The Treatment of the Precursor Lesions of the Uterine Cervix

The Filantropia Hospital Experience

E. Căne[1], MD, I. George[1], MD,
Mioara Ionescu[2], MD, Gh. Peltecu[3], MD, PhD

1. Filantropia Clinical Hospital of Obstetrics and Ginecology, Bucharest, Romania
2. Polizu Clinical Hospital, Bucharest, Romania
3. "Carol Davila" University of Medicine and Pharmacy, Bucharest, Filantropia Clinical Hospital of Obstetrics and Ginecology, Bucharest, Romania

Correspondence:
Gheorghe Peltecu
e-mail: peltecu@dnt.ro

Abstract

Objective: *The aim of the study is to explore the correlation between cytology, colposcopy, HPV status and histopathology in precursor lesions of the cervical cancer.*
Method: *This retrospective study involved a total of 483 women between 19 and 66 years old which undergone NETZ (needle excision of the transformation zone) for cervical dysplasia during 2 years period (2006-2007) in Department of Gynecology, Filantropia Hospital, Bucharest, Romania.*
Results: *Precursor lesions of the cervical cancer are quite frequent among women at fertile age; the highest incidence was between 26 and 40 years old (58,6%). The majority of subjects had low-grade lesions (LSIL) (60,1%). Dysplasia with negative colposcopy is uncommon (2,3%) and usually is correlated with minimal histopathological changes. Among tested patients the great majority were HPV high-risk positive (81,2%) with a direct proportional correlation between severity of the lesion and frequency of the infection. The histopathological examination revealed that the most frequent disorder is CIN II (59,1%); the invasive lesion was identified in 1,3% subjects. The severity of the lesions was directly correlated with age (the mean age of women with inflammatory findings was 33 and with high-grade lesion was 39).*
Conclusions: *Cervical dysplasia is a preneoplastic lesion; cytology, colposcopy, biopsy and also HPV testing are essential investigations.*
Keywords: *cervical dysplasia, cervical intraepithelial neoplasia, colposcopy, human papilloma virus, needle excision of the transformation zone.*

Introduction

Cervical cancer still represents one of the malignancies with high incidence in developing countries while in developed countries this pathology is regressing because of the efficient screening programs. The use of cervical screening leads to increased frequency of cervical preneoplastic lesions. Romania has the highest cervical cancer mortality rate in Europe.

Since 1977, the human papilloma virus (HPV) is recognized as the etiologic agent of the cervical cancer which is a sexually transmitted disease.

There are over 200 types of HPV: high- risk for cervical cancer (16, 18, 31, 33, 35, 45, 51, 56, 58, 59, 68) and low-risk (6, 11, 40, 42-44, 54, 61, 70, 72, 81).

The anti-HPV vaccine made the cervical cancer primary prophylaxis possible. The secondary prophylaxis is also very effective. The cervical dysplasia cure is accurately assessed by the combination of negative Pap smear and negative DNA-HPV test.

The majority of the HPV infections are subclinical and transitory (>80% disappear within 2 years) due to the cellular immune response. After infection, HPV is latent for 2-12 months. The cellular immune response starts in about 3 months since the inoculation of infection and eliminates the virus or suppresses it down to undetected levels.

In some subjects, the infection can cause warts (condyloma) and low-grade cervical lesions. Sometimes, in certain cases, the high risk HPV types (16, 18, 31, 45) can be persistent and progress to high-grade lesions and cervical cancer in few years[1]. The mean interval of natural progression to invasive cancer is about 13 years.

Diagnosis

Diagnosis of preneoplastic lesions is based on cytology, colposcopy and the final diagnosis is established by histopathological examination of the tissue sample.

Cytology examination. Bethesda System

The Bethesda System and its 2001 revisions aim to simplify Papanicolaou (Pap) smear reporting and to make it more reproducible (Table 1)[4].

Colposcopy

Colposcopy identifies a series of lesions associated with preneoplastic cervical lesions (acetowhite changes, leukoplakia, punctation and mosaic).

