Coll. Antropol. **27** (2003) 1: 239–246
UDC 618.146-076.5
Original scientific paper

Diagnostic Value of Cytology and Colposcopy for Squamous and Glandular Cervical Intraepithelial Lesions

Marija Pajtler[1], Silvana Audy-Jurković[2], Ana Ovanin-Rakić[2], Zvonimir Makarović[1], Miodrag Milojković[1] and Nikola Ljubojević[2]

[1] Department of Clinical Cytology, University Hospital »Osijek«, Osijek, Croatia
[2] Institute for Gynaecological Cytology, Department for Obstetrics and Gynaecology, School of Medicine, University of Zagreb, Zagreb, Croatia

A B S T R A C T

The main objective of work was to determine a diagnostic value of cytology and colposcopy as a method of screening and differential diagnosis, as well as to determine the relative value of some colposcopic features of squamous and glandular cervical intraepithelial lesions. Cytological diagnosis and colposcopy findings is compared with histological ones for 187 patients with intraepithelial lesions (142 squamous and 45 glandular ones with or without squamous components) and determined the sensitivity and positive predictive value of cytology and colposcopy, including the types of colposcopic abnormalities associated with squamous/glandular intraepithelial lesions. The sensitivity of cytology as a screening method for SIL (squamous intraepithelial lesions) is 89% and for GIL (glandular intraepithelial lesions) 98%. Positive predictive value of differential cytology for SIL is 59% and for GIL 53%. Sensitivity of colposcopy for both lesions' type is 87%. Acetowhite epithelium occurs far more often with SIL, whereas atypical vessels and unequal, dilated gland openings with GIL ($p<0.05$). Cytology and colposcopy as screening methods have a high sensitivity. Nevertheless, cytology is far more accurate in determining differential diagnosis of SIL than GIL and some colposcopy abnormalities suspicious of GIL should be further tested in praxis.

Key words: *cervix; cytology; colposcopy; squamous intraepithelial lesions (SIL); Glandular intraepithelial lesions (GIL).*

Received for publication April 2, 2002

Introduction

Organized population screening for cervical cancer and treatment of pre-invasive abnormalities reduces the incidence of squamous cervical cancer[1,2]. As a result, increasingly conservative management strategies of squamous precancerous, and very early invasive lesions are possible.

Although most cervical cancers are squamous, adenocarcinoma accounts for up to 30%[3] of cases. Screening has not had any impact on the incidence of adenocarcinoma of the cervix because preinvasive glandular lesions are not easily recognized. Preinvasive glandular lesions are classified as low-grade and high-grade glandular intraepithelial neoplasia, with high-grade CIN being the same as adenocarcinoma in situ (AIS). The ratio of AIS to CIN3 varies in different series from 1:26 to 1:239, with average of about 1:50.[4] Unlike CIN, which occurs almost exclusively within the transformation zone, AIS can occur throughout the endocervical canal, and lesions may be multi -focal. Pap smear screening is unsatisfactory, and disease has no morphologic reliable colposcopic features. However, as approximately two-thirds of AIS cases also have squamous disease, diagnosis is often the fortuitous result of detecting and treating coexisting CIN.

The aim of this work was to determine a really diagnostic value of cytology and colposcopy as a method of screening and differential diagnosis, as well as to determine the relative value of some colposcopic features of squamous and glandular cervical intraepithelial lesions.

Material and Methods

We included 187 women with histological diagnosed intraepithelial cervical lesions in our study, in order to determine the detection and diagnostic value of cytology and colposcopy. 142 had SIL and 45 had GIL (41 coexist with SIL and 4 pure glandular lesions). The histological finding was compared with cytological[5] and colposcopic[6], separately for squamous and glandular lesions. We evaluated the cytology as a screening method by taking all positive findings as true positive and all other as false negative. Determining the value of differential cytology in the case of glandular intraepithelial lesions, we considered true positive the abnormal cytological findings that had glandular component recognized (n=44), whereas all other findings were false negative. When we talk about squamous intraepithelial lesions, the diagnostic value of differential cytology was evaluated comparing abnormal cytological findings (n= 126) with histological diagnosis in the case of compatibility same grade (0°) or within one (1°) grade[7]. If cytological and histological diagnosis coincide for the same grade, they are the same, but if they match within one grade, histological diagnosis and cytological diagnosis are the same, with two other adjoining diagnosis added.

