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The Evaluation of Colposcopic Examinations and Cervical Histopathology Results of Women With Abnormal PAP-smear and/or HPV Positivity: A Sample From Amasya

Anormal PAP-smear ve/veya HPV Pozitifliği Olan Kadınların Kolposkopik Muayeneleri ve Servikal Histopatoloji Sonuçlarının Değerlendirilmesi: Amasya Örneği

Banuhan ŞAHİN, Esra GÜNER, Osman Fadıl KARA

Amasya University, Sabuncuoğlu Şerefeddin Training and Research Hospital, Amasya, Turkey

ORCID ID: Banuhan Şahin 0000-0002-8711-1584, Esra Güner 0000-0001-5809-4511, Osman Fadıl Kara 0000-0001-9029-8733

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Corresponding Address
Banuhan Şahin

E-mail
banuhansahin@gmail.com

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ABSTRACT

Aim: To analyze the colposcopic examinations and cervical histopathology results of women who presented at our clinic with abnormal PAP-smear and/or human papilloma virus (HPV) positivity.

Material and Methods: A retrospective examination was made of the colposcopy findings, number of punch biopsies, and final histo-pathological results of patients who presented at the gynecology polyclinic between January 2018 and January 2020 with a smear result showing atypical squamous cells of undetermined significance (ASCUS), low-grade squamous intraepithelial lesions (LGSIL), high-grade squamous intraepithelial lesions (HGSIL), and atypical squamous cells cannot exclude high-grade squamous intraepithelial lesion (ASC-H), and/or HPV test was 16, 18 and other types of positivity. The Chi-square test was applied in the comparisons of the findings.

Results: Evaluation was made of 214 patients with a mean age of 46.54±10.76 years. The PAP-smear results were recorded as ASCUS in 71 (33.2%) patients, ASC-H in 2 (0.9%), LGSIL in 23 (10.7%), HGSIL in 8 (3.7%) and normal or showing inflammation in 110 (51.4%). HPV 16 positivity was determined in 58 (27.1%) patients, HPV 18 positivity in 12 (5.6%), other high-risk type (HR-) HPV positivity in 84 (39.3%) and other type HPV positivity in 53 (24.8%). The colposcopy findings were recorded as leukoplakia in 60 (28%) patients, a punctuation appearance in 40 (18.7%), mosaic appearance in 26 (12.1%), and atypical vascularization in 24 (11.2%). We detected that biopsy was taken from all the colposcopies we made. A single punch biopsy was taken from 53 (24.8%) patients, and multiple biopsies were taken from 161 (75.2%). The histo-pathological results were reported as LGSIL in 45 (21%) patients, HGSIL in 15 (7%) and carcinoma in 1 (0.5%). No correlation was determined between the colposcopic examination findings and the number of punch biopsies (p=0.655). As the number of punch biopsies increased, so the probability of LGSIL, HGSIL and carcinoma increased (p=0.006).

Conclusion: Leukoplakia was the most common colposcopic finding. Gynecologists were in favor of taking multiple biopsies in the clinic. LGSIL was the most encountered histo-pathological result. Colposcopy examination findings did not affect the number of punch biopsies, but it was observed that the possibility of detecting cervical premalignant and malignant lesions increased as the number of punch biopsies increased.

Key Words: Cervical cancer, Colposcopy, HPV, PAP-smear, Punch biopsy

ÖZ

Amaç: Kliniğimize anormal PAP-smear ve/veya insan papilloma virüsü (HPV) pozitifliği ile başvuran kadınların kolposkopik muayeneleri ve servikal histopatoloji sonuçlarını analiz etmek.