Acetowhite changes represent the white zone that appears after treatment of the cervix with acetic acid (3-5%). The acetic acid does not affect the mature epithelium rich in glycogen, but colors the dysplastic epithelium in white because of the high protein content. The metaplasic epithelium is very thin - unlike CIN which becomes white - so it will become grey and translucent. Leukoplakia (white epithelium after acetic acid application) –hyperkeratosis - is the most frequent cause is HPV infection. Punctations (a zone of red dots - dilated capillaries which ends to the surface) in well circumscribed areas indicates an abnormal epithelium, most frequent CIN. Mosaicism (an abnormal pattern of interconnecting small blood vessels) is associated with high grade lesions – CINII/III[5].

Histopathology

In mild dysplasia (CIN I) only few cells in the basal third of the epithelium are abnormal, while in moderate dysplasia (CIN II) the abnormal cells involve about 2/3 of the thickness of the surface lining of the cervix. In severe dysplasia or carcinoma in-situ (CIN III) the entire thickness basal epithelium is abnormal. Spontaneous regression rate of CIN 1 is about 60-85%. The regression usually solves in about 2 years. All lesions CIN II and III need treatment. The progression CIN2 to CIS is 20% and invasion in about 5% of patients[6].

Management of Precursor Lesions of Cervical Cancer

There are few subgroups of population for whom the management is a little bit different because of their characteristics: adolescents (aged <20), pregnant women, postmenopausal women and immuno-compromised women. The adolescents have a higher prevalence of the HPV infection, more frequent minor lesions and a very low risk of cervical invasive cancer compared to older patients because most of the HPV infections disappear spontaneously in 2 years time and have little short term significance. Therefore, the colposcopy should not be performed as a first line investigation. During pregnancy, endocervical curettage is forbidden, while the colposcopic guided biopsy is indicated for HSIL or when invasive cancer is suspected. Colposcopy is a reasonable investigation for the low risk pregnant women[7].

ASC-US

High risk DNA-HPV testing, repeated cervical smear and colposcopy are all acceptable methods in the management of ASC-US lesions for the patients aged over 20 years. The patients ASC-US and DNA- HPV negative for the high risk types will be followed up at 12 months. Patients with ASC-US and DNA-HPV positive should be treated as the patients with LSIL and evaluated by colposcopy. Endocervical curettage is preferred for the patients without colposcopic lesions or with unsatisfactory colposcopy. The management after colposcopy for ASC-US/DNA- HPV positive patients, which do not have CIN diagnosed, consists in repeating the DNA-HPV test every 12 months or repeating Pap smear every 6-12 months. DNA-HPV testing is not recommended earlier than 12 months. Repeating cytology at 6 months is indicated until two consecutive negative results are obtained, then normal follow up is recommended[8]. Colposcopy is recommended for patients with ASC-US or severe lesions at the repeated testing, without taking into account DNA- HPV status.

Excisional diagnostic procedures are not recommended in the treatment of the patients with ASC-US as an initial diagnosis, in the absence of CIN II/III histopathological diagnosis.

ASCH

The management of ASC-H implies the colposcopic evaluation from the beginning. If there is an evident colposcopic lesion, biopsy is recommended. For the patients without CIN II/III the follow up is acceptable by testing DNA- HPV every 12 months or repeating cytology every 6-12 months. If DNA -HPV testing is ne-

Table 1

The 2001 Bethesda System for Reporting Cervical Cytologic Diagnoses[8]

Specimen type
Conventional smear (Pap smear)
Liquid-based preparation

Specimen adequacy
Satisfactory for evaluation
Unsatisfactory for evaluation

Interpretation/result
A. Negative for intraepithelial lesion or malignancy
1. Microorganisms (Trichomonas, Candida, Gardnerella etc.)
2. Other non-neoplastic findings (inflammation or reactive cellular changes; radiotherapy; IUD; atrophy, glandular cells status post hysterectomy)

