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GRADING THE SEVERITY OF PREINVASIVE CHANGES OF THE UTERINE CERVIX BY COLPOSCOPY AND EXFOLIATING CYTOLOGY

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Summary. *Colposcopy is a subjective diagnostic method with high sensitivity (96%) and low specificity (57%). Because of low specificity, the scoring system for colposcopic findings is important when deciding on the necessity of cervical biopsy, and it contributes to the decreasing of unnecessary biopsy. The colposcopic scoring system and the expected histopathological findings showed a good overall agreement (76%) with the highest value (90.32%) in the group of HSIL. Exfoliating cytology has low sensitivity (64%) and high specificity (88%) with a low negative predictive value (60%) and a high positive predictive value (90%). An agreement of PAP classification with histopathological classification is moderately good (55.58%). For these reasons, it is necessary to introduce and apply a uniform cytologic-histopathological classification of precancerous cervical lesions.*

Key words: *Colposcopy, cytology, histopathology, precancerous lesion*

Introduction

As it is possible to visualize the uterine cervix, the majority of the changes appearing on this organ can be quickly spotted. However, the incidence of premalignant and even malignant changes of the uterine cervix is increasing.

Cervical cancer is the second most frequent cancer in women (until 1979 it was the first most frequent cancer in Serbia), accounting for 12% of all carcinogenic diseases in women. The frequency of invasive cervical cancer is decreasing and that of carcinoma *in situ* is increasing by 2% a year. Malignant diseases of the lower genital tract account for 63% and the cancer of the uterine cervix accounts for 58.3% of all malignant tumours of the female genital tract (1). It is believed that 2.6% of women with cancer have invasive cervical cancer, and that this disease causes 3-5% of all cancer deaths (2).

According to the World Health Organization (WHO), every year 500,000 women worldwide get cervical cancer and 230,000 of them die because of this disease (3). Standard rates of incidence for this disease are 10-20 in 100,000 population.

In Serbia, approximately 2,100-2,200 women get cervical cancer and 600-650 die from it every year (4). These data fully correspond to the medium incidence of 15-45 women in 100,000 population registered in other European countries (5). Preinvasive changes of the uterine cervix usually appear 10-15 years before the invasive carcinoma. Previously rarely diagnosed in sexually active young women, these changes now have an incidence of 70.8 in 1,000 women under 20 years of age (5).

When changes are diagnosed early, conization is the sovereign method of treatment that enables a 100% cure and preserves fertility. The percentage of curing depends on the condition of the edges of the conizat, the sort of conization, degree and kind of the H changes on the conizator, as well as on the degree of the postoperative HPV positive (6). With late diagnosis and after an extensive surgery, the success of the treatment is less than 30% (4). While performing the screening USA National Cancer Institute came to the conclusion that, after getting normal results, all sexually active women need to come for regular check-ups once in every three years. This kind of screening helps women aged 20-75 years reduce mortality from invasive carcinoma by 90% (7). A more frequent follow-up is of utmost necessity in young patients, especially if they are exposed to co-carcinogenic risks such as smoking, immunodeficiency and the use of oral contraception (8).

The results concerning the degree of confidence in diagnosis of preinvasive neoplastic lesions of the uterine cervix differ from author to author, depending on the detection method applied. Given the stage of the disease, sensitivity of cytology ranges between 61.2% and 88%, mean 70%, while that of colposcopy can even reach 90%. Together these two methods ensure an almost 100%-confidence in the diagnosis (9).

Targeted biopsy under the control of colposcope, as the third method in diagnosis, enables us to get a sample from the correct area in the uterine cervix for histopathological diagnosis. In that way, we have a 10 times higher chance of correct diagnosis that will determine the treatment of the change (10). Besides biopsy, the curettage of the cervix canal is also important in the

early detection of ECC. Its role is especially important when the colposcopic results are not satisfactory. It has been reported in some research papers that ECC can find CIN in 1.4-17.9% cases even when results are satisfactory (11).

Different authors report different percentages of progression stage, regression or stagnation of preinvasive changes. The latest 2004 studies show that CIN I regresses in 60% and CIN II in 46%, while progression is detected in 8% CIN I cases and 34% CIN II cases (12). It is believed that the average duration of intraepithelial changes is 13 years. According to some research studies, however, invasive cancer can even take 17 years to develop from precursors (13). The potential of CIN progression has also been examined at the level of molecular markers. It has been found out that a combination of high KI67 stratification index and reduced expression of pRB of the cell in the lower third of the peeling epithelium is a high predictive factor in the progression of the disease (14). On the other hand, knowing natural disease development and its association with the occurrence of invasive carcinoma is of the utmost importance for the existence of two basic assumptions: (a) that a large number of patients with intraepithelial neoplasias would develop invasive carcinoma if untreated, and (b) that a majority of invasive forms of planocellular cancer is preceded by a visible intraepithelial phase.

