Özgün Araştırma | Original Article

Jinekoloji - Obstetrik ve Neonatoloji Tıp Dergisi
The Journal of Gynecology - Obstetrics and Neonatology

DOI: 10.38136/jgon.846750

Analysis of colposcopic findings of high-risk HPV positive women with unsatisfactory cervical cytology

Yetersiz servikal sitolojiye sahip yüksek riskli HPV pozitif kadınların kolposkopik bulgularının analizi

Ayçağ YORGANCI [1] Orcid ID:0000-0003-2565-6789
Mustafa Erkan Sarı [2] Orcid ID:0000-0003-1202-9823
İlker SELÇUK [2] Orcid ID:0000-0003-0499-5722
Hakan YALÇIN [2] Orcid ID:0000-0002-9027-1351
Tayfun GÜNGÖR [2] Orcid ID:0000-0003-0499-5722
Mehmet Mutlu MEYDANLI [2] Orcid ID:0000-0001-6763-9720

[1] University of Health Sciences Ankara Dr. Zekai Tahir Burak Women's Health Education and Research Hospital, Department of Obstetrics and Gynecology, Ankara, Turkey

[2] University of Health Sciences Ankara Dr. Zekai Tahir Burak Women's Health Education and Research Hospital, Department of Gynecologic Oncology, Ankara, Turkey

ÖZ

Amaç: Çalışmanın amacı Kanser Erken Tanı ve Tarama Merkezlerinden Jinekolojik Onkoloji polikliniğine sevk edilen, yetersiz servikal sitolojili ve yüksek riskli insan papilloma virüsü (HPV) pozitifliği olan kadınların kolposkopik biyopsi sonuçlarının incelemektir.

Gereç ve Yöntemler: Bu retrospektif çalışmada Mart 2015-Ekim 2017 tarihleri arasında kliniğimize yönlendirilen yetersiz servikal sitoloji ve yüksek riskli HPV pozitifliği olan kadınlara kolposkopi eşliğinde servikal biyopsi ve endoservikal küretaj yapıldı. Hastalar HPV tiplerine göre gruplandırıldı. Endoservikal küretaj, servikal biyopsi ve servikal konizasyon sonuçları analiz edildi.

Bulgular: Yetersiz servikal sitolojisi ve yüksek riskli HPV pozitifliği olan 46 hasta 30 aylık dönemde bu çalışmaya dahil edildi. Yirmi bir hastada (% 45,7) HPV 16 ve/veya HPV 18 ve 25 hastada (% 54,3) "16 olmayan 18 olmayan" HPV yüksek risk alt tipi mevcuttu. Servikal biyopsi sonuçları 20 hastada (% 43.5) normal histopatoloji, dört hastada (% 8.7) "HPV etkisi", 17 hastada (% 37) düşük dereceli skuamöz intraepitelyal lezyon (L-SIL) ve 5 hastada (% 10.9) yüksek dereceli skuamöz intraepitelyal lezyon (H-SIL) olarak bildirildi. Endoservikal küretaj incelemesinde üç hastada H-SIL (% 6.5) ve yedi hastada L-SIL (% 15.2) tespit edildi. Yedi (% 15.2) hastaya H-SIL nedeniyle konizasyon yapıldı ve konizasyon materyelinde üç cerrahi sınırları negatif H-SIL ve dört L-SIL bildirildi.

Sonuç: Yetersiz servikal sitolojisi ve yüksek riskli HPV pozitifliği olan kadınlar için HPV alt tiplerinden bağımsız olarak H-SIL riski arttığından kolposkopi yapmak çok önemli görünmektedir.

Anahtar Kelimeler: servikal sürüntü; yetersiz servikal sitoloji, insan papilloma virüsü, kolposkopi

ABSTRACT

Aim: We aimed to analyze the colposcopic directed biopsy results of women with unsatisfactory cervical cytology and high-risk human papilloma virus (HPV) positivity, who were referred to the Gynecologic Oncology outpatient clinic from Cancer Early Diagnosis and Screening Centers.