The value of colposcopy was determined taking all abnormal colposcopic findings as true positive and all normal colposcopic findings as false negative. We compared the frequency occurrence of some colposcopic abnormalities for squamous and glandular lesions (clean or in the combination with squamous component).

Since the examinee population was determined according to histological finding of intraepithelial lesion, comparison with cytological and colposcopical findings has given either true positive (TP) or false negative (FN) results, on the basis of which from parameters of diagnostic value would be able to determine the sensitivity (Se) and the positive predictive value (PPV) and it was 100%. Therefore the detection value of cytology and colpos-

copy was described as sensitivity, but it did not refer to diagnostic value in the case of differential cytology of squamous lesions. She is described as sensitivity, specificity, positive and negative predictive value.

Results

Out of 142 histological diagnosed, squamous intraepithelial lesions, there were 126 cytological true positive and 16 false negative findings (Table 1). Sensitivity of cytology as a screening method in the case of SIL was 89% (Table 4). In order to determine the value of differential cytology, we compared cytological-histological compatibility of the same grade and within the one grade (Table 2). The sensitivity increased with severity of the lesion. Specificity and negative predictive value were equally high for all lesions. However, positive predictive value is significantly higher for bordering spectra lesions (dysplasia levis and carcinoma in situ), than for medium ones (dysplasia media and dysplasia gravis). All parameters, used to evaluate diagnostic value of differential cytology for SIL within the one grade, were mostly more sensitive than these in the case of same grade and exceptionally the same. The total positive

TABLE 1
COMPARISON OF CYTOLOGY AND HISTOLOGY
IN SQUAMOUS INTRAEPITHELIAL LESIONS (N= 142)

Histology	Cytology					Total
	NEG	DL	DM	DG	CIS	
DL	7	16	–	–	–	23
DM	3	7	2	2	–	14
DG	3	9	6	19	5	42
CIS	3	1	4	8	47	63
Total	16	33	12	29	52	142

NEG – negative; DL – dysplasia levis; DM – dysplasia media; NEG – negative; DG – dysplasia gravis; CIS – carcinoma in situ

TABLE 2
DIAGNOSTIC VALUE OF DIFFERENTIAL CYTOLOGY FOR SQUAMOUS INTRAEPITHELIAL LESIONS FOR CYTOLOGICAL-HISTOLOGICAL COMPATIBILITY SAME GRADE (0°) AND WITHIN THE ONE GRADE (1°)

Cytology	N	Diagnostic value of differential cytology (%)							
		Se		Sp		PPV		NPV	
		0°	1°	0°	1°	0°	1°	0°	1°
DL	33	48	48	94	94	70	70	86	86
DM	12	17	52	91	97	42	79	92	92
DG	29	66	75	80	88	45	71	90	90
CIS	52	90	92	82	90	75	87	94	94
Total	126	67	73	87	93	59	79	90	90

Se – sensitivity; Sp – specificity; PPV – positive predictive value; NPV – negative predictive value; NEG– negative; DL – dysplasia levis; DM – dysplasia media; DG – dysplasia gravis, CIS – carcinoma in situ; 0° –compatibility same grade; 1° – compatibility within one grade

TABLE 3
COMPARISON OF CYTOLOGY AND HISTOLOGY IN GLANDULAR INTRAEPITHELIAL LESIONS (N=45)

Cytology	Histology					Total
	AIS	AIS+CIN	GIL	GIL+CIN	GIL+CIM	
NEG	–	1	–	–	–	1
AIS	2	4	–	–	–	6
AIS+CIN	–	7	–	–	1	8
AC	1	4	–	–	–	5
CIN	–	10	–	8	1	19
GIL+CIN	–	–	1	2	–	3
AC+ CIN	–	2	–	–	–	2
CP	–	1	–	–	–	1
Total	3	29	1	10	2	45

