pp. 66-69 (2014)

"See and treat" strategy for HSIL: correlation between colposcopy and histopathology

Calina Dragosloveanu[1], Radu Vladareanu[2]

1. Clinical Hospital of Obstetrics and Gynecology "Prof. Dr. Panait Sarbu", Bucharest, Romania
2. Department of Obstetrics and Gynecology, "Carol Davila" University of Medicine, Elias University Hospital, Bucharest, Romania

Correspondence: Calina Dragosloveanu, e-mail: calinadragosloveanucd@yahoo.com

Abstract

We sought to determine the correlation between the colposcopic impression (by means of RCI- Reid Colposcopic Index) and histopathology in patients who have undergone LEEP (,see and treat' strategy) for cytological high-grade dysplasia. This was a prospective study carried out in "Prof. Dr. Panait Sârbu" Hospital in Bucharest over a 10-month period. A total of 112 women diagnosed with HSIL on PAP exam underwent LEEP without prior colposcopically directed biopsy. We assessed the relationship between the histologic diagnosis and the colposcopic aspect (RCI), age, parity, AFSI (age at first sexual intercourse) and AFP (age at first pregnancy) AFSI latency. Among 112 women treated, 102 (91.07%) had histologically proven high-grade dysplasia (≥CIN2) and 2 (1.78%) of them had microinvasive squamous cell carcinoma. 80 patients (78.43%) of the 102 had high-grade colposcopic impression; of the 30 patients with normal/low-grade colposcopy, 22 (73.3%) had high-grade lesions on final histologic exam. The correlation between RCI and histology was fair (κ=0,205; 95% CI, 0.08-0.32, p=0.001). There was no statistically significant connection between age, AFSI, parity, AFP-AFSI latency and RCI and histologic result. The correlation between RCI and histologic findings is fair , especially for CIN3 lesions; the high percentage (91.07%) of histologically proven high-grade dysplasia on LEEP specimens make ,see and treat' strategy an attractive option in the management of HSIL results on PAP smears.

Keywords: *colposcopy, RCI, cervical cancer, CIN, see and treat, AFSI, AFP-AFSI*

Introduction

Worldwide, cervical cancer remains one of the major health problems despite the remarkable progress that has been made in the prevention and treatment of the precursor lesions (CIN 3) mostly due to the partnership between cervical cytology screening and colposcopy[1]. Once the second most common cancer in women both for incidence and mortality rates, it is now ranked as 11th in incidence and 13th in mortality in the United States; yet, in Romania statistics show that cervical neoplasia is the 3rd cause of death in female population (and the 2nd in the 15-44 age group) comprising 4.343 cases diagnosed each year[2].

Management of HSIL PAP reports encompasses two alternatives, as recommended by ASCCP guidelines: colposcopic examination with appropriately directed cervical biopsies and endocervical sampling or an immediate loop electrosurgical excision (LEEP) without prior colpobiopsy[3] the 'see and treat' strategy (not if patient is pregnant or an adolescent). LEEP is an effective option in treating pre-invasive cervical lesions[4,5] allowing a final histologic diagnosis (including the extent, depth and margins status of the excised piece) and thus reducing the possibility of skipping a micro-invasive carcinoma. Studies show that this approach has comparable results with the three-step strategy (colposcopy- biopsy- LEEP), is cost-effective and less time-consuming as it requires a single hospital visit, no hospital admission and outpatient follow-up[6].

Received: *February 23, 2014*
Revised: *March 20, 2014*
Accepted: *June 26, 2014*

The colposcopic examination in patients with high-grade dysplasia on cytology has two main objectives: locating the most appropriate site for biopsy and ruling out invasive disease[7]. The limiting factor in using colposcopy as a diagnostic and therapeutic method is that its accuracy depends directly on the expertise of its operator; therefore, the impression is traditionally assessed and reported using a scoring system called the reid colposcopic index (RCI)[8] which was proved to have a good reproducibility in clinical studies[9,10].

The accuracy of cervical colposcopically directed biopsies is still a subject of controversy. Kirkup and Hill reported an excellent correlation between histological diagnosis from colpobiopsies and definitive diagnosis after conization/hysterectomy[11]. On the other hand, many subsequent studies reported agreement rates of no more than 43-51%[12].