Materials and Methods: In this retrospective study, women with high-risk HPV subtypes who applied to our clinic between March 2015 and October 2017 with an inadequate cervical cytology underwent colposcopy-directed biopsy. Patients were grouped according to HPV types. The results of endocervical curettage, cervical biopsy, and cervical conization were analyzed.

Results: Forty-six patients with unsatisfactory cervical cytology and high-risk HPV were included in this study during the 30-month period. Twenty-five (54.3%) of the patients had "non-16 non-18" HPV subtypes, while 21 (45.7%) had HPV 16 and/or HPV 18. Cervical biopsy results revealed high-grade squamous intraepithelial lesion (H-SIL) in 5 (10.9%) patients, low-grade squamous intraepithelial lesion (L-SIL) in 17 (37%), "HPV effect" in 4 (8.7%) and normal histopathology in 20 (43.5%) patients. The endocervical curettage revealed three (6.5%) women with H-SIL and seven (15.2%) with L-SIL. Seven (15.2%) patients underwent conization due to H-SIL and there were three H-SIL with negative margins and four L-SIL in the final histopathology report.

Conclusion: Performing colposcopy seems to be crucial for women with inadequate cervical cytology and high-risk HPV regardless of HPV subtypes as there is an increased risk of H-SIL in this patient population.

Keywords: cervical smear; unsatisfactory cervical cytology, human papillomavirus, colposcopy

INTRODUCTION

Cervical smear is one of the few screening methods reducing invasive cancer incidence and mortality with proven effectiveness (1). However, the adequacy of the cervical smear is the first step in the examination of a cervical smear according to the Bethesda system (2). The cervical smear is categorized as "satisfactory for evaluation" if there is well visualized squamous

Sorumlu Yazar/ Corresponding Author:
Ayçağ Yorgancı
Ministry of Health Ankara City Hospital Department of Ob&Gyn, Üniversiteler Mahallesi 1604. Cadde No: 9 Çankaya 06800
E-mail: aycagyorganci@gmail.com

Başvuru tarihi :25.12.2020
Kabul tarihi : 09.02.2021

cellularity with the definition of presence or absence of endocervical/transformation zone component. Additionally, any other obscuring or interfering factors (blood, inflammation, air-drying artifact, lubricant) should be specified as quality of indicators. Thus, an unsatisfactory cervical smear shows insufficient cellularity or has more than 75% obscured cells, if no other technical or labeling mistakes are found. The clinical significance of unsatisfactory cervical smears is that the samples are not reliable for detection of any precancerous and cancerous lesions. Unsatisfactory cervical smears might be due to the problems with sample collection, however, cervical ectopy, atrophy, inflammation, and neoplasia might also lead to unsatisfactory results. Therefore, it is controversial whether women with an unsatisfactory cervical cytology are more likely to develop intraepithelial lesions or cancer on follow-up than women with satisfactory tests (3-6).

Population-based cervical cancer screening program of Turkey, which is conducted by Family Health Centers (ASM) and Cancer Early Diagnosis, Screening and Training Centers (KETEM), aims to screen women between ages 30-65 with high-risk human papillomavirus (HPV) testing and reflex cervical cytology in the case of HPV positivity (7). The results of our national cervical cancer screening program showed that the percentage of unsatisfactory cervical smears in HPV positive women was 14.1% in the initial publication of one million cases (7). Recently, the results of four million women are reported with a 16.2% of unsatisfactory cervical smears in HPV positivity (8). Based on this information, we aimed to analyze the colposcopic directed biopsy results of patients with high-risk HPV positivity and cervical cytology.

MATERIALS AND METHODS

In this retrospective study, the colposcopic findings of women who were referred from ASM and KETEM to the Gynecologic Oncology outpatient clinic of Ankara Zekai Tahir Burak Women's Health Research and Education Hospital between March 2015 and October 2017 were analyzed. The study was approved by the review board of the institution (08/29.06.2015). Inclusion criteria were women who had high-risk HPV subtypes with an unsatisfactory cervical cytology. Age, body mass index (BMI), gravida, parity, education level, smoking behavior, menopausal status, positive HPV subtypes were recorded from the medical files. The colposcopic findings together with histopathologic results of cervical biopsy, endocervical curettage (ECC), and loop electrosurgical excisional procedure (LEEP), if performed, were analyzed.

