Pap Smear Adequacy – Is the Assessing Criterion Including Endocervical Cells Really Valid?

M. Pajtler[1] and S. Audy-Jurković[2]

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

A B S T R A C T

The significance of endocervical cylindrical cells (EC) as a criterion of sample adequacy has been established on 1,000 patients by comparing VCE smears (vaginal, cervical, endocervical) with or without EC in relation to prevalence of abnormal cells, prevalence of histological diagnosed lesions and sensitivity and negative predictive value of Pap smear, as well as by comparison of negative findings without EC with control smears with the aim of discovering overlooked lesions. A considerably greater yield of cytological (107/536 in relation to 49/464) and histological (105/536 in relation to 55/464) (p<0.05) abnormalities in smears with EC support the hypothesis that the presence of EC is strongly and positively associated with prevalence of disease. In contrast, the presence of EC predicts only a moderate improvement in Pap smear quality with a weaker effect on sensitivity (95% in relation to 80%). During two-years monitoring of patients with negative Pap smear and negative colposcopy (403 with EC and 390 without EC in smears), no positive cytology/histology diagnosis was made. Also, because the prevalence of missed lesions among negative Pap smears is extremely low in absolute terms, no appreciable impact on negative predictive value was observed (98.8% in relation to 97.3%).

Introduction

Although many papers have already pointed out to the problem of inadequate samples, it was only in Bethesda 1988 system of cytological findings classification (TBS)[1] included the evaluation of sample adequacy as a starting point of any cytological finding. It is generally agreed that smears with scant cellularity, inadequately fixed smears, smears obscured by blood, inflammatory exudate or foreign material that hinder the analysis of cell particulars should be considered

non-satisfactory. On the other hand, TBS as a criterion of sample adequacy includes the presence of cells from the endocervical/transformation zone, searching for, »at a minimum, of two clusters of well-preserved endocervical glandular and/or squamous metaplastic cells, with each cluster composed of at least five cells.«.

The hypothesis that endocervical cylindrical cells (EC) or metaplastic cells point to a satisfactory smear is based on the fact that most squamous intraepithelial lesions (SIL) occur in transformation zone (TZ). That is the reason why there is a lower probability for a negatively interpreted finding to be the consequence of error in sample-taking if the cytological sample contains cells normally found in or near the transformation zone.

Numerous papers were written about the significance of EC as an adequacy criterion even before TBS, the results of the latter being often controversial and confusing. This criterion is favored by the works which show that displastic/SIL cells are more often found in smears in which EC are present[2–6], whereas it is not favored by those which show that women without EC do not manifest[7–9] a higher probability of a falsely-negative finding[7,10–12] or a higher probability of squamous lesion in subsequent smears. A logical explanation is offered by Birdsong[13] pointing that aforementioned studies can be divided into two groups and asked a different question, in which case one would not exclude the other. One group asks the question: Is the presence of EC connected with the presence of abnormal cells? The other one asks the question: Is the absence of EC in negative smears connected with a higher probability of false-negative interpretation?

In order to verify the hypothesis in practice in this paper is analyzed the association between the presence of EC and 1) prevalence of abnormal cells, 2) prevalence of histological diagnosed lesions and 3) sensitivity and negative predictive value of Pap smear.

Materials and Methods

The prospective study encompasses a group of 1,000 non-pregnant women between the age of 20 and 50 from whom, during a clinical examination, a VCE smear (vaginal, cervical, endocervical) was taken with wooden spatula and a cotton swab and it was stained according to Papanicolaou method; the findings were classified according to the Croatian modification of TBS[14]. After that in all patients a native and than extended colposcopy with 3% solution acetic acid was carried out. The findings were formulated in accordance with the terminology agreed upon at 7th World Congress for cervix pathology and colposcopy held in Rome in 1990[15]. Within six months 207 patients with a cytological and/or colposcopical positive finding were subjected to histological verification. The patients with a negative cytological finding, but without histological examination had a cytological follow-up for next two years with a minimum of four VCE smears. The first of control endocervical smear is obtained with the cytobrush (Cytobrush Plus, Medscand Medical), and the other with the cotton swab.