Gereç ve Yöntemler: Ocak 2018 ve Ocak 2020 tarihleri arasında jinekoloji polikliniklerimize başvurmuş smear sonucu: atipik skuamoz hücreler (ASCUS), düşük dereceli servikal intraepitelyal lezyon (LGSIL), yüksek dereceli servikal intraepitelyal lezyon (HGSIL) ve atipik skuamoz hücreler-yüksek dereceli lezyonun ekarte edilemediği (ASC-H) olan ve/veya HPV testi:16, 18, ve diğer tipleri pozitif olan kadınların yapılmış kolposkopik muayene bulguları, punch biyopsi sayıları ve en nihai histopatolojik sonuçları retrospektif olarak incelendi. Bulguların karşılaştırılmasında Ki-kare testi kullanıldı.

Bulgular: Çalışmaya dahil edilen 214 hastanın yaş ortalaması 46.54 ± 10.765 idi. PAP-smear sonuçları sırasıyla; 71 (%33.2) hastanın ASCUS, 2 (%0.9) hastanın ASC-H, 23 (%10.7) hastanın LGSIL, 8 (%3.7) hastanın HGSIL ve 110 (%51.4) hastanın normal veya inflamasyon şeklinde idi. HPV 16 pozitifliği 58 (%27.1), HPV 18 pozitifliği 12 (%5.6), diğer yüksek risk tip HPV pozitifliği 84 (%39.3), diğer tip HPV pozitifliği ise 53 (%24.8) kadında mevcuttu. Kolposkopi bulgusu olarak 60 (%28) kadında lökoplaki, 40 (%18.7) kadında beneklenme, 26 (%12.1) kadında mozaik görünüm ve 24 (%11.2) kadında atipik damarlanma mevcuttu. Yaptığımız tüm kolposkopilerden biyopsi alındığını tespit ettik. 53 (%24.8) kadından tek punch biyopsi alınmışken, 161 (%75.2) kadından çoklu punch biyopsi alınmıştı. Histopatolojik sonuçlar 45 (%21) kadında LGSIL, 15 (%7) kadında HGSIL ve 1 (%0.5) kadında karsinom olarak raporlanmıştı. Kolposkopik muayene bulguları ile punch biyopsi alma sayısı arasında ilişki izlenmedi (p=0.655). Ancak, punch biyopsi sayısı arttıkça LGSIL, HGSIL ve karsinom olasılığı da artmaktaydı (p=0.006).

Sonuç: Lökoplaki en sık görülen kolposkopik bulguydu. Klinikte, jinekologlar birden fazla biyopsi almaktan yanaydı. LGSIL en sık karşılaşılan histo-patolojik sonuçtu. Kolposkopi muayene bulguları punch biyopsi sayısını etkilememekteydi, ancak punch biyopsi sayısı arttıkça servikal premalign ve malign lezyonları yakalama olasılığının da arttığı görüldü.

Anahtar Sözcükler: HPV, Kolposkopi, PAP-smear, Punch biyopsi, Serviks kanseri

INTRODUCTION

Cervical cancer is the third most commonly seen cancer in females and the second most common cause of female cancer-related deaths (1). More than 80% of sexually active females will be infected by genital human papilloma virus (HPV) at some point in their lifetime. The majority of genital HPV infections are asymptomatic and are cleared from the body in 1-2 years (2). One of the high-risk HPV type (HR-HPV) is necessary for the development of cervical cancer and HR-HPV is determined in 99% of cervical cancers (3). Although 14 of the HPV types are the high-risk feature, HPV 16 and especially HPV 18 play a role in approximately 70% of cervical cancer cases (4, 5).

As the process of progression from HPV infection to cancer is slow, it is possible to prevent cervical cancer with screening programs. The American Society for Colposcopy and Cervical Pathology (ASCCP) and the American Cancer Society (ACS) recommend a cervical cancer smear test every 3 years before the age of 30 years, and a smear test and an HPV-DNA test (cotest) once every 5 years after the age of 30 years (6). Primary HPV screening has started to become more widespread in recent years and is used in various countries (7, 8). Patients with type 16 or type 18 positivity in primary HPV screening tests are examined with colposcopy independently of the smear result. When there is abnormal cytology in patients with other high-risk HPV positivity, colposcopy is recommended and in the presence of normal cytology, a cotest after 1 year (9).