According to our national cervical screening program, two cervical samples are taken from each woman. The first sample is used for conventional cytology. The latter is taken with a different brush and placed in a transport medium used for HPV DNA analysis. The HPV DNA analysis is performed by Hybrid Capture 2 (Qiagen, Hilden, Germany) method and the genotyping is performed with the CLART kit (Genomica, Madrid, Spain). There are 14 high-risk HPV types searched for (16/18/31/33/35 /39/45/51/52/56/58/59/68/73). If the HPV test is positive, reflex cytology is considered. All high-risk HPV positive women with abnormal cytology or woman who are HPV 16 and/or 18 positive are referred for colposcopy. The details of screening program and the infrastructure and quality control of the laboratory processes are described elsewhere (7).

Colposcopy was performed by a micro colposcope with Leica M60LED optics (MIKRO, Prague, Czech Republic). After applying a 3% acetic acid solution to the ectocervix, the cervix was examined by colposcopy. Colposcopic findings were defined according to the International Cervical Pathology and Colposcopy Federation criteria (9). Colposcopy was considered satisfactory if the cervix could be fully assessed and not blocked by bleeding, inflammation or scarring. The squamocolumnar junction was considered to be fully apparent when the whole junction was visible. A colposcopically directed biopsy was taken from the area with the most abnormal appearance, and then ECC was performed. If there was no obvious abnormal colposcopy finding, two random cervical punch biopsies were taken from the transformation zone, and then ECC was performed. If colposcopy was unsatisfactory, two random cervical punch biopsies were taken at 12 o'clock and 6 o'clock (the midpoint of the anterior and posterior lip of the cervix, respectively) followed by ECC.

Loop electrosurgical excisional procedure was performed if high-grade squamous intraepithelial lesion (H-SIL) was found in the initial histopathologic examination. The cases were described according to the most severe histological findings obtained from cervical punch biopsy, ECC or LEEP conization. Findings were categorized for analysis as normal and/or inflammation, koilocytosis (HPV effect), low-grade squamous intraepithelial lesion (L-SIL), and H-SIL.

The data were transferred to the computer using SPSS version 22 (IBM, Armonk, NY, USA). Descriptive statistics were used for the demographic data.

RESULTS

There were 46 women with high-risk HPV and unsatisfactory cervical cytology during the 30-month study period. The median age was 45 (range 31-67) and 63% of the patients were premenopausal. Twenty-five (54.3%) of patients had "non-16 non-18" HPV subtypes, while 21 (45.7%) had HPV 16 and/or 18. The demographic characteristics of the study participants are given Table 1.

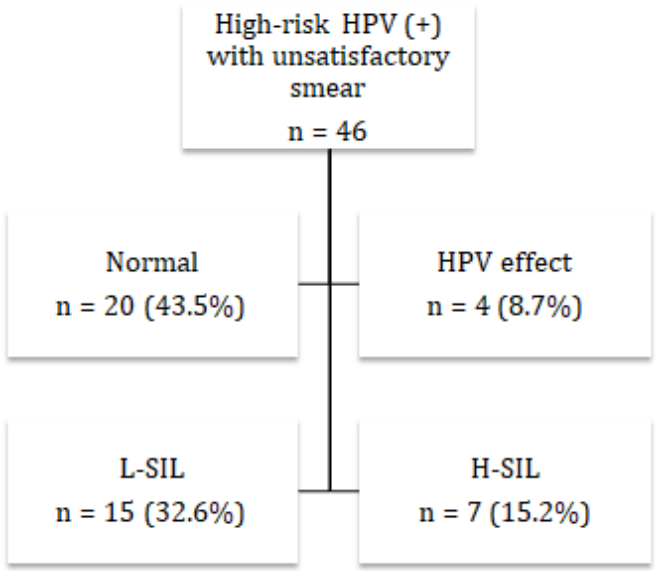
Table 1: The demographic characteristics of the study participants.