B. Other endometrial cells (in woman ≥40 years of age)

C. Epithelial cell abnormalities:
1. Squamous cell
a. Atypical squamous cells (ASC)
- ASC of undetermined significance (ASC-US)
- ASC, cannot exclude high-grade squamous intraepithelial lesion (ASC-H)

b. Low-grade squamous intraepithelial lesion (LSIL) encompassing: HPV, mild dysplasia, and CIN
c. High-grade squamous intraepithelial lesion (HSIL) encompassing: moderate and severe dysplasia, carcinoma in situ, CIN II, and CIN III Squamous cell carcinoma
2. Glandular cell
a. Atypical glandular cells (AGC) specify endocervical, endometrial, or glandular cells not otherwise specified (NOS)
b. Atypical glandular cells, favor neoplastic specify endocervical or not otherwise specified (NOS)
c. Endocervical adenocarcinoma in situ (AIS)
d. Adenocarcinoma

D. Other malignant neoplasms

gative or two consecutive smears are negative, return to normal follow up is recommended.

■ **LSIL**

Colposcopy is recommended from the beginning for LSIL cytology. Endocervical curettage is preferred for the patients without colposcopic lesions or with unsatisfactory colposcopy. After colposcopy, for the patients with LSIL without histopathological CIN II/III, the recommended attitude is DNA-HPV testing at every 12 months or repeated cytological at 6-12 months. If the DNA- HPV testing or two successive cytological results are negative, normal follow up is recommended. If HPV DNA testing is positive or at least one cytological testing result is ASC-US or higher, colposcopy has to be repeated.

■ **HSIL**

For HSIL lesions the risk for preinvasive disease is 70-75% and for invasive disease is 1-2%[8]. So, colposcopy and biopsy are indicated ab initio. Endocervical evaluation (cytological, colposcopic or curettage) is mandatory, excepting the case when the excision biopsy is taking into account. When colposcopy and endocervical cytological evaluation are negative, the diagnosis of HSIL is reconsidered. If the cytological results persist, excisional biopsy is recommended[8].

■ **AGC**

Fractioned curettage (endocervical and endometrial) and colposcopy are recommended for the patients with AGC/AIS aged over 40 years old. Also endometrial curettage is to be done for the patients over 40 years old with risk factors for endometrial cancer. DNA -HPV testing is not routinely recommended. The most frequent viral types associated with endocervical adenocarcinoma are 16, 18 and 45.

Surgical treatment

Precursor lesions of the cervical cancer can be treated through local destructive methods or excision. The local destructive methods (cryotherapy, electrodiatermy, laser vaporization) are no more a standard therapy because they do not allow the histopathological examination of the specimen.

Excisional methods are loop/needle electrosurgical excision procedures, laser excision and cold knife excision. Loop electrosurgical excision (LEEP) can be done as an out patient procedure, with local anesthesia. Needle electrosurgical excision of the transformation zone (NETZ) has the advantage of excising the lesion as a single piece, easier to be histopathologically assessed and allowing the optimal tailoring of the specimen to be resected (height and wide) (Figure 1)[8]. The use of cold knife leaves the borders of the specimen clean, but the complications are more frequent. Postoperative complications are hemorrhage, infections and cervical stenosis, as well as the rise of the risk for premature delivery in a subsequent pregnancy (if the specimen height is over 1.5 cm). The frequency of these complications is very low[9,10].

Cold knife conization has the advantage of preserving the specimen intact for the histopathological examination and allowing for a good evaluation of the tissue margins. Although the cure rate is the same as with the electrocauter use, the frequency of complications is double.

Total hysterectomy, abdominal or vaginal, represents a very rare indication in the therapy of precursor lesions of the cervical cancer. It is the choice when the lesion wasn't totally resected, persistent abnormal Pap smear, lesion extended to the vaginal vault, associated gynecologic pathology, difficult follow up after conization.

Clinical study

Background

Despite of many studies that analyze the correlation between cytology, histopathology and colposcopy in precursor lesions of the cervical cancer, the results were contradictory. Our study tries to establish a correlation between cytological abnormalities and colposcopical and histopathological findings.