The rate of false-negative results in cytology and colposcopy differs in various studies. In cytology the number varies between 24.4% and 49% (15). Colposcopy also yields false-negative results to a certain extent, especially in elderly women, in women previously treated with a destructive technique, in chronic inflammations or conditions after performing conization (Sturmdorff suture). This is the reason why we should combine all these methods and, in the case of a positive result, perform a targeted biopsy. Including colposcopy in cytological detection increases the detection of lesions by 15.3% (15).

Only a histopathologist can give a final diagnosis on the grade of the lesion based on the sample retrieved by targeted biopsy. Often the intensity of colposcopic or cytological image is not in concordance with histopathological diagnosis. The rate of concordance will depend on many technical details, the clinician's experience and, above all, the area where the material for histopathological analysis is taken. The wrong area chosen for biopsy will lead to a mistake in grading the change, which in turn will lead to mistreatment. Bearing this in mind, the doctor who deals with the issue should perform the detection himself and choose a sample for histopathological analysis from the proper area (10).

The Aims of the Study

1. Determining the validity of the colposcopic image in grading the severity of visible lesions to the uterine cervix.
2. Establishing the importance of cytology in determining the stage of preinvasive lesions to the uterine cervix and compatibility of PAPA classification with the histopathological stage of the disease.

Patients and Methods

The research was performed at the Department for Early Detection of Carcinoma of the Clinic for Gynaecology and Obstetrics, Niš, and the Institute of Pathology, Niš, on 100 subjects who had a pathological colposcopic or cytological diagnosis of the uterine cervix and were examined after February 1, 2003. All of the subjects had their changes histopathologically verified with a targeted biopsy. Colposcopies were performed with a Karl Zeiss (Jena) colposcope. The official international nomenclature in colposcopy established in Rome, 1990, was taken for the nomenclature of colposcopic results. Cytological preparations were put under an Olympus microscope and classified into five groups according to Papa classification. The material for HP analysis was taken with a targeted biopsy under the control of a microscope, and after that it was fixated in vials with a 10%-formaldehide for 12 hours. Laboratory cross-sections 5 mm thick were stained with HE and AB-PAS histochemical method and classified according to Bethesda SIL terminology. The obtained results were statistically processed in line with a comparative model against with several categories. Data were statistically processed.

Results

The most common pathological result in our research was the mosaic (Table 1). Compared to other pathological results, the frequency of the mosaic was shown statistically significant $\chi^2_e = 43.84 > \chi^2, 0.01 = 13.27$.

The frequency of the colposcopic result of condilomas (HPV infection) was higher in younger patients (Table 1), which is to be expected since this type of infection is associated with sexual activity. This difference was not statistically significant, as $\chi^2_e = 1.9 < \chi^2\ 0.05 = 3.65$.

Pathological colposcopic results were mostly localized on the front lip of the uterine cervix (Table 2) and shown as statistically significant ($\chi^2_e = 89.73 > \chi^2\ 0.01 = 9.21$).

The pathological cytological result was the reason for performing a targeted biopsy on 37% of the patients.

Table 1. Colposcopic result in patients

Age (years)	Ectopy	REE	Kondil.	Leucopl.	Aceth. wh.	Punctat.	Mosaic	ATZ	Total
<25	0	0	8	1	3	4	9	1	26 (17.93)
26–35	0	0	5	1	3	12	13	1	35 (24.13)
36–45	0	2	7	2	8	12	19	3	53 (36.55)
>45	0	2	3	5	9	7	3	2	31 (21.37)

This rate is much lower than in colposcopic indications for biopsy - 63% (Table 3). Reasons for such a distribution of indications are related to sensitivity and specificity of these methods. Colposcopy has this high a rate of indication for biopsy due to its low specificity and high sensitivity to the high rate of false-positive results and the low rate of false-negative results.

Table 2. Localization of pathological colposcopic results

Localization	Number	Percent
Anter. Labia	90	73.77
Poster. Labia	26	21.31
Lateral.	6	4.92
Total	122	100.00

Table 3. Cytological results of patients

Cytological results	Number	Percent
PA: II	45	45.00
PA: II b	18	18.00
PA: III	37	37.00
Total	100	100.00

A total mean concordance of pathological colposcopical results and expected HP results is 75.33%, which falls under the category of a good match (Table 4). Concordance is higher in more severe histological results where the concordance rate is 90.32%, which falls under the category of a very good match.