	N (%)
Age (median, min.-max.)	45 (31-67)
Gravidity (median, min.-max.)	3 (1-5)
Parity (median, min.-max.)	2 (1-5)
BMI (median, min.-max.)	25.1 (19.6-35.4)
Education Level	
Primary school	22 (47.8%)
High school	13 (28.3%)
University	11 (23.9%)
Contraception method	
None	17 (37%)
OCP	3 (6.5%)
IUD	11 (23.9%)
Coitus interruptus	15 (32.6%)
Smoking behavior	
Yes	25 (54.3%)
No	21 (45.6%)
Menopausal status	
Premenopausal	29 (63%)
Postmenopausal	17 (37%)
HPV types	
HPV 16 and/or 18	21 (45.7%)
Others	25 (54.3%)

BMI Body mass index; OCP Oral contraceptive pills; IUD Intrauterine device; HPV Human papillomavirus

The colposcopic findings were considered as satisfactory in all women. Cervical biopsy results revealed H-SIL in five (10.9%) patients, L-SIL in 17 (37%), "HPV effect" in four (8.7%), and normal histopathology in 20 (43.5%) patients. In the ECC results, three (6.5%) patients were diagnosed with H-SIL and seven (15.2%) were diagnosed with L-SIL. The final categorization of the patients according to the most severe histological findings obtained from cervical punch biopsy, endocervical curettage or LEEP conization are given in Figure 1.

Figure 1: The final categorization of the patients according to the most severe histopathological findings obtained from cervical punch biopsy, endocervical curettage or cervical conization.



There were a total of seven (15.2%) patients who had H-SIL in either cervical biopsy (n = 5) or ECC (n = 2) specimens. In these patients, HPV 16 was detected in three, HPV 31 in two, HPV 51 in one and HPV 16 and 59 in one case. These seven patients underwent LEEP. In the pathologic evaluation of the LEEP specimens, three patients had H-SIL with negative margins, and four patients had L-SIL.

DISCUSSION

Our study showed that 15.2 % women who had high-risk HPV with unsatisfactory cervical smear cytology have H-SIL at the final histopathologic evaluation. With the inclusion of L-SIL diagnosis, the cervical neoplasia rate increases up to 47.8 %.

According to the 2001 Bethasda System, minimum 8000–12000 well visualized squamous cells are required for conventional cervical smears to be considered satisfactory, whereas 5000 for liquid based cervical smears (10). In the current 2014 Bethesda System, it has been lowered to 2000 cells among women with only atrophic changes (11). Before the era of HPV testing, the American Society for Colposcopy and Cervical Pathology (ASCCP) has recommended repeat cervical cytology for unsatisfactory smears within 2-4 months (12). Ransdell et al. followed women who had unsatisfactory smears and 16% of those who had repeat testing showed SIL or neoplasia in the follow-up examinations (3). In another study with a 5-year follow-up, women with unsatisfactory smears showed H-SIL more

often than women with normal results though not statistically significant (2.2% vs. 1.3%, respectively) (4). Nygard et al. also found 1.6-4.0 times higher H-SIL or invasive squamous cancer risk in women with unsatisfactory cervical smear when compared to women with normal smear (6). On the contrary, Adams et al. reported similar outcomes among women with unsatisfactory and normal smears in 5-year follow-up (5). However, there are methodical differences about inclusion criteria and the sample collection (conventional vs. liquid based cytology) between these studies.

After the introduction of HPV testing in cervical cancer screening programs, in a preliminary report of 304 unsatisfactory smears with HPV testing, 11 of them were positive for high-risk HPV (13). As the detection rate of L-SIL was 45% for HPV positive and 0.05% for HPV negative cases, the authors suggested that HPV testing could be used for risk stratification in unsatisfactory smears. Afterwards, it has been found that positive HPV testing for unsatisfactory smears is the most significant predictor for H-SIL both compared to all satisfactory smears and normal satisfactory smears [Hazard Ratio = 14.5 (95% CI, 12.6-16.6) and Hazard Ratio = 17.8 (95% CI, 15.5-20.6), respectively] (14). Consequently, the updated 2019 ASCCP guidelines state that women who had unsatisfactory smear and a HPV 16 or 18 positivity should be referred to colposcopy (15). If the HPV genotype is unknown, both direct referral to colposcopy and repeat testing is acceptable (15). According to our national cervical cancer screening program, if a woman is high-risk HPV positive and cervical cytology is abnormal including unsatisfactory results, she is referred to colposcopy. Our results support this approach, as we found the rate of H-SIL as 15% in high-risk HPV positive women with unsatisfactory smears.

