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Comparison of Pap-smear and Colposcopy in the Absence of HPV Test for the Diagnosis of Premalignant and Malignant Cervical Lesions

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ABSTRACT

In this study, we aimed to evaluate the Pap-smear results and colposcopic findings of 163 patients admitted to the colposcopy unit of our hospital with the histopathological examination results of cervical sampling for abnormal Pap-smear and/or colposcopy findings in the absence of HPV test.

All patients underwent gynaecological examination, and Pap-smear test was performed. Subsequently, the cervix was examined by colposcopy. Local medical treatment, Pap-smear follow up, cervical sampling or surgery was recommended according to Pap-smear, colposcopic examination results and other clinical examination findings.

Negative predictive value (NPV), positive predictive value (PPV), sensitivity and specificity of Pap-smear were 88.1%, 13.3%, 28.5% and 74%, respectively. NPV, PPV, sensitivity and specificity of colposcopy were 93.3%, 14.3%, 85.7 and 76.2%, respectively.

The combined use of Pap-smear and colposcopy in the detection of premalignant and malignant lesions of the cervix increases the success and enables early diagnosis and appropriate treatment in the absence of HPV test.

Key Words: Colposcopy, cervical smear, cervical malignancy

Introduction

Cervical cancer is the most common gynaecological cancer in developing countries (1). The most crucial feature of cervical cancer is that it has a long pre-malign period and develops from premalignant lesions which are not adequately followed or treated (2). For this purpose, screening the population in the asymptomatic period and performing other diagnostic procedures in necessary cases are of clinical importance. When premalignant lesions are detected, it is possible to treat these lesions without progressing to in-situ and/or invasive cancer with appropriate follow up and treatment (2). As a matter of fact, the incidence of invasive cervical cancer has decreased considerably in developed countries where screening and follow-up methods are performed well (3).

Papanicolaou smear (Pap-smear, cervicovaginal cytology), has an essential role in cervical screening. In the evaluation of Pap-smear results, the Bethesda System terminology developed for cytological reports took its final form in 2014 (4). In this system, premalignant squamous lesions are divided into four headings: Atypical squamous cell of undetermined significance (ASCUS), atypical squamous cells-cannot exclude high-grade squamous intraepithelial lesion (ASC-H), the low-grade squamous intraepithelial lesion (LSIL), the high-grade squamous intraepithelial lesion (HSIL). According to this system, mild dysplasia (CIN I) is considered as LSIL, while moderate (CIN II) and severe (CIN III) dysplasia are considered as HSIL. Glandular epithelial abnormalities are classified as atypical glandular cells (AGC), endocervical in situ adenocarcinoma (AIS) and adenocarcinoma (endocervical, endometrial, extrauterine and non-specific).

Colposcope has been developed as a binocular microscope that allows direct observation of abnormal areas and lesions that can be overlooked by other methods since the false-negative and false-positive rates of Pap-smear are significantly higher and blind cervical biopsies bypass small lesions (5). However, the sensitivity and specificity

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of colposcopy, interobserver agreement, repeatability difficulties indicate that the accuracy of this method is suboptimal (6).

HPV testing and genotyping are not always possible, although HPV has proven its role in the etiology of cervical cancer. In this study, we aimed to evaluate the Pap-smear results, colposcopic examination findings and histopathologic examination results of patients who had an abnormal smear and/or colposcopy in the absence of HPV test.

Materials and Methods

This study was performed with the approval of Dicle University Faculty of Medicine Ethics Committee, evaluating the results of 163 married patients referred to the colposcopy unit of the same hospital due to their smear results or gynaecological examination findings. Age, educational status, number of pregnancies, contraception method, smoking, Pap-smear results, colposcopic examination findings and histopathological examination results were evaluated. According to cervical examination findings, the patients included in the study were bleeding with touch, abnormal cervical discharge, chronic cervicitis findings, cervical erosion, hypertrophic cervix, suspicious mass or ulcer appearance in the cervix. Pregnant women, women who had vaginal preparations or vaginal douches in the last 48 hours were excluded from the study.

For cervical cytology, the cervical smear was taken with cytobrush and spread thinly on the slide and fixed with 95% ethyl alcohol. The slides were stained with Papanicolaou staining protocol in the pathology department. Pap-smear results were defined based on the 2001 Bethesda system by the pathologist.

Colposcopy Technique: Subepithelial vascular structures were examined by damping 10 cc saline to the cervix. Subsequently, 5% acetic acid solution was applied, and the cervix was examined with Leisegang brand (Model 1DW-LED) binocular colposcope, which can be connected to a teaching monitor. Cervical tissue was evaluated for normal and abnormal colposcopic findings with a magnification of 7.5/15/30, respectively. Atypical vessels, acetowhite epithelium, punctuation and mosaicism were evaluated as abnormal colposcopy findings.