The purpose of our study is to evaluate the diagnostic efficacy of the colposcopic impression using the RCI and to estimate the correlation between the RCI and histopathologic findings in LEEP specimens. We have also assessed the impact that age, parity, age at first sexual intercourse (AFSI) and latency between age at first pregnancy (AFP) and AFSI had on the results.

Methods

The present study is a prospective study carried out on 112 patients diagnosed with high grade squamous intraepithelial lesion (HSIL- Bethesda System Terminology 2001) on LBC PAP examination, between

March 2013- January 2014 in the Clinical Hospital of Obstetrics and Gynecology "Prof. Dr. Panait Sarbu", Bucharest. Exclusion criteria were: age less than 21 years, pregnancy, unsatisfactory colposcopy and overt colposcopic cancer. Age, parity (nulliparous/parous=at least one vaginal live birth), AFSI (age at first sexual intercourse), latency between age at first pregnancy (AFP) and AFSI were obtained by complete patients history examination. The study was approved by the Committee of Ethics and Research in Humans of our institution.

All patients signed an informed consent according to the World Medical Association Declaration of Helsinki regarding both colposcopy and LEEP procedure. The colposcopic examination was carried out in our clinics Colposcopy Department by certified obstetrician-gynecologists who had practiced colposcopy for at least 3 years and the diagnosis was made by RCI. The total score of the lesion was the following: 0-2 p (normal/CIN1- low grade lesion), 3-5p (CIN1/CIN2- intermediate grade lesion) and 6-8p (CIN2/CIN3- high grade lesion) [13]. All 112 patients underwent LEEP regardless of the colposcopic findings; in every case, a standard large loop excision of the entire transformation zone and the entire visualized lesion, under intravenous general anesthesia in the operating room was performed. The diameter of the loop was selected on the basis of the size of the lesion and the diathermy power was set at 60 W for "cut" mode and 45 W for 'coagulation' mode in "blended" setting. The surgical site was cauterized to prevent bleeding. We assessed post-interventional bleeding (hemorrhage which required surgical suturing and/ or vaginal packing) and infectious complications (defined as purulent vaginal discharge, cervicitis, endometritis and pelvic inflammatory disease). Antibiotic prophylaxis was not routinely prescribed and patients were advised to avoid vaginal douching and sexual intercourse for at least six weeks after the intervention.

The LEEP specimens were removed, formalin fixed and sent for histologic evaluation in the Department of Pathology of our hospital where they were paraffin embedded and the slides obtained hematoxylin-eosin stained. The results were reported at 2 weeks and the first follow-up examination was set at 6 weeks postintervention. Diagnosis of dyplasia was made according to the World Health Organization Classification of Tumors: benign (including cervicitis, cervical papilloma, flat/exophytic condyloma), CIN1/2/3, microinvasive carcinoma[14] and the surgical status of the margins was also described. In cases in which the differentiation between CIN 2 and CIN1/3 was difficult we used immunohistochemistry staining: Ki67 and p16 markers. Overtreatment rate was defined as the proportion of histologic results containing ≤CIN1 according to the recommendations of NHSCSP 2010 guidelines[15].

Data obtained were statistically analyzed using standard methods of descriptive statistics (means, median, SD), cross-tabulation, "κ" value of assessing the degree of correlation between colposcopic impression using RCI and histopathology, using IMB SPSS Statistics 20.0.0. We calculated the sensitivity, specificity and predictive values with the disease threshold of ≥CIN2. The level of significance was set at 5% ($p<0.05$).

Results

During the study period, 112 women diagnosed with cytological HSIL underwent colposcopy (the results being assessed with RCI) and LEEP on the same visit-"see and treat" approach. The mean age of the patients was 40.7 years (age group of 23-65 years; SD:11.9) and the median 38 years; the mean AFSI was 18.9 years (age group 15-24 years; SD:2.1) with 58.03% of the patients having AFSI 17-20 years. 32.14% of the women were nulliparous, and of the 76 parous, 45 (59.21%) women had AFP-AFSI latency >2 years.