AIS – adenocarcinoma in situ; GIL – glandular intraepithelial lesions less than (less than) AIS; CIN – cervical intraepithelial neoplasia; CIM – carcinoma planocellulare cum invasione minimali; AC – adenocarcinoma; CP – carcinoma planocellulare; NEG – negative

TABLE 4
DIAGNOSTIC VALUE OF THE CYTOLOGY AS A METHOD OF A SCREENING AND OF THE DIFFERENTIAL CYTOLOGY (N = 187)

Histology	N	Cytology		Se*	PPV**
		False negative	True positive		
SIL	142	16	126	89	59
GIL	45[a]	1	44	98	53

SIL – squamous intraepithelial lesions; GIL – glandular intraepithelial lesions (dysplasia and adenocarcinoma in situ); [a](4 GIL, 41 GIL + squamous component),
Se* – sensitivity of the cytology as a method of a screening,
PPV** – positive predictive value of the differential cytology

predictive value of differential cytology within same grade was 59% and within the one grade was 79% (Table 2).

The cytological finding in the case of histological diagnosed glandular intraepithelial lesions was shown in Table 3. Out of 45, there were only 4 (9%) clean glandular lesions, whereas 41 (91%) contain a coexisting squamous lesion. Abbreviation GIL stands for marked dysplasia and AIS (adenocarcinoma in situ) is presented as an isolated diagnosis. Cytology as a screening method had the sensitivity of 98%, whereas positive predictive value of differential cytology is 53% (Table 4).

Out of 187 women with histological diagnosis of SIL or GIL, 163 had colposcopic finding true positive and 24 had false negative. Sensitivity of colposcopy is 87% and it is the same for squamous and glandular intraepithelial lesions (Table 5). Comparing some colposcopic abnormality occurrences in cases of SIL and GIL, (Table 6), it was noticed that acetowhite epithelium was far more detected in SIL, whereas atypical blood vessels and dilated unequal »gland« openings in GIL ($p<0.05$). All other colposcopical abnormalities did not show any other significant difference in their occurrence.

TABLE 5
DIAGNOSTIC VALUE OF THE COLPOSCOPY AS A METHOD OF A SCREENING FOR SQUAMOUS AND GLANDULAR INTRAEPITHELIAL LESIONS (N= 187)

Histology	N	Colposcopic finding		Se
		False negative	True positive	
SIL	142	18	124	87
GIL	45[a]	6	39	87

SIL – squamous intraepithelial lesions; GIL – glandular intraepithelial lesions (dysplasia and adenocarcinoma in situ); [a](4 GIL, 41 GIL + squamous component); Se – sensitivity of the colposcopy as a method of a screening

TABLE 6
ABNORMAL COLPOSCOPIC FINDINGS IN SQUAMOUS AND GLANDULAR INTRAEPITHELIAL LESIONS (N= 187)

Abnormal colposcopic findings	SIL (142)		GIL (45)à	
	N	%	N	%
Acetowhite epithelium	98	69	20	44
Leukoplakia	16	11	3	7
Punctation	38	27	14	31
Mosaic	50	35	12	27
Atypical vessels	2	1	10	22
Lesions with large »gland« opening	–	–	3	7

SIL –squamous intraepithelial lesion; GIL – glandular intraepithelial lesion;
[à](4 GIL, 41 GIL + squamous component)

Discussion

Cytology value in detecting and diagnosing SIL is well known and respected. Sensitivity varies from 40% to 90%[8–11], matching the results of this study, which shows sensitivity of cytology as a screening method to be 89%. Positive predictive value of differential cytology for compatibility of the same grade is 59% and 79% within the one grade. Most of the published papers show positive predictive value increasing with severity of lesion, but in our study we have found positive predictive value to be rather high for mild dysplasia (70%) and cancer in situ (75%), but equally low results for mediate (42%) and severe dysplasia (45%) in case of the compatibility of the same degree.