Cytology has shown lower concordance values with histopathology - 55.8% (Table 5), which falls under the category of a moderately good match. The reason for a lower concordance are low-grade premalignant changes (LSIL) where the changed cells are localized deep in the epithelial layer so they are not reachable for sampling and cannot be found on a cytological preparation. With LSIL changes the cytological results were normal (PA = II) in 43.33% of cases. As with colposcopy, cytology also has a higher concordance rate in high-grade changes (HSIL) - 74.19% (a good match). The rate of normal (false-negative) results is significantly lower for HSIL changes - 16.12%.

Table 4. Concordance of colposcopical and histological results

Grad. col.	Benign. H.P.	LSIL	HSIL	Concordance
I grade	**15**	2	0	88.20%
II grade	24	**25**	3	48.07%
III grade	0	3	**28**	90.32%
Total	39	30	31	100.00%

I grade <5; II grade 6-9; III grade >10 point

Table 5. Concordance of cytological and histological results

Cytological result	Benign H.P	LSIL	HSIL	Concordance
PA: II	**27**	13	5	69.23%
PA: II b	8	**7**	3	23.33%
PA: III	4	10	**23**	74.19%
Total	39	30	31	100.00%

Discussion

The most common reason for performing a targeted biopsy of the uterine cervix in our research was the pathological colposcopical result. In only 8 patients with normal colposcopic results was a biopsy of the uterine cervix performed due to pathological cytological results. The most common colposcopic result is a mosaic in 44, then punctuation in 35 and acetowhite epithelium in 23, while leukoplakia was found in only 9 cases. An accompanying colposcopic result of vulvo- and vaginoscopia is HPV infection, and condilomas in 23% of the patients. In that group the highest rate (57.1%) was registered in women under the age of 25, whereas in the oldest age group it decreased to 11.11%. This kind of distribution should be seen as part of sexual activities of the youngest age group. Table 2 shows that the proportionally most common localization of pathological results was on the front lip of the uterine cervix, in 90% of the cases. This localization is statistically significant and related to the pathological histological result, compared to colposcopic results where it was not found to be statistically relevant.

The most important part of a colposcopical examination is determining the grade of severity of the colposcopic result by looking at certain characteristics of the lesion. In this paper we have tried to classify colposcopic results in 3 groups by giving points to 5 characteristics of the colposcopic image. Every characteristic could be rated as (a) changes that do not have clinical significance; (b) changes that have a clinical significance; and (c) changes that are very clinically significant. Depending on the total score, the results were graded as follows: the score <5 for benign changes, the score 6-9 for low-grade lesions that should correlate with LSIL changes after biopsy, and the score >10 for lesions that should correlate with HSIL. The characteristics of the colposcopic image that were rated include: colour intensity, area, outside margins, intercapillary distance, the speed of formation of white colour, and the duration of white colour.

The highest concordance rate of the colposcopic result stage and histopathology was for high-grade lesions (90.32%) and the lowest for LSIL changes (only 48.7%). LSIL changes were declared benign in 46.15% of the cases. This relatively high concordance rate of the colposcopic image and the expected normal HP stage was 88.2% for benign changes, of which only 11.70% had the colposcopic image overrated as low-grade lesions. The mean concordance rate of the colposcopic image and the expected HP stage was 75.33%, which is a good match. Considering the fact that concordance rates <20 belong to a very bad match category, the rates 21-40 were bad, 41-60 moderately good, 61-80 good, and 81-100 very good.

The calculated sensitivity of colposcopic examination, which shows the proportion of sick subjects correctly identified by the test out of the total number of sick people, is high (96%), while the specificity is low

(57%). Low specificity shows that colposcopy is a less potent method in recognizing healthy people correctly identified by the test. This is the reason why the scoring system of colposcopic results is most important when deciding on the necessity of performing the biopsy of a pathological colposcopic result. In this way the number of unnecessary biopsies will decrease, thereby contributing to increasing the specificity of colposcopic examination. In our research there were 40% of patients with pathological colposcopic and normal histological results. A combination of cytology with colposcopy increases the sensitivity and specificity of the test to almost 98%. What is important is that the marking of the colposcopic result is highly relevant and useful in differential diagnosis, leading to a higher concordance of colposcopic results with the hystopathological ones and helping when deciding on a potential biopsy of a pathological colposcopic result. This approach is especially important in pregnant women with a suspicious result. In these cases it is essential to avoid unnecessary biopsy and bleeding with colposcopic images that do not show microinvasion and invasion since only these stages are treated in pregnancy.