Method

The aim of the study is to explore the correlation between cytology, colposcopy, HPV status and histopathology in precursor lesions of the cervical cancer. This retrospective study involved a total number of 483 women between 19 and 66 years old which undergone a NETZ procedure (needle excision of the transformation zone) for cervical dysplasia during 2 years time (2006-2007) in Department of Gynecology, Filantropia Hospital, Bucharest, Romania.

Out of a total of 483 women selected in the study, 328 charts were reviewed for cytological data, and 329 for colposcopic data. DNA-HPV was available for only 88 cases of which over 80% were HPV high-risk. Histopathological findings were available for 309 patients.

Results

The study group was divided by age using intervals of 5 years. The maximal incidence was between 26 and 40 years old - almost 60% of the study group (Figure 2).

For cytology the Bethesda System was used and the patients were as-

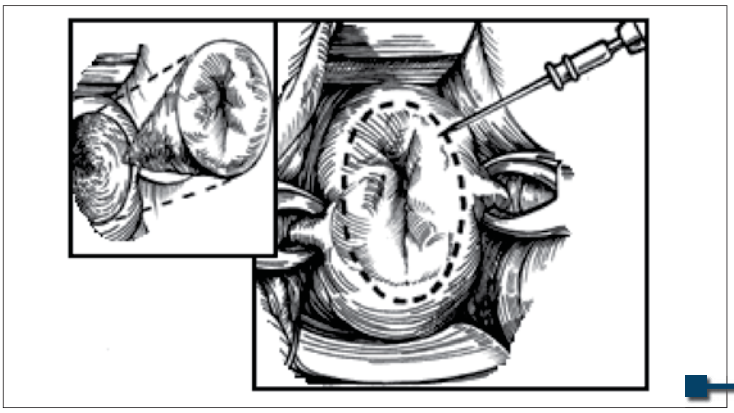

Figure 1. Needle excision of the transformation zone (NETZ)