Out of 45 histological diagnosed GIL, only 4 (9%) had clean glandular lesions and others had besides glandular also contain a coexisting squamous lesion. It is worth mentioning that those 4 had only glandular component and that their cytological finding was true positive. Out of 41 combined intraepithelial lesions, glandular component was recognized in 20 cases (49%), making sensitivity of differential cytology to be 53%, whereas as a method for lesion detection regardless of epithelium type, cytology has very high sensitivity of 98% that should be attributed to present squamous component.

Some other authors mention similar results. Lee et al.[12], working with sample of 34 histological diagnosed AIS, out of which, 16 (47%) had CIN, have found that the sensitivity for AIS is from 55% to 72% (depending whether the false negative finding was a consequence of sampling error, screening error or interpretation error). Luesley et al.[13] have reported

about the results based on the sample of 19 AIS cases and 12 glandular atipija, whereas 19 were combined with CIN. In 71% of the cases they have predicted accurately the glandular lesion component.

For last 15 years the small numbers of glandular intraepithelial lesions in comparison to squamous lesions have been studied and their morphological features described[14–19], due to the lack of experience and not give enough attention to their detection in the smears. This explains also the result revisions of false negative results. Lee et al.[20] have found out of 17 false negative results, 13 with AGCUS (probably neoplastic) and Pajtler et al.[21] has found out of 9 false negative results, which had been revised, 3 with cytomorphological changes matching those of AIS. In order to improve diagnostic accuracy of cytology, it is important while performing smear analysis to consider the possible coexistence of glandular atipija with identified squamous and to looked for it. Detected atipija on glandular epithelium with CIS are explained as a consequence of gland penetration with atypical squamous epithelium.

According to meta-analysis, diagnostic values of colposcopy[22] are: mean sensitivity 95%, specificity 45%, positive predictive value 82% and negative predictive value 79%. The analysis is based on squamous intraepithelial and early invasive lesions, whereas glandular lesions are not particularly pointed out. Sensitivity of colposcopy is 87%, regardless what histological type of lesion it is and it matches quoted results. Nevertheless, it raises a question whether colposcopy accuracy refers to glandular as well as to squamous intraepithelial lesions, or the obtained results are based on only present squamous lesions. Comparing some colposcopic abnormalities' occurrence in the case of SIL and GIL, it has been confirmed that acetowhite epithelium is more often found in the case of SIL, but atypical blood vessels and dilated, unequal gland openings with GIL ($p< 0.05$). There has not been found any difference in occurrence of other colposcopic abnormalities. Although the number of women with glandular intraepithelial lesion happens to be too small to reach a conclusion regarding specific colposcopic criteria, these results correspond with recent reports, suggesting that there are specific colposcopic criteria for AIS or for mild intraepithelial glandular lesions[23–25]. These criteria refer to lesions covered with glandular epithelium not contiguous with squamocolumnar junction, and they very often have papillary look with budding epithelium, with unequal gland openings and atypical blood vessels. Milojković et al.[26] has found in 12 patients with AIS and CIN that lesion was within big ectopion, surrounded with colposcopic normal glandular epithelium, but outside the transformation zone, as it was the case of squamous lesions.

Conclusion

Cytology and colposcopy as screening methods, but without predicting histological types and lesion grade, have high sensitivity so for cytology it is 89% in the case of histological SIL diagnosis and 98% in the case of GIL, 87% for colposcopy for both types of histological diagnosed lesions.

Positive predictive value of differential cytology in case of squamous lesions is 59%, and 53% for glandular lesion. It must be pointed out that these values can not be compared, since evaluating differential cytological diagnosis, we have tried to differ four subgroups of squamous lesions, but in the case of glandular epithelial lesions only one (smaller the number of groups is, higher is the accuracy). Therefore value of 53% is significantly smaller than 59%.

According to colposcopic abnormality type we cannot differ for certain, SIL

from GIL. Besides GIL are very often accompanied with squamous lesions and specific criteria proving their presence have not been confirmed in praxis yet.