Colposcopy evaluation as an advanced stage may be necessary in the evaluation of abnormal PAP-smear and HPV-DNA tests used in cervical cancer screening. Biopsy accompanied by colposcopy is accepted as the gold standard in the evaluation of cervical lesions (10). Colposcopy is applied to groups seen to be at risk after the screening HPV and smear tests. Although this is a time-consuming procedure for the clinician that requires experience, early diagnosis and treatment of precancerous lesions is possible with this method (11, 12).

We think the relationship between PAP-smear results, HPV type distributions, colposcopic evaluations and histopathologic outcomes is important to combat cervical cancer from regional to national management. The aim of this study was to examine the colposcopy and histopathology results of patients who applied to colposcopic evaluation because of an abnormal PAP-smear result and/or a positive HPV test in Amasya. Furthermore, it was also aimed to contribute to the epidemiological data that can assist us to foresee the utility effects of colposcopic evaluation in cervical dysplasia.

MATERIAL and METHOD

A retrospective examination was made of the data of 214 patients who presented at the gynecology polyclinic of Amasya Sabuncuoğlu Şerefeddin Training and Research Hospital between January 2018 and January 2020 with an abnormal PAP-smear result and/or HPV positivity. In fact 256 patients with an abnormal PAP-smear result and/or HPV positivity had applied to our clinic within last two years but forty-two women were excluded the study because of their missing data. All the cases had been referred from primary healthcare centers in the context of the National Cervical Cancer Screening Program. HPV-DNA determination was made with the Hybrid Capture 2 test (Qiagen HC2) and genotyping with the CLART kit (Genomica) in the National HPV Laboratory. Patients who had undergone cervical excision, hysterectomy, radiotherapy or chemotherapy because of previous cervical cancer or pre-invasive disease were excluded from the study. All the patients were managed in accordance with the National Cervical Cancer Screening Program. The study was carried out with the permission of Amasya University Ethics Committee (Permission granted/Decision no: 2019/8-45).

For each patient a record was made of age, obstetric history, menopause status, and smoking status. The smear test results of the patients were recorded as atypical squamous cells of undetermined significance (ASCUS), low-grade squamous intraepithelial lesions (LGSIL), high-grade squamous intraepithelial lesions (HGSIL), and atypical squamous cells cannot exclude high-grade squamous intraepithelial lesion (ASC-H). The results of the HPV-DNA typing were recorded as HPV type 16, HPV type 18, other high-risk HPV types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 82), and other HPV types. Colposcopy examinations were made using a binocular colposcope (Olympus OCSS-BA) with a 40-fold magnification capacity and a green filter, connected to a digital screen.

After washing the cervix with saline, examination was made in respect of atypical vascularization using the green filter, then 3% acetic acid was applied to the cervix. Areas of atypical vascularization, aceto-white areas and other abnormal findings were recorded and punch biopsies were taken. The highest grade lesion from the histo-pathology results was accepted as the final pathology result.

Statistical Analysis

Data obtained in the study were analyzed statistically using SPSS vn 20.0 evaluation version software (SPSS Inc, Chicago, IL, USA). Descriptive statistics were recorded as number and percentage for categorical variables and as mean±standard deviation, median, minimum and maximum values for quantitative variables. In the comparisons of the differences between categorical variables, the Pearson Chi-square test was used. A value of $p<0.05$ was accepted as statistically significant.

RESULTS

Evaluation was made of the data of 214 patients with a mean age of 46.54±10.76 years and median parity of 3 (range, 0-8). Of the total patients, 79 (36.9%) were in the postmenopausal period, 135 (63.1%) were premenopausal, and 35 (16.4%) were smokers. The PAP-smear, HPV type, colposcopic evaluation and histo-pathology results are shown as pie charts in Figure 1. The PAP-smear results were recorded as normal in 88 (41.1%), infection in 22 (10.3%), ASCUS in 71 (33.2%), ASC-H in 2 (0.9%), LGSIL in 23 (10.7%), and HGSIL in 8 (3.7%). HPV 16 positivity was determined in 58 (27.1%) patients, HPV 18 positivity in 12 (5.6%), other HR-HPV positivity in 84 (39.3%) and other type HPV positivity in 53 (24.8%). The HPV test was negative in 7 (3.3%) patients (Table 1). Abnormal PAP-smear and HR-HPV types were more detected in non-smoking group.

