Acıbadem Univ. Sağlık Bilim. Derg. 2022; 13 (4): 574-578
https://doi.org/10.31067/acusaglik.1137841

ORIGINAL ARTICLE / ARAŞTIRMA YAZISI

Obstetrics and Gynecology / Kadın Hastalıkları ve Doğum

Is it Really Necessary to Perform Colposcopy in Patients with Ascus and HR HPV Positivity?

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ABSTRACT

Introduction: Papanicolaou (Pap) smear is a very important screening method for detection of cervİcal cancer or cell changes that can lead to it. Atypical squamous cells of undetermined significance (ASCUS) is the most common abnormality seen among all cervical cytologies with the percentage of 4-5% . Human papillomavirus (HPV) infection is regarded as a major cause of cervical intraepithelial neoplasia (CIN) and cervical cancer. Colposcopy is recommended for all women with high-grade squamous intraepithelial lesion (HSIL) and atypical squamous cells-cannot exclude high-grade squamous intraepithelial lesion (ASC-H) for cervical cancer screening . It is also recommended for high-risk HPV (HR HPV) positive women with ASCUS. The aim of this study is to evaluate the importance of colposcopy in patients with ASCUS and HR HPV positivity.

Materials and Methods: We performed a retrospective study approved by the ethics committee of Acıbadem University. Women with diagnosis of ASCUS and HR HPV positivity who underwent colposcopic evaluation at 2 different gynecologic oncology clinics of our university from January 2011 to January 2019 were included in our study. The age range was from 21 to 48 and the mean age of patients' was 29. Subjects who were pregnant, hysterectomized or had previous cytological abnormalities were excluded.

Conclusion: In this study, we aimed to evaluate the significance of colposcopy in patients with ASCUS and high-risk HPV positivity, especially strains 16 and 18. As mentioned in some other studies, immediate colposcopy is an expensive screening procedure for further evaluation of ASCUS .

Keywords: Ascus, hpv, colposcopy

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Yüksek riskli HPV pozitif ve ASCUS tanılı hastalarda kolposkopik inceleme ne kadar gerekli?

ÖZET

Pap smear rahim ağzı kanseri veya buna yol açabilecek hücre değişikliklerinin tespiti için çok önemli bir tarama yöntemidir. Önemi belirsiz atipik skuamöz hücreler (ASCUS),tüm servikal sitolojiler arasında %4-5 görülme sıklığı ile en sık görülen anormalliktir.İnsan papilloma virüsü (HPV) enfeksiyonu ,servikal intraepitelyal neoplazi (CIN) ve rahim ağzı kanserinin başlıca nedeni olarak kabul edilir.Servikal kanser taramasında yüksek dereceli skuamöz intraepitelyal lezyon (HSIL) gelen hastalara kolposkopi önerilir.Kolposkopi aynı zamanda yüksek riskli HPV pozitif ve ASCUS tanılı hastalara da önerilir.Bu çalışmanın amacı ASCUS ve yüksek riskli HPV pozitifliği olan hastalarda kolposkopinin önemini değerlendirmektir.

Anahtar Sözcükler: Ascus,hpv,kolposkopi

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Received: 29 June 2022
Accepted: 05 September 2022

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Papanicolaou (Pap) smear is a very important screening method for detection of cervİcal cancer or cell changes that can lead to it. Atypical squamous cells of undetermined significance (ASCUS) is a commonly seen abnormality among all cervical cytologies with the percentage of 4-5% (1). Human papillomavirus (HPV) infection is accepted as a main reason of cervical intraepithelial neoplasia (CIN) and cervix cancer. According to the results of cervical cytology, treatment of most abnormalities is clearly defined by guidelines. However, there is still controversy about treatment of ASCUS and ideal clinical approach to these women is a topic of conflict (2). Repeating the cytological testing, performing colposcopy or determining the high risk types of HPV are all reasonable managements of women with ASCUS (3).

Human papillomaviruses are known to be responsible of various squamous tumors in the skin, and on gastrointestinal, respiratory and genitourinary tract. The HPV lesions seen in the uterine cervix are associated with concomitant CIN, cervical carcinoma in situ (CIS) and invasive cervical cancer. That causes HPV screening tests to be a part of evaluating patients with ASCUS (4). Specific HPV types in HPV screening tests may vary between laboratories. Although types 16 and 18 are accepted oncogenic and cause for 70% of cervical cancers worldwide, at least 12 more types are also known to be oncogenic (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) (5).

Colposcopy is advised for all the women in who are diagnosed withhigh-grade squamous intraepithelial lesion (HSIL) and atypical squamous cells-cannot exclude high-grade squamous intraepithelial lesion (ASC-H) for cervical cancer screening (6). It is also recommended for high- risk HPV (HR HPV) positive women with ASCUS.