The finding of endocervical cylindrical cells as a criterion of sample adequacy was assessed by comparing a VCE smear with and without EC in relation to prevalence of abnormal cells, prevalence of histological diagnosed lesions and sensitivity and negative predictive value of Pap smear, as well as by comparison of negative findings without EC with control smears with the aim of discovering overlooked lesions. All intraepithelial and invasive lesions were considered as a positive cytological and histological finding,

while the rest of them were considered as a negative.

Results

Out of the first 1,000 cytological smears in 536 (53.6%) cases the sample adequacy was assessed as satisfactory for evaluation, while in the remaining 464 (46.4%) cases the sample was assessed as satisfactory although limited. There were no unsatisfactory for evaluation samples. In all of the 464 patients the sample was assessed as »less than optimal« because it did not contain EC (100%), whereas in 12 patients (2.6%) there was also some other reason (Table1).

The cytological finding was positive in 107 out of 536 (20%) samples with EC and in 49 out of 464 (11%) samples without EC (Table 2). The difference is statistically significant (P < 0.05).

Table 3 shows the number and result of colposcopical-guided biopsies in relation to the presence of EC and of cytological abnormalities. During two-years monitoring of patients with negative Pap smear and negative colposcopy (403 with EC and 390 without EC in smears), no positive cytology/histology diagnosis was made. Thus, cervical lesions diagnosed remained 105 and 55, respectively. The frequency of CIN2–3 / carcinoma cases in

the two groups was 18 % (98/536) and 8 % (39/464).

Table 4 shows the main outcome measures based on data in Table 3. In accordance with the prevalence of positive cytology results, the prevalence of histologi-

TABLE 1
EXPLANATION FOR LESS THAN OPTIMAL
VCE SAMPLES (N=464)

Explanation	n	%
No endocervical cylindrical cells	464	100.00
Scant cellularity	5	1.10
Partially or completely obscuring blood	3	0.66
Partially or completely obscuring inflammation	2	0.44
Excessive cytolysis or autolysis	1	0.22
Poor fixation or preservation	1	0.22

TABLE 2
CYTOLOGICAL FINDING IN RELATION TO
ENDOCERVICAL CYLINDRICAL CELLS
(N=1,000)

Endocervical cylindrical cells	Cytological finding		Total
	Negative	Positive	
Present	429	107	536
Not present	415	49	464
Total	844	156	1,000

TABLE 3
ENDOCERVICAL CYLINDRICAL CELLS IN RELATION TO
CYTOLOGICAL-HISTOLOGICAL COMPATIBILITY (N=207)

Endocervical cylindrical cells	Cytological finding	Histological finding			Total
		None*	Negative	Positive	
Present	Negative	403	21	5	429
	Positive	–	7	100	107
	Total	403	28	105	536
Not present	Negative	390	14	11	415
	Positive	–	5	44	49
	Total	390	19	55	464

* Negative colposcopy with 2-year negative cytology follow-up

TABLE 4

DIAGNOSTIC VALUE OF CYTOLOGY IN RELATION TO ENDOCERVICAL CYLINDRICAL CELLS

Endocervical cylindrical cells	Diagnostic value (%)		
	P	S	NPV
Present	20	95	98,8
No present	12	80	97,3

P = prevalence of histological diagnosed lesions; S = sensitivity; NPV = negative predictive value

TABLE 5

ENDOCERVICAL CYLINDRICAL CELLS IN SMEARS TAKEN WITH COTTON SWAB AND CYTOBRUSH IN WOMEN WITH NEGATIVE CYTOLOGICAL FINDINGS AND A LACK OF HISTOLOGICAL VERIFICATION (N=793)

Smears taken with cytobrush	Smears taken with cotton swab		Total
	EC present	EC no present	
EC present	389	351	740
EC not present	14	39	53
Total	403	390	793

EC = endocervical cylindrical cells

cal diagnosed lesions was greater among cases with EC in Pap smear (P<0.05). The increase in sensitivity was significant (P<0.05) but far less pronounced. The impact on negative predictive value was negligible and no significant.