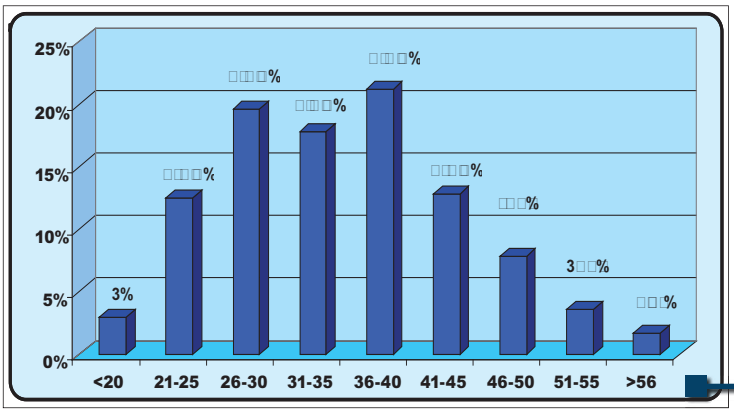

Figure 2. Study group. Age distribution

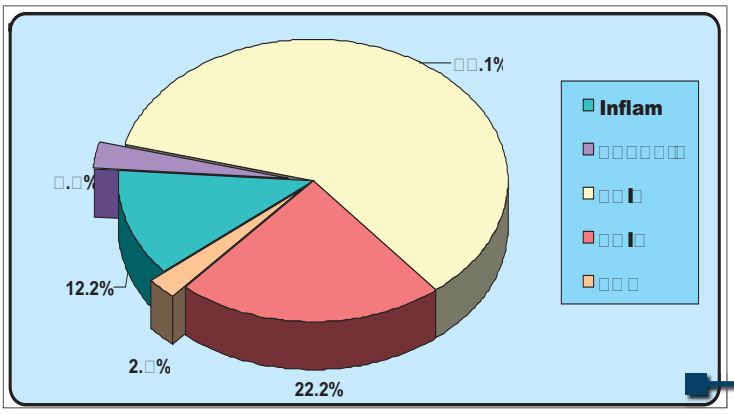

Figure 3. Bethesda System Distribution

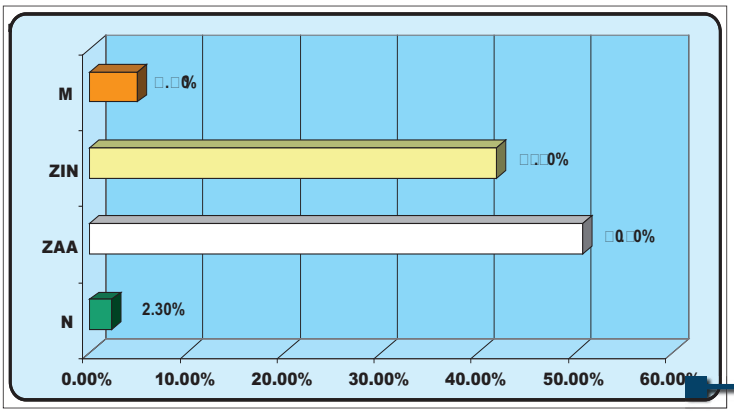

Figure 4. Colposcopical abnormalities

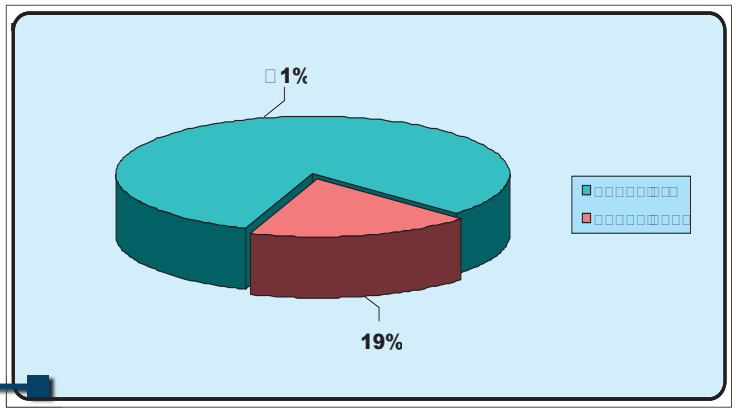

Figure 5. HPV status

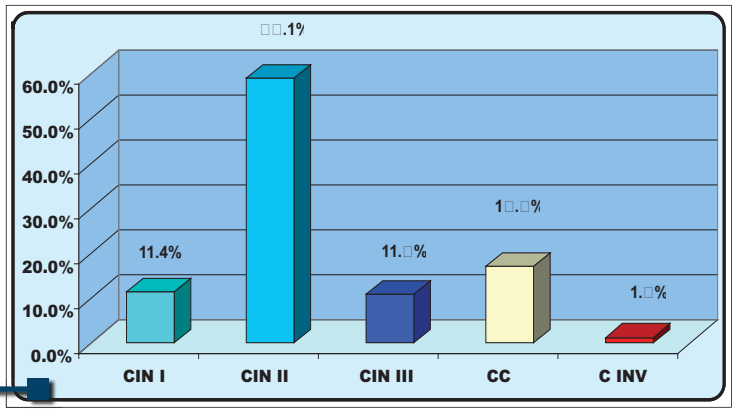

Figure 6. Distribution of histopathological findings

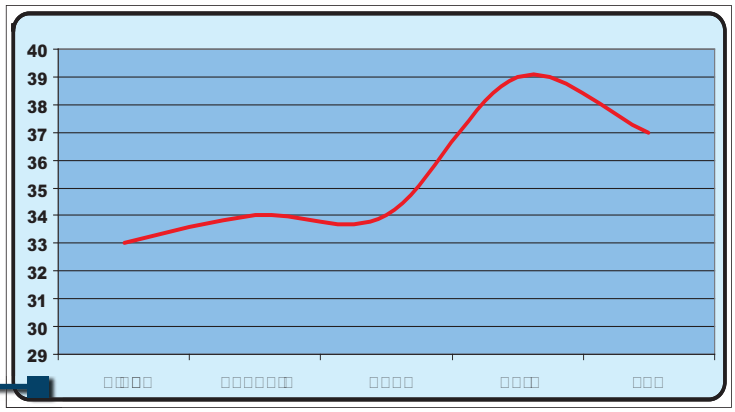

Figure 7. Correlation between age and cytology

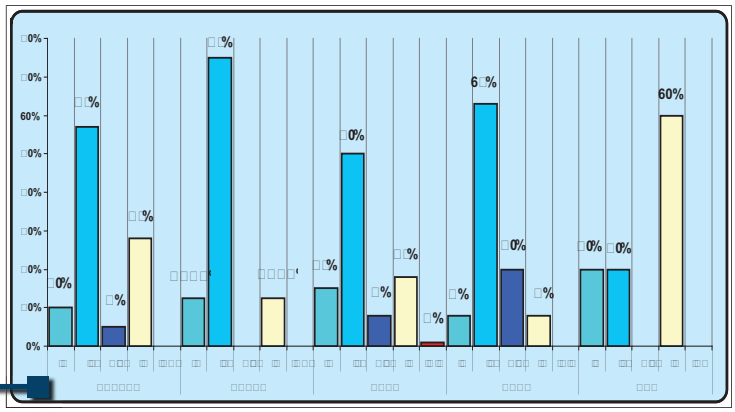

Figure 8. Distribution of histopathological findings by cytology

signed in the following categories: Inflammation, ASC-US/H, LSIL, HSIL and AGC. The LSIL category was the most frequent (about 60%) and ASC-US/H, and AGC had the lowest incidence (Figure 3).

Colposcopical findings were assigned in four groups: normal examination, acetowhite zone (AWZ), iodine negative zone (INZ) and epithelial metaplasia (M). We found that only few patients had a normal colposcopy (Figure 4).

Among tested patients the great majority were HPV high-risk positive (about 80%) (Figure 5).

Histopathological findings were distributed in five categories: CIN I, CIN II, CIN III, chronic cervicitis (CC) and invasive carcinoma (INV C). The most frequent disorder was CIN II (59,1%) while invasive carcinoma was a rare finding. CIN I and CIN II lesions were found out in equal proportion - about 11% (Figure 6).