After deciding cervical sampling by smear and/or colposcopic findings, the sampling method to be selected was determined according to the additional findings obtained in the patient's gynaecological examination. Loop electrosurgical excision procedure (LEEP) or conization was recommended for patients with chronic cervicitis, ectropion, cervical deformation/laceration (emmet tears, fish mouth, stellate). A cervical punch biopsy was performed to those with the normal gynaecological examination. Polypectomy was performed in patients with cervical polyps who had a normal cytological and colposcopic examination, and cervical cauterization was performed in patients with nabothian cysts due to chronic cervicitis.

Statistical Analysis: SPSS 16.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. A descriptive analysis of the records was performed following completion of the audit. Categorical data were expressed as number and percentage.

Results

One hundred and twenty-seven (77.9%) of the patients were in the reproductive age group (20-49 years). The number of smokers was 12, and all of them had normal Pap-smear results. Seven of these patients underwent cervical sampling for colposcopy findings. The result of 2 cases was LSIL.

Pap-smear test results were normal in 148 patients (90.7%), ASCUS in 10 patients (6.2%) and LSIL in 5 patients (3.1%) (Table 1).

Colposcopic examination findings of 121 patients (74.2%) were normal, and abnormal findings were observed in 42 (25.8%) patients (Table 2). Abnormal colposcopy findings were seen in 4 of 10 ASCUS cases and 3 of 5 LSIL cases.

Advanced examination and treatment modalities recommended by evaluating the examination, Pap-smear and colposcopy findings of the patients are shown in table 3.

Histopathological examination was performed in 8 patients who were reported as ASCUS at Pap-smear test. Results of 6 patients were reported as chronic cervicitis, 1 as LSIL, and 1 as squamous cell cancer. Histopathological examination of 3 patients with Pap-smear test LSIL was reported as LSIL (table 4). NPV, PPV, sensitivity and specificity values were found to be 88.1%, 13.3%, 28.5% and 74.0% for cytological examination;

Table 1. Pap-smear results of the patients

Pap-smear results	Number	%
Normal	148	90.7
ASCUS	10	6.2
LSIL	5	3.1
Total	163	100,0

Table 2. Colposcopy findings of the patients

Colposcopy findings	Number	%
Normal	121	74.2
Abnormal	42	25.8
Total	163	100.0
Abnormal colposcopy findings	**Number**	**%**
Atypical vessels	14	33.3
Atypical vessels + acetowhite epithelium	7	16.7
Atypical vessels + punctuation	5	11.9
Acetowhite epithelium	9	21.4
Acetowhite epitel + punctuation	2	4.8
Acetowhite epitel + punctuation + mosaicism	3	7.1
Punctuation	2	4.8
Total	42	100.0

Table 3. Recommended advanced examination and treatment modalities

Recommended advanced examination and treatment	Number	%
Local treatment	104	63.8
LEEP + endocervical curettage	17	10.4
Directed cervikal punch biyopsy	17	10.4
Conization	16	9.9
Polypectomy	6	3.6
Cervical cauterization	2	1.2
Polypectomy + LEEP + endocervical curettage	1	0.6
Total	163	100.0

93.3%, 14.3%, 85.7% and 76.2% for colposcopy, respectively (Table 5).

Discussion

It is known that smoking is a co-factor in the formation of premalignant and malignant lesions of the cervix (6). In this study, LSIL was reported in 2 patients who had normal Pap-smear test results but underwent cervical sampling for abnormal colposcopy findings.

ASCUS is the most commonly reported cervical cytology abnormality in most studies (7, 8). In this study, the rate of patients with ASCUS was 6.2%. Insinga et al. reported an annual incidence of 1.2 per 1000 for CIN 1 and 1.5 per 1000 for CIN 2-3 (a7). Although our research cases were not statistically sufficient for such an evaluation when compared with Insinga's rates, it was found that our case group and perhaps the regional population they represented were in the high-risk group.

In our study, among the abnormal colposcopy findings, two findings that were the basis of other accompanying findings were atypical vessels and the presence of acetowhite epithelium. Atypical vessels are more specific and have a higher diagnostic value than acetowhite epithelium (9). Because acetowhite epithelium is seen in cases of immature squamous metaplasia, regeneration,

Table 4. Histopathology results of the patients with abnormal Pap-smear

Results of histopathology	ASCUS	LSIL	Total
Chronic cervicitis	6 (75%)	3(100%)	9 (81.8%)
LSIL	1 (12.5%)		1 (9.1%)
Squamöz cell CA	1 (12.5%)		1 (9.1%)
Toplam	8 (100%)	3 (100%)	11

Table 5. Sensitivity, specificity, negative predictive and positive predictive values of Pap-smear and colposcopy

Method	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)
Pap-smear	28.5	74.0	88.1	13.3
Colposcopy	85.7	76.2	93.3	14.3

ectropion or congenitally (10). However, considering the possibility of HPV infection, CIN, AIS, adenocarcinoma or invasive squamous carcinoma with the presence of acetowhite epithelium, HPV DNA screening and/or colposcopy directed cervical biopsy and histopathological examination will be prudent.