Since the first of the 793 control smears was taken with the cytobrush, the EC finding of those samples was compared with the first smears taken with the cotton swab (Table 5).

In smears taken by cytobrush the EC were found in 93.3% of cases, which is significantly more frequent than in smears taken with the cotton swab (50.1%) (P<0.05). However, in spite of the high proportion satisfactory samples, there were no newly discovered abnormalities.

Discussion

Most authors agree that the presence of EC in cervical smears points to its origin from the transformation zone, but they do not agree about their use as a sample adequacy criterion and about the recommendations it entails.

The group of studies supporting the hypothesis that EC are an good indicator of a satisfactory smear, proved that the abnormal cells are more often present in samples containing EC than in those not containing them[2–6]. However, both for the patient and for her doctor it is more important to know whether the proportion of false negative findings is higher in samples without EC than in those with EC. In four large retrospective studies the EC finding in the first screening was compared with the finding with epithelial abnormalities in the second screening. No more abnormal findings were found in women whose first finding did not contain EC than in those whose first finding did. In other words, no greater risk of a squamous intraepithelial lesion (SIL) following the smear without EC[7,10–12] was proved. The results and conclusions of the other two studies of the same kind were quite opposite[3,6].

In the two studies in which numerous parameters, including the EC finding in smears preceding the histological diagnosis of the cervical intraepithelial neoplasm gradus 3 (CIN 3), no significant differences were found in terms of the presence/absence of EC[7–9]. In one of the few studies based on a histological criterion no difference in the accuracy of abnormality discovery [9] was found when smears with and without EC were taken under control of a colposcope from patients with histologically confirmed dysplasia. Those results do not confirm the hypothesis that endocervical cylindrical cells are an appropriate indicator of sample adequacy.

Birdsong[13] has correctly understood that it is justifiable here to wonder whether the conclusions of these seemingly opposite groups of studies concerning the significance of EC as indicators of sample adequacy are really contradictory. However confusing this might appear, these two groups are actually asking different questions. One of them is asking: Is the presence of EC related to the presence of abnormal cells? The others are asking the question: Is the absence of EC in negative smears related to a higher probability of false-negative interpretation? Both studies we have quoted answer »Yes« to the first question and »No« to the second, which may be surprising but not contradictory. The presence of EC may be connected with the presence of abnormal cells, while their absence still does not necessarily imply a lower sensitivity. This is in keeping with the perception that the presence of EC is connected with the presence of abnormal cells. However, there is firm evidence that smears without EC do not imply a higher probability of being false-negative than those containing EC.

A considerably greater yield of cytological and histological abnormalities in smears with EC support the hypothesis that the presence of EC is strongly and positively associated with prevalence of disease. In contrast, the presence of EC predicts only a moderate improvement in Pap smear quality with a weaker effect on sensitivity. Also, because the prevalence of missed lesions among negative Pap smears is extremely low in absolute terms, no appreciable impact on negative predictive value was observed.

In practice this means that smears with EC represent just a sample taken from or near TZ, but it also means that negative smears without EC which, in accordance with the applied classification, are »less than optimal«, do not need to be repeated earlier than those with EC. That conclusion is in keeping with recommendations of Bethesda 2001 classification[16] that in order to prove the presence of the TZ component it is necessary to find at least 10 well- preserved endocervical or squamous metaplastic cells, the absence of which, however, does not point to the need of an earlier repetition of smear-taking.