Age distribution of the cytological lesions analyze reveals a direct correlation between the mean age and the severity of the lesions. Mean age of women with inflammatory changes was 33 years old and with HSIL was 39 years old. ASC-US and LSIL categories had intermediate values - 34 years old (Figure 7).

When studied the correlation between histopathological examination and cytology, the most frequent type of lesion was CIN II; CIN I vary between 8 and 15% if we exclude the AGC category which had too few cases to have a statistical significance. The frequency of CIN III is higher for advanced cytological findings: 5% CIN II for inflammation, 8% for LSIL and 20% for HSIL (Figure 8).

HPV infection was studied in the context of cytological findings. It was shown that there is a higher percentage of infected subjects in the category of advanced cytological lesions. So the numbers are: 75% for ASCUS, 80% for LSIL And 100% for HSIL (Table 2).

Colposcopical changes were separated in four categories: normal colposcpy (N), acetowhite zone(AWZ), iodine negative zone (INZ) and metaplasia (M). We found a greater frequency of changes that suggest

Table 2

HPV status and distribution of histopathological lesions on cytology categories

HPV	Inflammation	ASCUS	LSIL	HSIL
Pozitive	73%	75%	80%	100%
Negative	27%	25%	20%	0%

dysplasia - acetowhite epithelium and iodine negative zone (Figure 9).

Conclusions

Cervical dysplasia is a pre-neoplastic lesion characteristic for fertile age; the maximal incidence was between 25 and 40 years old (58.6%).

The majority of subjects had low-grade lesions (60.1%).

Dysplasia with negative colposcopy is infrequent (2.3%) and usually is correlated with minimal histopathological disorder.