In our study we planned to investigate the importance of colposcopy in patients with ASCUS and HR HPV positivity.

MATERIALS AND METHODS

Study Population

We performed a retrospective study approved by the ethics committee of Acıbadem University. Women with diagnosis of ASCUS and HR HPV positivity who underwent colposcopic evaluation at 2 different gynecologic oncology clinics of our university from January 2011 to January 2019 were included in our study. The age range was from 21 to 48 and the mean age of patients' was 29. Subjects who were pregnant, hysterectomized or had previous cytological abnormalities were excluded.

Cervical Cytology

The technology of Gamidor was used for the tests. Pap smear was plannnded by using liquid- based cervical cytology with thin layer cell preparation process. Bethesda classification system was used to analyze samples (7). The results were analyzed as normal, atypical squamous cells of undetermined significance (ASCUS), low-grade squamous intraepithelial lesion (LSIL), atypical squamous cells-cannot exclude high-grade squamous intraepithelial lesion (ASC-H) and high-grade squamous intraepithelial lesion (HSIL).

HR HPV DNA was determined by hybrid capture 2 (HC-2) assay. 14 types of HR HPV (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) were detected by PCR (8). HPV DNA results were defined as positive with a high oncogenic risk HPV strain (16 or 18), positive with other HPV strains or negative.

Colposcopy

Patients with diagnosis of ASCUS and HR HPV positivity who consented to the procedure underwent colposcopic examination after applying 3% acetic acid solution and painting of the cervix with Lugol's solution. The results were grouped into 2 categories: normal colposcopic findings (original squamous epithelium, columnar epithelium and normal transformation zone) and pathological results (acetowhite epithelium, mosaic epithelium, leucoplasia and presence of atypical vessels). For examinations that suggested any cervical abnormality, biopsies were taken from the pathological finding zones, and if there was no visible lesion, from 4 quadrants.

Endocervical curettage was performed in all cases.

Statistical Methods

The data were inputed into a computerized database. The Statistical Package for the Social Sciences (IBM SPSS) software version 23.0 (SPSS, Armonk, NY, USA) was used for analyzing data. Pearson Chi-Square tests for contingency tables were used to assess the associations between categorical variables, and Cramér's V coefficient was used as a measure of association. All statistical tests were investigatsignificant at $p < 0.05$.

RESULTS

Among 115 patients evaluated for ASCUS smear result according to the Bethesda classification system, 28 (45.9%) had normal biopsy results, 21 (34.4%) were found to have CIN1, and 12 (19.7%) were found to have CIN2-3. The

distribution of histopathological diagnosis from biopsies of patients with ASCUS can be observed on Table 1.

Table 1. Biopsy results					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	NORMAL	28	45.9	45.9	45.9
	CIN1	21	34.4	34.4	80.3
	CIN2-3	12	19.7	19.7	
	Total	61	100.0	100.0	100.0

Colposcopic appearance after the acetic acid application can be observed on Table 2. Of the 61 patients, 19 (31.1%) had normal colposcopic findings, 28 (45.9) had acetowhite epithelium, and 14 (23.0) had mosaic epithelium.

The comparison between colposcopic appearance and biopsy results can be observed on Table 3.

Table 2. Colposcopic appearance after the acetic acid application					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Normal Findings	19	31.1	31.1	31.1
	Mosaic Appearance	13	21.3	21.3	52.5
	Acetowhite Appearance	28	45.9	45.9	98.4
	Mosaic-Punctuation	1	1.6	1.6	
	Total	61	100.0	100.0	100.0

Among the patients with normal colposcopic findings, 17 (89.5%) had normal biopsy results, 2 (10.5%) were found to have CIN1, and none (0.0%) were found to have CIN2-3. Of the patients with acetowhite appearance, 11 (39.3%) had normal biopsy results, 15 (53.6%) were found to have CIN1,and 2 (7.1%) were found to have CIN2-3. Among the patients with mosaic appearance, none (0.0%) had normal biopsy results, 4 (28.6%) were found to have CIN1, and 10 (71.4%) were found to have CIN2-3.

The distribution of HPV results according to colposcopic appearance can be observed on Table 4.

Among the patients with with normal colposcopic findings, 4 (21.1%) were positive with a high oncogenic risk HPV strain (16 or 18), 5 (26.3%) were positive with other HPV strains, and 10 (52.6%) had negative HPV result. Of the patients with acetowhite appearance, 12 (42.9%) were positive with a high oncogenic risk HPV strain (16 or 18), 12 (42.9%) were positive with other HPV strains, and 4 (14.2%) had negative HPV result. Among the patients with mosaic appearance, 7 (50.0%) were positive with a high oncogenic risk HPV strain (16 or 18), 5 (35.7%) were positive with other HPV strains, and 2 (14.3%) had negative HPV result.