In order to increase differential diagnostic accuracy of GIL, cytologist must get more experiences in his observation, following accepted cytomorphological criteria, so that analysing the smears, he considers the possibility of coexistence of glandular atipija with identified squamous one and looks for it. Colposcopist should learn recently presented, colposcopic pictures and check their importance in praxis.

REFERENCES

1. DRAŽANČIĆ, A., M. STRNAD, S. AUDY-JURKOVIĆ, M. TOMLJANOVIĆ, S. JUKIĆ, N. VEČEK, Incidence and cancer prevention of female genital tract in Croatia. In: ELJUGA, D., A. DRAŽANČIĆ (Eds.): The prevention and diagnostic tumors of female genital tract. (Nakladni zavod Globus, Zagreb, 1998). — 2. ANONYMOUS: Incidencija raka u Hrvatskoj. Bilten br. 23. (Hrvatski zavod za javno zdravstvo, Zagreb, 2001). — 3. JUKIĆ, S., I. DAMJANOV, D. BABIĆ, J. FORKO-ILIĆ, D. JUKIĆ, M. KOS, M. NOLA: Pathology of the female genital tract. (AGM, Zagreb, 1999). — 4. ETHERINGTON, I.J., D. M. LUESLEY, Journal of Lower Genital Tract Disease, 5 (2001) 94. — 5. AUDY-JURKOVIĆ, S., Z. Singer, M. Pajtler, A. Dražančić, V. Grizelj, Gynaecol. Perinatol., 1 (1992) 185. — 6. STAFL, A., G. D. WILBANKS, Obstet. Gynecol., 77 (1991) 13. — 7. REPŠE-FOKTER, A.: Differential cytology of premalignant and malignant lesions of cervix uteri in pregnancy and puerperium. M. Sc. Thesis. (University of Zagreb, Zagreb, 1992). — 8. KWIKKEL, H. J., M. J. QUAAK, C. DE WITH, Eur. J. Obstet. Gynecol. Reprod. Biol., 21 (1986) 101. — 9. HELMERHORST, T. J. M., G. H. DIJKHUIZEN, J. J. CALAME, H. J. KWIKKEL, J., G. STOLK, Eur. J. Obstet. Gynecol. Reprod. Biol., 24 (1987) 721. — 10. ANDERSEN, E. S., K. NIELSEN, B. PEDERSEN, Gynecol. Oncol., 59 (1995) 143. — 11. PAJTLER, M., A. OVANIN-RAKIĆ, S. AUDY-JURKOVIĆ, Diagnostic cytology of the uterine cervix: The value of differential cytology. In: ELJUGA, D., A. DRAŽANČIĆ (Eds.): The prevention and diagnostic tumors of female genital tract. (Nakladni zavod Globus, Zagreb, 1998). — 12. LJUBOJEVIĆ, N., S. BABIĆ, S. AUDY-JURKOVIĆ, A. OVANIN-RAKIĆ, S. JUKIĆ, D. BABIĆ, G. GRUBIŠIĆ, B. RADAKOVIĆ, D. LJUBOJEVIĆ-GRGEC, Coll. Antropol., 25 (2001) 467. — 13. LJUBOJEVIĆ, N., S. BABIĆ, S. AUDY-JURKOVIĆ, A. OVANIN-RAKIĆ, S., JUKIĆ, R. HASIĆ, B., RADAKOVIĆ, M. ČUBRILO-TUREK, D. LJUBOJEVIĆ, S. LJUBOJEVIĆ, Coll. Antropol., 22 (1998) 533. — 14. LEE, K. R., L. J. MINTER, S. R. GRANTER, Am. J. Clin. Pathol., 107 (1997) 30. — 15. LUESLEY, D. M., J. A. JORDAN, C. B. J. WOODMAN, N. WATSON, D. R. WILLIAMS, C. WADELL, Br. J. Obstet. Gynaecol., 94 (1987) 699. — 16. AYER, B., F. PACEY, M. GREENBERG, L. BOUSFIELD, Acta. Cytol., 31 (1987) 397. — 17. BETSILL, W. L., Jr., A. H. CLARK, Acta. Cytol., 30 (1986) 115. — 18. RAAB, S. S., C. ISACSON, L.J. LAYFIELD, J. C. LENEL, D. D. SLAGEL, P.A. THOMAS, Am. J. Clin. Pathol., 104 (1995) 574. — 19. LEE, K. R., E. A. MANNA, T. ST. JOHN, Diagn. Cytopathol., 13 (1995) 202. — 20. CENCI, M., R. MANCINI, I. NOFRONI, A. VECCHIONE, Acta Cytol. 44 (2000) 319. — 21. CENCI, M., R. MANCINI, I. NOFRONI, A. VECCHIONE, Acta. Cytol., 44 (2000) 327. — 22. LEE, K. R., L. J. MINTER, S. R. GRANTER, Am. J. Clin. Pathol., 107 (1997) 30. — 23. PAJTLER, M., M. MILOJKOVIĆ, Differential cytology of the glandular lesions of the uterine cervix. In: Book of Abstracts (II. Croatian Congress of Clinical Cytology with International Participation, Zagreb, 2000). — 24. MITCHELL, M. F., D. SCHOTTENFELD, G. TORTORELO-LUNA, S. B. CANTOR, R. RICHARDS-KORTUM, Obstet. Gynecol., 91 (1998) 626. — 25. SINGER, A., J. M. MONAGHAN: Lower genital tract precancer: Colposcopy, pathology and treatment. (Blackwell Science, Oxford, 2000). — 26. WRIGHT, V. C., Journal oh Lower Genital Tract Disease, 3 (1999) 83. — 27. WRIGHT, V. C., H. C. ETTLER, Colposcopic features of adenocarcinoma in situ and adenocarcinoma of the cervix. In: Abstract book. (EUROGIN 2000: 14th International Multidisciplinary Congress, Paris, 2000) — 28. MILOJKOVIĆ, M., Z. TOPOLOVEC, Z. KASAČ, M. ROSSO, Gynaecol. Perinatol., 10 (2001) 59.