The positive predictive value of a colposcopic result is 61.4%, showing what is the likelihood that the person with a pathological result is actually sick, while the negative predictive value is high (96.5%), indicating the possibility that the person with a normal result is not sick.

In our research we have classified cytological results according to Papanicolaou classification. PA II is a normal cytological result with a possible presence of inflammation elements. Category IIb shows initial changes on the cells that are described in the cytological result as a couple of enlarged nuclei, signs of mild dyscaryosis, coilocytosis, etc. This cytological category would match the histopathological LSIL result, which means that the lower third of the epithelium was infected due to dyskaryotic cells and cytopathological changes significant for HPV infection. PA III involves all the signs that characterize an atypical cell: dyskaryosis, hyperchromatosis, and pathological mitoses. This result is in line with HSIL histological changes. The concordance rate of cytology and histopathology was the highest for the most severe HSIL changes (75%) and the lowest for LSIL (23.3%). In benign results the concordance was 69.23%, whereas in 30.76% of pathological cytological results histology was normal. The average concordance of cytology and histology was 55.58%, which falls under the category of a moderately good match. The analysis of cytological sensitivity showed relatively low values (64%), while specificity was high (88%). The capability of cytology to predict a pathological histological result is high (96%), while the negative predictive value is low (60%). Low cytological sensitivity is definitely the result of the fact that low-grade lesions are located in deeper layers of the epithelium and that they do not need to be present in the smear, as well as of restrictions on preparation and interpretation of the cytological result.

Conclusion

1. Colposcopy is a subjective diagnostic method with high sensitivity (96%) and low specificity (57%)
2. Due to low specificity of colposcopy, the colposcopical scoring system is important when deciding on the necessity of performing biopsy on a pathological colposcopic result so as to decrease the percentage of unnecessary biopsies, especially in pregnant women.
3. The concordance of the colposcopic result scoring and the expected histopathological result shows a good match (76%) and is highest for the most severe HSIL changes (90.32%).
4. Exfoliating cytology has low sensitivity (64%) and high specificity (88%) with a low negative predictive value (60%) and a high predictive value (90%). Due to these reasons it is necessary to combine this method with colposcopy so that the rate of false-negative cytological results could decrease.
5. The concordance rate of cytological PAPA and histological Bethesda classification is low (55.58%) falling under the category of a moderately good match. Because of this we should work on a quick acceptance and application of the new unique cytological-pathological classification according to Bethesda that is already used in the world.

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STEPENOVANJE TEŽINE PREINVAZIVNIH PROMENA GRLIĆA MATERICE KOLPOSKOPIJOM I EKSFOLIJATIVNOM CITOLOGIJOM

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Kratak sadržaj: *Kolposkopija je subjektivna dijagnostička metoda sa visokom senzitivnošću (96%) i niskom specifičnošću (57%). Zbog niske cpecifičnosti kolposkopije sistem skorovanja kolposkopskog nalaza je bitan pri odlučivanju o neophodnosti uzimanja biopsije sa nekog patološkog kolposkopskog nalaza kako bi se smanjio procenat nepotrebno urađenih biopsija (naročito u kategoriji gravidnih žena). Podudarnost skorovanja kolposkopskog nalaza i očekivanog histopatološkog nalaza pokazuje dobro slaganje (76%) i najveće je za najteže histološke promene HSIL gde iznosi 90,32%. Eksfoklijativna citologija ima nisku senzitivnost (64%) a visoku specifičnost (88%), sa niskom negativnom prediktivnom vrednosti (60%) i visokom pozitivnom prediktivnom vrednosti (90%). Iz tih razloga je neophodno ovu metodu kombinovati sa kolposkopijom kako bi se smanjio procenat lažno negativnih citoloških nalaza. Slaganje PAPA citološke klasifikacije i histološke po Bethesdi je niska 55,58% i spada u kategoriju umereno dobrog slaganja. Iz ovih razloga bi trebalo raditi na ubrzanom prihvatanju i primeni nove jedinstvene citološko-histološke klasifikacije po Bethesdi, koja se inače već koristi u svetu.*

Ključne reči: *Kolposkopija, citologija, histopatologija, prekancerozne lezije*