Colposcopy was applied to all the patients. The findings were recorded as leukoplakia in 60 (28%) patients, punctuation in 40 (18.7%), mosaic appearance in 26 (12.1%), and atypical vascularization in 24 (11.2%). The colposcopy examination was reported as normal in 64 (29.9%) patients. Lesion borders could be visualized in 99 (46.3%) cases. A single punch biopsy was taken from 53 (24.8%) patients, and multiple biopsies were taken from 161 (75.2%). The histo-pathological results were reported as LGSIL in 45 (21%) patients, HGSIL in 15 (7%) and carcinoma in 1 (0.5%). In 41 (19.2%) patients the results were normal, cervicitis was reported in 100 (46.7%) and metaplasia in 12 (5.6%) (Table 2). Abnormal colposcopic findings and advance histo-pathological results were more detected in non-smoking group.

The results of the correlation analysis applied showed no correlation between the colopscopic examination findings and the number of punch biopsies ($p=0.655$). As the number of punch biopsies increased, so the probability of LGSIL, HGSIL and carcinoma was determined to increase ($p=0.006$) (Table 3).

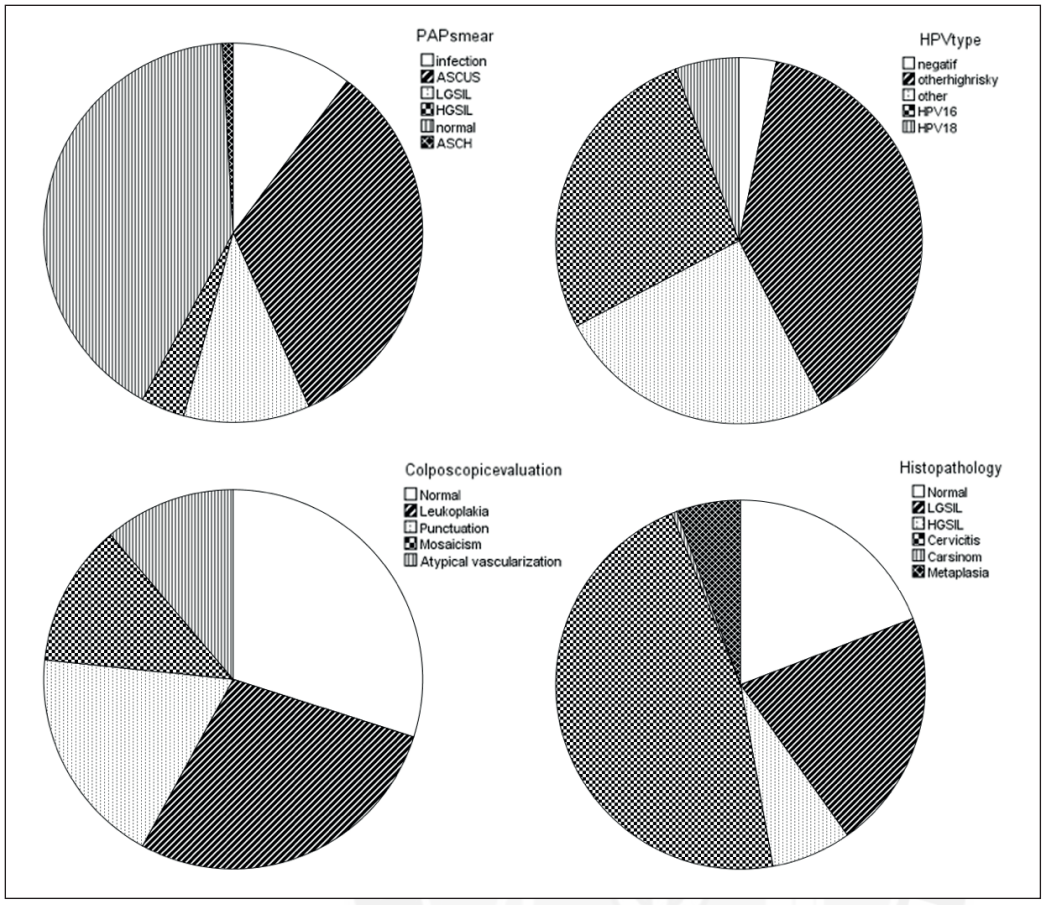

Figure 1: Pie graphics of PAP-smear, HPV type, colposcopic evaluation and histo-pathology results.

Table 1. Demographic data, PAP-smear and HPV types.

		Smoking (+) n=35	Smoking (-) n=179	Total n=214
Age	Mean ± sd	43.11 ± 9.67	47.21 ± 10.86	46.54 ± 10.765
Parity	Median (min-max)	2 (0-5)	3 (0-8)	3 (0-8)
Menopause	Pre-	26 (12.1%)	109 (50.9%)	135 (63.1%)
	Post-	9 (4.2%)	70 (32.7%)	79 (36.9%)
PAP-smear	Normal	18 (8.4%)	70 (32.7%)	88 (41.1%)
	Infection	5 (2.3%)	17 (7.9%)	22 (10.3%)