REFERENCES

1. ANONYMOUS, Acta Cytol., 33 (1989) 567. — 2. ELIAS, A., G. LINTHORST, B. BEKKER, P. G. VOOIJS, Acta Cytol., 27 (1983) 225. — 3. VOOIJS, P. G., A. ELIAS, Y. VAN DER GRAAF, S. VELING, Acta Cytol., 29 (1985) 323. — 4. HENRY, J. A., V. WADE-HRA, Acta Cytol., 40 (1996) 529. — 5. YOUNG, W., Cytopathology, 11 (2000) 116. — 6. MINTZER, M., P. CURTIS, J. C. RESNICK, D. MORRELL, Cancer Cytopathology, 87 (1999) 113. — 7. MITCHELL, H., G. MEDLEY, Cytopathology, 6 (1995) 68. — 8. O'SULLIVAN, J. P., R. P. A' HERN, P. A. CHAPMAN, L. JENKINS, R. SMITH, A. AL-NAFUSSI, M. T. BRETT, A. HERBERT, M. E. MCKEAN, C. A. WADDELL, Cytopathology, 9 (1998) 155. — 9. SIDAWY, M. K., S. O. TABBARA, S. G. SILVER-BERG, Diagn. Cytopathol., 8 (1992) 5670. — 10. KIVLAHAN, C., E. INGRAM, Acta Cytol., 30 (1986) 258. — 11. MITCHELL, H., G. MEDLEY, Lancet, 337 (1991) 265. — 12. BOSS, A. B., M. VAN BALLEGO-OIJEN, M. ELSKE VAN DEN AKKER-VAN MARLE, A. G. HANSELAAR, G. J. VAN OORTMARSSEN, J. D. HABBEMA, Am. J. Clin. Pathol., 115 (2001) 851. — 13. BIRDSONG, G. G., Diagn. Cytopathol., 24 (2001) 79. — 14. AUDY-JURKOVIĆ, S., Z. SINGER, M. PAJTLER, A. DRAŽANČIĆ, V. GRIZELJ, Gynaecol. Perinatol., 1 (1992) 185. — 15. STAFL, A., G. D. WILBANKS, Obstet. Gynecol., 77 (1991) 13. — 16. ANONYMOUS: http://bethesda2001.cancer.gov/ post wrkshp_recs.htlm. (Workshop, Bethesda 2001).

M. Pajtler

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

PRIMJERENOST PAPA RAZMAZA: JESU LI ENDOCERVIKALNE CILINDRIČNE STANICE UISTINU VALJANI KRITERIJ OCJENE?

S A Ž E T A K

Značenje endocervikalnih cilindričnih stanica (EC) kao kriterija primjerenosti uzorka je određeno na 1.000 ispitanica usporedbom VCE (vaginalni, cervikalni, endocervikalni) razmaza sa i bez EC u odnosu na prevalenciju abnormalnih stanica i histološki dijagnosticiranih lezija, osjetljivost i negativnu prediktivnu vrijednost, te usporedbom negativnih nalaza bez EC s kontrolnim razmazima u smislu naknadnog otkrivanja propuštenih lezija. Značajno veći broj citoloških (107/536 u odnosu na 49/464) i histoloških (105/536 u odnosu na 55/464) (p<0,05) abnormalnosti u razmazima sa EC je jako i pozitivno povezan s prevalencijom lezija. Suprotno tome, prisustvo EC predstavlja samo izvjesno poboljšanje kvalitete Papa razmaza s malim efektom na njegovu osjetljivost (95% u odnosu na 80%). Tijekom dvogodišnjeg praćenja bolesnica s negativnim citološkim i kolposkopskim nalazom (403 sa EC i 390 bez EC u razmazima), nije bilo novootkrivenih pozitivnih histoloških/citoloških nalaza. Negativna prediktivna vrijednost se nije značajno razlikovala u odnosu na prisustvo EC (98,8% u odnosu na 97,3%), što ukazuje na činjenicu da razmazi bez EC ne nose nužno veći rizik lažno negativnog nalaza.