Lesion).

The natural evolution of intraepithelial lesions of high degree that are not treated can lead to regression, persistence, progression.

Badea⁽¹⁴⁾ presents the result of the studies he published, reviewed and quoted in his argument, for Bethesda conduct recommendations, referring to the evolution of CIN2 and CIN3 lesions that are not treated:

	Regression	Progression	Persistence
CIN2	43%	22%	38%
CIN3	32%	14%	56%

We can conclude that CIN lesions of high degree have a higher evolution to progression or persistence rather than to regression. Thus we are justified to recommend an interventionist conduct both for CIN2 and CIN3 type lesions that will be able to perform ablation of the pathologic epithelium.

Conduct

The theory according to which the excision of the lesion is the only fair treatment is unanimously accepted. This ablation can be made by using many procedures (3):

A. Cone biopsy

The advantages of choosing cone biopsy are:

- Histopathologic examination of the whole affected area, avoiding the risk of a poor harvest of the tissue specimen from the peripheral area of the lesion and skipping the analysis of a micro-invasive or invasive lesion;
- You avoid the incomplete, local treatment of a sub-evaluated lesion;
- The lesions are extended on a wide area and/or ascended towards the endo-cervix;
- A micro-invasion is suspected based on the previous results of cytology, colposcopy and biopsy;
- It reduces “cervix mutilation” at minimum;
- It protects the function of the endocervical glands and keeps tissue around the endocervical canal;
- It solves the cases that did not respond to other local destructive therapies;
- It can eliminate microinvasion;
- The necessary equipment is cheap, the cost is reduced and it can also be performed outpatient, with local anaesthesia.
- The relapses are avoided if the intervention is performed correctly.

B. Cervix amputation

This extensive technique is indicated when there are also other pathologic elements associated such as:

- cervix lengthening;
- hypertrophy of the vaginal portion of cervix;
- cervix with old, irregular ruptures;
- second degree prolapse that needs to be corrected.

C. Total hysterectomy

Total hysterectomy made the vaginally or abdominally is a rare indication in CIN3 lesions. It is justified in certain circumstances:

- associated benign gynaecologic pathology, uterine fibroids, endometriosis, uterine prolapse;

- microinvasive carcinoma on the cone biopsy piece;
- the difficult supervision of the patients and/or inefficient communication with them;
- extended lesion on the vaginal vault;
- cancerophobia.

D. Systemic medication for increasing immunity (Isoprinosine) with a role in increasing the local T lymphocytes.

Supervision

No matter what therapeutic method the doctor applies, the patients must be instructed to respect the following indications:

- sexual rest for 6 weeks;
- external local hygiene without vaginal lavages;
- avoid physical effort and prolonged standing;
- medical check-up after 6-8 weeks.

The patients must also be informed that in the first 10-12 days they will notice a special vaginal discharge, sometimes with an unpleasant smell, which is part of the healing process of the destroyed tissue that covers with a crust a part of the exo-cervix. It will be eliminated at the end of this interval when it is possible to cause a small bleeding that will not last long. If the bleeding is more consistent the patient must go to the doctor for a consult.

Post-treatment supervision

All the methods used in treating CIN lesions have a margin of error; that is why the patient supervision plays an essential role in assessing the healing and detecting some possible residual or recurrent lesions that are susceptible to become invasive cancer.

The residual lesion is the persistence or appearance of CIN type lesion in the first 12 months after treatment, and the recurrent lesion is the appearance of a lesion many years after a conservative treatment is performed.

There are many supervision protocols, but they have not made a randomized prospective study which to compare their effectiveness.

In order to be realistic, a protocol must consider the therapeutic results in CIN lesions, the possibility of having regular medical check-ups and also compliance (the interest manifested by the patient for a systematic supervision).

The supervision of the cases must be done by clinical, cytologic and colposcopic examination.

The first cytologic examination is recommended to be made after 12 weeks. If it is performed earlier, the metaplasia reparatory processes can be mistaken for some pathologic elements. It is also recommended for the patient to have a colposcopic examination in order to establish the location of the new squamo-cylindric junction. If it is ascended in endocervix it is recommended to make micro-colpohysteroscopy or endocervical curettage of control.

The frequency of the following examinations varies depending on author: 1 check-p every 6 months – minimum 3 years, 3 check-ups every 3 months, then every year for 5 years, after 3 months, 6 months, then every year etc., until obtaining 3 negative cytologic results. Some authors also recommend ADN-HPV at 6 months after treatment (8,10,11,12).

Treatment of cervical preinvasive neoplasias for the patients infected with HIV (Human immunodeficiency virus)

Preinvasive and invasive cervical neoplasia in patients infected with HIV is treated generally after the same principles and protocols, but still there are certain particularities because of the

way the lesions evolve, especially prognosis, because the number of spontaneous regression of dysplasia is small, and that of recurrence and evolution to CI is much bigger.

The standard treatment by ablation is recommended to be first line in LSIL lesions associated with HIV-HPV. Excisional procedures have minimum benefit, because of the high rate of recurrence. Probably immunosuppression makes healing difficult, and the persistence of HPV infection is responsible for the recurrence of dysplasia lesions.

After excision, 77% out of 43 de patients HIV positive and 19% out of 103 seronegative patients have recurred. In the cases when, after excision, the margins of the specimen are positive, recurrence is 100% for the patients who are HIV positive and 32% for the seronegative ones.

Globally, the rate of recurrence of dysplasia for the patients who are HIV positive is of 62% after the first treatment, 43% after the second treatment and 50% after the third excisional treatment (9).

These adjuvant therapies were proposed:

- 5-Fluorouracil topic (5-Fu) after LLETZ electroexcision (large loop excision of the transformation zone) - recurrence 28% for short term while 47% of the patients treated only with LLETZ;
- Imunomodulator Imiquimod (INN) seems to be more effective as topic treatment;
- HAART (highly active antiretroviral therapy) seems to be the medical therapy that influences the most the evolution of cervical dysplasia for the patients with HIV by partially re-establishing their immunocompetence.

The multivariable analysis of the results of a French study showed that the patients who are not treated with HAART have a risk of recurrence that is twice as high after an excisional treatment; on the other hand this association can increase the global prevalence of CIN for these patients by increasing the life span.

Local medication:

- Antimitocites: Podofilin, Condyline, Colchicine
- Destructive chemical agents: trichloroacetic acid, dicloroacetic acid, nitrous oxide;
- Antiviral: Interferon - topic application, intralesional Cidofovir.

CONCLUSIONS

No matter what the applied treatment, every category of patients must be monitored systematically, at an interval of maxim three months.

We noticed that, without organizing and selecting the patients with risk, with preinvasive cervical lesions, so that they can be able to benefit from a confirmation of the diagnosis by colposcopy, biopsy and/or finding ADN-HPV, we cannot apply a proper conduct in accordance with the consensus guides.

Anti-HPV vaccination can be considered a partner of the screening programme for reducing the incidence and decreasing mortality caused by cervical cancer.

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