	ASCUS	6 (2.8%)	65 (30.4%)	71 (33.2%)
	ASC-H	0	2 (0.9%)	2 (0.9%)
	LGSIL	5 (2.3%)	18 (8.4%)	23 (10.7%)
	HGSIL	1 (0.5%)	7 (3.3%)	8 (3.7%)
HPV type	HPV 16	13 (6.1%)	45 (21%)	58 (27.1%)
	HPV 18	3 (1.4%)	9 (4.2%)	12 (5.6%)
	Other HR-HPV	14 (6.5%)	70 (32.7%)	84 (39.3%)
	Other HPV	4 (1.9%)	49 (22.9%)	53 (24.8%)
	Negative	1 (0.5%)	6 (2.8%)	7 (3.3%)

ASCUS: Atypical squamous cells of undetermined significance, **LGSIL:** Low-grade squamous intraepithelial lesions, **HGSIL:** High-grade squamous intraepithelial lesions, **ASC-H:** Atypical squamous cells cannot exclude high-grade squamous intraepithelial lesion, **HR-HPV:** High risky HPV.

Table 2. Colposcopy and histo-pathology results

		Smoking (+) n=35 (16.4%)	Smoking (-) n=179 (83.6%)	Total n=214 (100%)
Colposcopy and histo-pathology results	Normal	11 (5.1%)	53 (24.8%)	64 (29.9%)
	Leukoplakia	5 (2.3%)	55 (25.7%)	60 (28%)
	Punctuation	6 (2.8%)	34 (15.9%)	40 (18.7%)
	Mosaicism	4 (1.9%)	22 (10.3%)	26 (12.1%)
	Atypical vascularization	9 (4.2%)	15 (7%)	24 (11.2%)
Lesion borders were seen		22 (10.3%)	77 (36%)	99 (46.3%)
Lesion borders were not seen		13 (6.1%)	102 (47.7%)	115 (53.7%)
Biopsy	One	10 (4.7%)	43 (20.1%)	53 (24.8%)
	2	8 (3.7%)	48 (22.4%)	56 (26.2%)
	3	3 (1.4%)	25 (11.7%)	28 (13.1%)
	4	14 (6.5%)	63 (29.4%)	77 (36%)
Histo-pathology	Normal	9 (4.2%)	32 (15%)	41 (19.2%)
	Cervicitis	13 (6.1%)	87 (40.7%)	100 (46.7%)
	Metaplasia	1 (0.5%)	11 (5.1%)	12 (5.6%)
	LGSIL	9 (4.2%)	36 (16.8%)	45 (21%)
	HGSIL	3 (1.4%)	12 (5.6%)	15 (7%)
	Carcinoma	0	1 (0.5%)	1 (0.5%)

LGSIL: Low-grade squamous intraepithelial lesions, **HGSIL:** High-grade squamous intraepithelial lesions.