The comparison between HPV results and biopsy results can be observed on Table 5.

Table 3. Colposcopic appearance vs. Biopsy results						
			Biopsy results			Total
			NORMAL	CIN1	CIN2-3	
Colposcopic appearance	Normal Findings	Count	17	2	0	19
		% within Colposcopy Findings with acetic acid	89.5%	10.5%	0.0%	100.0%
	Mosaic Appearance	Count	0	3	10	13
		% within Colposcopy Findings with acetic acid	0.0%	23.1%	76.9%	100.0%
	Acetowhite Appearance	Count	11	15	2	28
		% within Colposcopy Findings with acetic acid	39.3%	53.6%	7.1%	100.0%
	Mosaic-Punctuation	Count	0	1	0	1
		% within Colposcopy Findings with acetic acid	0.0%	100.0%	0.0%	100.0%
Total		Count	28	21	12	61
		% within Colposcopy Findings with acetic acid	45.9%	34.4%	19.7%	100.0%

Table 4. Colposcopic appearance vs. HPV results

			HPV results			Total
			Negative	16-18 +	Other +	
Colposcopic appearance	Normal Findings	Count	10	4	5	19
		% within Colposcopy Findings with acetic acid	52.6%	21.1%	26.3%	100.0%
	Mosaic Appearance	Count	2	6	5	13
		% within Colposcopy Findings with acetic acid	15.4%	46.2%	38.5%	100.0%
	Acetowhite Appearance	Count	4	12	12	28
		% within Colposcopy Findings with acetic acid	14.3%	42.9%	42.9%	100.0%
	Mosaic-Punctuation	Count	0	1	0	1
		% within Colposcopy Findings with acetic acid	0.0%	100.0%	0.0%	100.0%
Total		Count	16	23	22	61
		% within Colposcopy Findings with acetic acid	26.2%	37.7%	36.1%	100.0%

Table 3. Colposcopic appearance vs. Biopsy results

			Biopsy results			Total
			NORMAL	CIN1	CIN2-3	
HPV results	Negative	Count	7	8	1	16
		% within HPV results	43.8%	50.0%	6.3%	100.0%
	16-18 +	Count	9	13	1	21
		% within HPV results	39.1%	56.5%	4.3%	100.0%
	Other +	Count	9	10	3	22
		% within HPV results	40.9%	45.5%	13.6%	100.0%
Total		Count	25	31	5	61
		% within HPV results	41.0%	50.8%	8.2%	100.0%

Among the patients who were positive with a high oncogenic risk HPV strain (16 or 18), 9 (39.1%) had normal biopsy results, 13 (56.5%) were found to have CIN1, and 1 (4.3%) were found to have CIN2-3. Of the patients who were positive with other HPV strains, 9 (40.9%) had normal biopsy results, 10 (45.5%) were found to have CIN1, and 3 (13.6%) were found to have CIN2-3. Among the patients with negative HPV results, 7 (43.8%) had normal biopsy results, 8 (50.0%) were found to have CIN1, and 1 (6.3%) were found to have CIN2-3.

DISCUSSION

Cervix cancer is the fourth most commonly occurring cancer in women, and lack of effective global screening programs in developing countries prevent decline in the incidence and related mortality (9). Since cervix cancer has a long pre-invasive stage, detection of cervical intraepithelial neoplasia (CIN) that can progress to be an invasive lesion holds importance for earlier treatment (10).

Being the most common Pap smear result (1), ASCUS still is a incompletely defined entity and management of these patients remains controversial. . Nearly 10% to 20% of patients with ASC-US prove to have a varying degree of cervical intraepithelial neoplasia (CIN), which are distinctive precursor lesions of cervical squamous cell carcinoma .As the result of ASCUS could have consequences of normal cervical mucosa to invasive cervical cancer ,it is always confusing for clinicians.Deciding how the manage ,how to treat the result of ASCUS is debated.

Repeating the Pap smear, performing a colposcopic examination or testing for HPV DNA positivity are all possible next steps. A study that compared management algorithms of women with ASCUS showed that repeating the cytologic testing combined with a HPV DNA test was 34% less costly than immediate colposcopy (11). However, patient follow-up still remains a problem in this management. Cytologic follow up is more acceptable than the other managements of diagnosis ASCUS.To repeat Pap smears

every six months for 2 years is recommended.As the high percentage of these will regress and will not require any treatment follow up seems to be the best option.

Moreover, this sensitive test combination has low-specificity, which makes it less useful against colposcopy in many settings (11).

In our study, we planned to investigate the significance of colposcopy in patients with ASCUS and high-risk HPV positivity, especially strains 16 and 18. As mentioned in some other studies, immediate colposcopy is an expensive screening procedure for further evaluation of ASCUS (12).

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