It is known that ASCUS cases should be followed up with repeated cytological examinations and/or colposcopic examinations (11). In one study, the prevalence of normal cervix, HSIL and invasive cancer was 58%, 7% and 0.5%, respectively, at the time of diagnosis of ASCUS. So even the first abnormal Pap-smear result may be indicative of cancer. Yang and Zachariah followed ASCUS cases for 14 months (12). They detected SIL rate of 67% in cases followed by biopsy and smear, and 17% in cases followed by smear alone. They suggest that the diagnosis of ASCUS on smears is a good predictor for SIL, but that follow-up with smears alone is more inadequate than biopsy follow-up. These retrospective studies are open to discussion in some aspects. An example of the subjects that can be discussed is the fact that the cases referred to colposcopic biopsy are already at high risk clinically and a higher rate of SIL is detected in the biopsy group. All these literature data show the necessity of cervical sampling and tissue diagnosis with cytology, repetition of cytology and colposcopy.

Cervical sampling was performed in 11 out of 15 patients with ASCUS or LSIL as a result of Pap-smear, in 9 cases chronic cervicitis, in one case LSIL, and in one case squamous cell cancer were detected. This is an expected result, and accurate and definitive treatment can be planned when screening and diagnostic procedures are performed within the algorithm. This evaluation is supported by the literature. In a study, when cytological results of histopathologically diagnosed HSIL and cervical cancer were evaluated, 82.61% of the were HSIL, 13.04% were ASCUS, and 4.35% were LSIL (13). In a study of 22663 cases study by Sankaranarayanan et al., they reported ASCUS in 8.8%, LSIL in 6.2% and HSIL in 1.8% in the cytological examination of the cases. They performed colposcopy directed biopsy in 5322 cases. Detected LSIL in 931 cases, HSIL in 355 cases and invasive cervical cancer in 74 cases (14).

In our study, when six patients whose histopathological result was reported as LSIL were examined, five of them showed abnormal colposcopic findings, although the Pap-smear test result was normal. Normal colposcopic findings were found in one case while Pap-smear result was ASCUS. One patient with histopathology of squamous cell carcinoma had ASCUS and abnormal colposcopic findings. These results are expected, and it is seen that smear and colposcopy are complimentary screening and diagnostic methods. When used together when necessary, it is of value in the proper planning of treatment and follow-up.

In the literature, different values are given for the sensitivity and specificity of Pap-smear. The most important reason for this is the differences in the methods to verify the Pap-smear result. The most accurate diagnosis is possible by histopathology of the cervix. In a meta-analysis of 62 studies, Pap-smear sensitivity ranged from 11-99%, and specificity ranged from 14-97% (15). They suggest that Pap-smear may be unable to achieve concurrently high sensitivity and specificity. In a study examining 1200 cases, they reported Pap-smear sensitivity as 72%, specificity as 90.2%, PPV as 55.7 and NPV as 94.9% (16). Rieck et al. reported a sensitivity of 78.9% and specificity of 71.3% for Pap-smear (17). In our study, NPV,

PPV, sensitivity and specificity values were found to be 88.1%, 13.3%, 28.5% and 74.0% for cytological examination; 93.3%, 14.3%, 85.7% and 76.2% for colposcopy, respectively. In the literature, Pap-smear sensitivity and specificity values show a wide distribution. Although the values obtained in our study are consistent with some studies, they show differences with others. This was thought to be related to the risk group of the patient population, the number of cases, different features or deficiencies likely to occur at each stage of cytological examination.

Different PPV's are given for Pap-smear. When positive cytology is confirmed by repeated smears, In one study, Pap-smear had a PPV of 65% for LSIL and a PPV of 20% for ASCUS (18). In our study, the most crucial reason for PPV differs from the literature results for Pap-smear is the differences in the methods confirming Pap-smear.

In a study by Kohli et al., the sensitivity and specificity of colposcopy were 96% and 48%, respectively. However, NPV and PPV were not reported in this study (19). In the study of Živadinović et al., the sensitivity and specificity of colposcopy were reported to be 96% and 57%, respectively and it was proposed to combine cytology with colposcopy to reduce the of false-negative cytology results (20). In the study of Wu et al., NPV was reported as 87.8%, PPV was 40.0%, sensitivity was 55.5%, and specificity was 79.4% for colposcopy. In our study, NPV was found to be 93.3%, and this value is consistent with other studies. The low PPV (14.3%) in our study can be explained by the fact that smear sensitivity and specificity values are low as in many studies, lack of past Pap-smear results of patients, low probability of most of them coming to control and follow-up, and lack of HPV DNA screening and typing.

HPV testing in cervical cancer screening is not always possible. Limitation and inadequacy of other screening and diagnostic methods such as Pap-smear and colposcopy should be known. In necessary cases, it is possible to increase sensitivity and specificity values with the sequential and combined use of these methods.

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