M. Pajtler

Department of Clinical Cytology, University Hospital Osijek, J. Huttlera 4, 31000 Osijek, Croatia

DIJAGNOSTIČKA VRIJEDNOST CITOLOGIJE I KOLPOSKOPIJE ZA SKVAMOZNE I GLANDULARNE INTRAEPITELNE LEZIJE VRATA MATERNICE

S A Ž E T A K

Cilj rada je bio odrediti dijagnostičku vrijednost citologije i kolposkopije kao metoda probira i diferencijalne dijagnoze, te relativnu vrijednost pojedinih kolposkopskih abnormalnosti za pločaste i cilindrične intraepitelne lezije cerviksa. Citološka dijagnoza i kolposkopski nalaz su uspoređeni s histološkim u 187 bolesnica s intraepitelnom lezijom (142 pločaste i 45 cilindričnih sa ili bez pločaste komponente). Na temelju toga je određena osjetljivost (O) citologije i kolposkopije u probiru, osjetljivost (O), specifičnost (S) i pozitivna prediktivna vrijednosti (PPV) diferencijalne citologije, te tipovi kolposkopskih abnormalnosti vezani uz pločaste / cilindrične intraepitelne lezije. O citologije kao metode probira za SIL (squamous intraepithelial lesions) iznosi 89%, a za GIL (glandular intraepithelial lesions) 98%. PPV diferencijalne citologije za SIL iznosi 59%, a za GIL 53%. O kolposkopije za oba tipa lezija iznosi 87%. Acetobijeli epitel je značajno češće nađen uz SIL, a atipična vaskularizacija i nejednaki, prošireni otvori žlijezda uz GIL ($P<0,05$). Citologija i kolposkopija kao metode probira, imaju visoku osjetljivost. Citologija je mnogo točnija u predviđanju diferencijalne dijagnoze SIL nego GIL, a određene kolposkopske abnormalnosti koje bi ukazivale na GIL treba provjeriti u praksi.