Table 3. Colposcopy findings and results according to the number of punch biopsies

	Number of punch biopsies				p value
	1	2	3	4	
HPV type					0.832
HPV 16	13 (24.5%)	13 (23.2%)	8 (28.6%)	24 (31.2%)	
HPV 18	2 (3.8%)	2 (3.6%)	1 (3.6%)	7 (9.1%)	
Other HR-HPV	22 (41.5%)	25 (44.6%)	12 (42.9%)	25 (32.5%)	
Other HPV	14 (26.4%)	15 (7%)	5 (17.9%)	19 (24.7%)	
Negative	2 (3.8%)	1 (0.5%)	2 (7.1%)	2 (2.6%)	
Colposcopy					0.655
Normal	21 (39.6%)	15 (26.8%)	6 (21.4%)	22 (28.6%)	
Leukoplakia	13 (24.5%)	20 (35.7%)	8 (28.6%)	19 (24.7%)	
Punctuation	10 (18.9%)	9 (16.1%)	4 (14.3%)	17 (22.1%)	
Mosaicism	3 (5.7%)	7 (12.5%)	5 (17.9%)	11 (14.3%)	
Atypical vascularization	6 (11.3%)	5 (8.9%)	5 (17.9%)	8 (10.4%)	
Histo-pathology					0.005
Normal	20 (37.7%) a	4 (7.1%) *b*	6 (21.4%) *a,b*	11 (14.3%) *b*	
Cervicitis	25 (47.2%) *a*	34 (60.7%) *a*	10 (35.7%) *a*	31 (40.3%) *a*	
Metaplasia	2 (3.8%) *a*	3 (5.4%) *a*	1 (3.6%) *a*	6 (7.8%) *a*	
LGSIL	6 (11.3%) *a*	11 (19.6%) *a*	9 (32.1%) *a*	19 (24.7%) *a*	
HGSIL	0 *a*	4 (7.1%) *a*	2 (7.1%) *a*	9 (11.7%) *a*	
Carcinoma	0 *a*	0 *a*	0 *a*	1 (1.3%) *a*	
Total	53 (100%)	56 (100%)	28 (100%)	77 (100%)	

LGSIL: Low-grade squamous intraepithelial lesions, **HGSIL:** High-grade squamous intraepithelial lesions. Each italic letter denotes a subset of 'number of punch biopsies' categories whose column proportions do not differ significantly from each other at the 0.05 level. Chi square and monte carlo simulation module was used.

DISCUSSION

In this study of 214 patients applied with colposcopy in our gynecology clinic during a 2-years period, 3.7% were determined with HGSIL in the PAP-smear result, HPV 16 or 18 was determined in 32.7% and other high-grade type HPV in 39.3%. Of all the colposcopy examinations, 29.9% were reported as normal, the lesion borders were not visualized in 53.7%, and a single biopsy was taken in only 24.8%. In the histo-pathological examinations, 7.5% of patients had HGSIL and above. While the colposcopy examination findings did not change the number of punch biopsies taken, as the number of punch biopsies taken increased, so histo-pathological results of HGSIL and above were seen to be encountered.

Cervical cancer develops with persistent HPV infection (13, 14). As a period of 5-10 years is required for the development of cervical cancer following infection, this broad time band offers the opportunity for the determination of persistent HPV infections (15, 16). The American Food and Drug Administration (FDA) has recently accepted the use of HPV as the primary screening method (17, 18, 19). Turkey was proudly one of the first countries to apply primary HPV screening. In 2014, the National Cervical Cancer Screening Program was started by the Cancer Office Ministry with primary HPV test screening for women aged 30-65 years (20). The screening rates in Turkey have increased 5-6-fold with HPV-based screening compared to the previously applied cytology-based screening (21).