Of the 112 patients who had LEEP, 102 women (91.07%) had a histologic result ≥ CIN2 (high grade dysplasia) and 2 of them (1.78%) were diagnosed with micro-invasive squamous cell carcinoma. For 3 of the patients with CIN2 histology we used immunohistochemistry staining (Ki67 and p16 markers) that concluded CIN3 as a final diagnosis. 10 patients had a histologic report of benign/low grade dysplasia (CIN1) meaning an overtreatment rate of 8.92%. 60.86% of the patients with CIN3 diagnosis were aged 21-39 years and the 2 cases with microinvasive carcinoma were over 40

Table 1 Correlation between RCI and histopathology

Correlation between RCI** and histopathology		Hp results					Total
		B*	CIN1	CIN2	CIN3	CIN4	
RCI B	B	1	2	3	3	0	9
	CIN1	2	3	7	9	0	21
	CICCIN2	0	2	16	24	0	42
	CICCIN3	0	0	5	33	2	40
Total		**3**	**7**	**31**	**69**	**2**	**112**

**B = Benign; **RCI = Reid Colposcopic Index*

years old. The "marginal" surgical status was no margin involvement in all 112 cases.

The detailed distribution of the histologic and colposcopic findings and their correlation is presented in Tables 1 and 2. Of the 102 women who had high grade dsyplasia on their pathology reports (≥CIN2), 80 patients (78.43%) had a corresponding colposcopy RCI (≥CIN2). Of the 82 patients with a high-grade colposcopic examination, 80 (97.5%) had histologically proved high-grade dysplasia; on the other hand, 22 of the 30 patients (73.3%) with a normal/low-grade colposcopy actually were found to have histologic high-grade dysplasia. The 2 patients with histologic microinvasive carcinoma were interpreted colposcopically as CIN3 (RCI= 8p).

Analyzing the accuracy, over/ underestimation of the association between RCI and histopathology we observed an accurate concordance of 47.3% (the highest percentage of accurate estimation (82.5%) was for CIN3 lesions), overestimation of 44.64% and underestimation of 8.04%; the "κ" value for the strength of correlation showed a fair correlation (κ=0,205; 95% CI, 0.08-0.32, p=0.001). The sensitivity, specificity, positive predictive value and negative predictive value of the colposcopic diagnosis of high-grade dysplasia (≥CIN2) were: 78.43%, 80%, 97.5%, 26.6%.

We found no statistically correlation between the histologic result/RCI and age, parity, AFSI and AFP-AFSI latency (p>0.05). There was no case out of the 112 treated with hemorrhagic/infectious post interventional complications.

Discussion

In the present study, of the 112 patients with cytological HSIL, 8.92% had a benign/low-grade dysplasia histologic diagnosis on LEEP specimens and 91.07% were diagnosed with high-grade dysplasia/microinvasive squamous cell carcinoma. Taking these results into account together with an overtreatment rate of 8.92% (which is consistent with the NHSCSP standard requirement of <10%[15]) we are of the opinion that "see and treat" strategy is an attractive option for HSIL cervical citology (with benefits that outweigh the risks). This is especially the case for patients at risk for noncompliance in the standard 'three-step' therapy which requires multiple hospital visits, higher costs and a greater discomfort[16,17]. However, the risks of overtreatment or of adverse effects resulting from LEEP should not be ignored[18].

Studies regarding the efficacy of the 'see and treat' approach report similar results with the ones we observed in our clinic. Nogara et al.[19] found that 72.6% of the patients with HSIL PAP reports had CIN2/3 or microinvasive carcinoma on LEEP specimens; Ferris et al[10] had 85.5% of the results with CIN2/3 lesions. Keijser et al.[4] carried on a study on 424 patients with abnormal cervical citology who underwent "see and treat" strategy and reported that 25% of the patients who had low-grade lesions on PAP exam had CIN2/3 histologic diagnosis and 74% of the patients who had high-grade PAP results had histologically proven CIN2/3 or microinvasive carcinoma. Similar data were reported by Szurkus et al.[5] who observed a 71% histologic high-grade dysplasia of 104 women with HSIL citology.