Among tested patients the great majority were HPV high-risk positive (81.2%) with a direct proportional correlation between severity of the lesion and frequency of the infection. The histopathological examination revealed that the most frequent disorder is CIN2 (59,1%); the invasive neoplasia was identified in 1,3% subjects. The severity of the lesions is directly correlated with age (the mean age of women with inflammatory findings was 33 and with HSIL was 39). ■

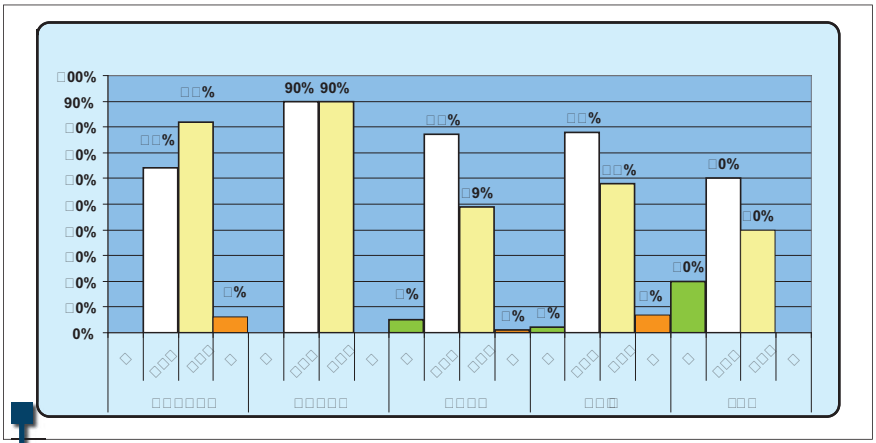

Figure 9. Colposcopic lesions and cytology

References

1. Woodman C, Collins S, Winter H et al. Natural history of cervical human papillomavirus infection in young women: a longitudinal cohort study. Lancet 2002, 357, 9271, 1831-6.
2. Gravitt PE, Jamshidi R. Diagnosis and management of oncogenic cervical human papillomavirus infection. Inf Dis Clin N Am 2005; 19:439-458.
3. Fehrmann F, Laimins LA. Human papillomaviruses: targeting differentiating epithelial cells for malignant transformation. Oncogene 2003; 22:5201-5207
4. Solomon D, et al. The 2001 Bethesda System: Terminology for Reporting Results of Cervical Cytology, JAMA, April 24, 2002, Vol. 287, No. 16, 2114-2119.
5. Addis I, Hatch K, Berek J. Intraepithelial Disease of the Cervix, Vagina, and Vulva in Berek & Novak's Gynecology 14th ed, 2007, 576-8.
6. Jill Koshiol, Lisa Lindsay, Jeanne M. Pimenta. Persistent Human Papillomavirus Infection and Cervical Neoplasia: A Systematic Review and Meta-Analysis. Am J Epidem 2008 168(2): 123-137.
7. Wright TC Jr. Massad LS, Duton CJ. 2006 consensus guidelines for the management of women with cervical intraepithelial neoplasia or adenocarcinoma in situ, Am J Obstet Gynecol. 2007 Oct;197(4): 337-9.
8. Ana-Cristina Anton, Peltecu Gh. Leziunile precursoare ale cancerului de col uterin în Tratat de chirurgie. Vol. V Ginecologie, coordonator Peltecu Gh, 2008: 101-112. Sub redacția Irinel Popescu, Editura Academiei Române, București.
9. Sadler L, Saftlas A, Wang W et al. Treatment for Cervical Intraepithelial Neoplasia and Risk of Preterm Delivery. JAMA. 2004;291:2100-2106.
10. Ferenczy A, Choukroun D, Falcone T et al. The effect of LEEP on subsequent pregnancy outcome. North American Experience. Am J Obstet Gynecol 1995; 172: 1246-50.
11. Garcia F, Saslow D. Prophylactic Human Papillomavirus Vaccination: A Breakthrough in Primary Cervical Cancer. Prevention Obstet Gynecol Clin N Am 34 2007: 761-776.
12. Saslow D, Castle PE, Cox JT, et al. American Cancer Society guideline for human papillomavirus (HPV) vaccine use to prevent cervical cancer and its precursors. CA Cancer J Clin. 2007; 57: 7-28.