It is very important to determine the prevalence and types of HPV that play a role in the etiology of cervical cancer from regional to national management. New data are constantly required to update the information on this subject. HPV prevalence and type distributions have been determined in various regions. Hasbek et al. detected that the most common genotype was HPV 16 in Sivas (22). Fındık et al. found that the most common HPV types were HPV16, HPV31, HPV51 in Konya (23). Therefore, HPV16 appears to be the most common in this two study as well as in the world and in Turkey. However, contrary to the literature, in both studies HPV18 prevalence was almost last, which indicates that subtypes differ from region to region. Akay et al. evaluated the biopsy results of HR-HPV positive cases and found that 56 cases (32.7%), 40 cases (23.4%) and 5 cases (2.9%) were LGSIL, HGSIL and cervical carcinoma, respectively (24).

The gynecology/colposcopy polyclinic of our hospital was selected by the Ministry of Health as a referral center for the province of Amasya. In the context of the screening program, colposcopy is applied to patients with indications who present at the polyclinic. Although 14 of HPV types are high risky, HPV 16 and HPV 18 are known to play a role in approximately 70% of cervical cancer cases (4). Therefore, in the screening program, colposcopy is recommended for patients with HPV 16 or HPV 18 positivity, regardless of the cytology results. In our clinic, colposcopy is applied to patients with HPV 16 or HPV 18 positivity, with a PAP-smear test result of LGSIL and above, and to patients where there is clinical suspicion (treatment-resistant vaginal discharge, post-coital bleeding, etc). According to a study in 2016, Güçkan et al. detected that the most frequently observed HPV type was HPV 16 (23.6%) and then HPV 51 was observed with 9% frequency in Amasya (25). We found other HR-HPV types were the most common encountered type among the colposcopy cases. 58 (27.1%) women had HPV 16. We attribute this to the fact that abnormal PAP smear results can be seen also with other HR-HPV types in women who applied for colposcopic evaluation.

In the current study, following the use of acetic acid, green filter and Lugol's iodine during colposcopy, the majority of patients were seen to have a cervix of normal appearance. However, it was determined that lesion borders could not be visualized in more than half of the colposcopy examinations. Two or more punch biopsies were taken in three-quarters of the patients, and final histo-pathological results of HGSIL and above were obtained in fewer than one in ten of the patients. The most significant finding was that the number of punch biopsies taken did not change according to the colposcopy appearance but as the number of punch biopsies taken increased, histo-pathological results of HGSIL and above were detected. Atakul presented that 122 of the 162 colposcopies they performed, had positive findings and 54.1% of these were LGSIL, HGSIL and cervical carcinoma in Aydın region (26). Güney found that 56 patient (26%) had HGSIL due to 212 patients' colposcopic examination in neighbor region, Çorum (27). However, biopsy numbers were not mentioned in either study.

The two most important factors affecting and limiting the results of this study were that it was a single-centre study and the number of patients was limited. There is a need for further more extensive studies with larger patient populations.

In conclusion, the results of this study showed that leukoplakia was the most common colposcopic finding

and LGSIL was the most encountered histo-pathological result. Gynecologists were in favor of taking multiple biopsies in Amasya. As the number of punch biopsies taken increased in accordance with the colposcopy guidelines, so the possibility increased of capturing premalignant and malignant lesions.

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Conflicts of Interest

The authors declare that they have no conflict of interest.

Financial Disclosure

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Ethical Approval

This study was approved by Non-Invasive Clinical Studies Ethics Board at the Faculty of Medicine at Amasya University Ethics Committee (Permission granted/Decision no: 2019/8-45).

Author Contrubitons

Concept, Design, Supervision: **Banuhan Şahin;** Materials, Data Collection and/or Processing: **Esra Güner;** Analysis and/or Interpretation, Literature Search, Writing Manuscript: **Banuhan Şahin;** Critical Review: **Fadıl Kara.**

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