Our investigation showed that 10 patients (8.92%) had histologically absent/low-grade dysplasia and 30 patients (26.7%) normal/low-grade colposcopic impression, less than those observed by Nogara et al.[19] and Livasy et al.[20] who reported in their study the absence of dysplasia in 14% of the specimens. Several possible explanations can be offered for these findings: a failure to remove small lesions during LEEP, the presence of small lesions removed in LEEP but not sampled in the histologic sections, equivocal pathology interpretation[19]. We have used in 3 cases IHC markers to conclude a final histologic diagnosis and to rule out possible misinterpretations.

The correlation between the colposcopic impression using RCI and histopathology was fair (κ=0.205; 95% CI, 0.08-0.32, p< 0.001), but less that the one obtained by Durdi et al. (κ= 0.73, p<0.001)[21]. The highest concor-

Table 2 Correlation between RCI and histopathology[a]

RCI**		Hp results					Total
		B*	CIN1	CIN2	CIN3	CIN4	
	B	0.89%	1.79%	2.68%	2.68%	0.00%	8.04%
	CIN1	1.79%	2.68%	6.25%	8.04%	0.00%	18.75%
	CIN2	0.00%	1.79%	14.29%	21.43%	0.00%	37.50%
	CIN3	0.00%	0.00%	4.46%	29.46%	1.79%	35.71%
Total		**2.68%**	**6.25%**	**27.68%**	**61.61%**	**1.79%**	**100.00%**

**B = Benign, **RCI = Reid Colposcopic Index; avalues are given as percentage*

dance (82.5%) was obtained for CIN3 and the lowest for benign impression (11.11%) showing that the colposcopic examination is more accurate for high-grade lesions, as Durdi et al suggested in their study[21]. Sensitivity and specificity of RCI for ≥CIN2 lesions was 78.43% and 80%, less that the ones reported by Mousavi et al. and Durdi et al.[9,21] 73.3% of the patients who had a normal/low-grade colposcopy (CIN1) were histologically proved to have high-grade dysplasia which is higher than observed by Szurkus et al.[5]. In addition, studies have shown that the accuracy of colposcopically guided biopsies for HSIL patients is limited[12,22] as they do not lower the rate of false positive results; also, "see and treat" approach is superior regarding number of hospital visits (thus reducing noncompliance), patients discomfort, anxiety and costs[23,5,17]. In surveys based on confidential questionnaires, the level of satisfaction with "see and treat" strategy was acceptable[6].

The most common complication following LEEP described in literature is hemorrhage[24]. In our study none of the patients was reported to have hemorrhagic/infectious complications, which comes in agreement with NHSCSP 2010 guidelines which recommend a <5% rate of post interventional complications[15].

The median age in our study was 38 years and 52 patients (46.4%) had ages ≤35 years ($p<0.001$). In young patients, the correct diagnosis and treatment of preinvasive cervical lesions is essential in preventing cancer of the cervix; yet, a close follow-up for possible adverse effects is required. LEEP is a conservative procedure and the lack of margin involvement in the specimens observed in our study should not be used as the only prognostic indicator for the disease recurrence[19]. Although studies show clearly risks on further obstetrical outcome in patients post-LEEP (premature birth, PROM, low birth weight)[18], we could not asses any of these risks, as no patient obtained a pregnancy during our study period.

Although age, parity, AFSI and latency between AFP and AFSI have been cited as risk factors for invasive cervical cancer in developing countries[25], in our study these parameters showed no statistical influence neither on the histologic diagnosis, nor on the RCI ($p>0.001$), as reported by Aue-aungkul et al. in their study[26].

The present study had a series of limitations: the small number of patients, lack of comparison with colposcopic impression without the use of RCI, short-term follow-up. Taking into account that 91.07% of the patients had a concordant histologic diagnosis with the cytologic report, an overtreatment rate less than 10%, a fair correlation between RCI and histolopathology, we conclude that "see and treat" approach (together with the colposcopic examination as a valid assisting tool) is an attractive alternative in the treatment of cytological HSIL.

Conclusions

To conclude, although we cannot ignore the risk of overtreatment and potential morbidity of LEEP, we are of the opinion that the benefits of a single hospital visit outweigh these shortcomings. However, post-treatment long-term follow-up is necessary. ■

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