The current study has some limitations that have to be considered. Firstly, it has been conducted in a single center with a relatively small number of patients. Additionally, the reasons of unsatisfactory smear diagnosis were not known as the patients were referred to our center with their results.

In conclusion, colposcopy seems to be crucial for women with high-risk HPV and unsatisfactory cervical cytology, regardless of HPV subtypes. There is an increased risk of H-SIL in this specific patient population.

REFERENCES

1. Bray F, Loos AH, McCarron P, Weiderpass E, Arbyn M, Moller H, et al. Trends in cervical squamous cell carcinoma incidence in 13 European countries: changing risk and the effects of screening. Cancer Epidemiol Biomarkers Prev. 2005;14(3):677-86.

2. Nayar R, Wilbur DC. The Pap Test and Bethesda 2014. "The reports of my demise have been greatly exaggerated." (after a quotation from Mark Twain). Acta Cytol. 2015;59(2):121-32.

3. Ransdell JS, Davey DD, Zaleski S. Clinicopathologic correlation of the unsatisfactory Papanicolaou smear. Cancer. 1997;81(3):139-43.

4. Hock YL, Ramaiah S, Wall ES, Harris AM, Marston L, Marshall J, et al. Outcome of women with inadequate cervical smears followed up for five years. J Clin Pathol. 2003;56(8):592-5.

5. Adams AL, Gidley J, Roberson J, Wang W, Eltoum I, Chhieng DC. Clinical significance of unsatisfactory conventional pap smears owing to inadequate squamous cellularity defined by the Bethesda 2001 criterion. Am J Clin Pathol. 2005;123(5):738-43.

6. Nygard JF, Sauer T, Nygard M, Skare GB, Thoresen SO. CIN 2/3 and cervical cancer in an organised screening programme after an unsatisfactory or a normal Pap smear: a seven-year prospective study of the Norwegian population-based screening programme. J Med Screen. 2004;11(2):70-6.

7. Gultekin M, Zayifoglu Karaca M, Kucukyildiz I, Dundar S, Boztas G, Semra Turan H, et al. Initial results of population based cervical cancer screening program using HPV testing in one million Turkish women. Int J Cancer. 2018;142(9):1952-8.

8. Gultekin M, Dundar S, Keskinkilic B, Turkyilmaz M, Ozgul N, Yuce K, et al. How to triage HPV positive cases: Results of four million females. Gynecol Oncol. 2020;158(1):105-11.

9. Bornstein J, Bentley J, Bosze P, Girardi F, Haefner H, Menton M, et al. 2011 colposcopic terminology of the International Federation for Cervical Pathology and Colposcopy. Obstet Gynecol. 2012;120(1):166-72.

10. Solomon D, Davey D, Kurman R, Moriarty A, O'Connor D, Prey M, et al. The 2001 Bethesda System: terminology for reporting results of cervical cytology. JAMA. 2002;287(16):2114-9.

11. Mirzamani N, Chau K, Rafael O, Shergill U, Sajjan S, Sumskaya I, et al. Quality assessment and improvement of "Unsatisfactory" liquid-based cervicovaginal papanicolaou smears. Diagn Cytopathol. 2017;45(10):873-7.

12. Massad LS, Einstein MH, Huh WK, Katki HA, Kinney WK, Schiffman M, et al. 2012 updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. J Low Genit Tract Dis. 2013;17(5 Suppl 1):S1-S27.

13. Zhao C, Austin RM. High-risk human papillomavirus DNA test results are useful for disease risk stratification in women with unsatisfactory liquid-based cytology pap test results. J Low Genit Tract Dis. 2009;13(2):79-84.

14. Owens CL, Buist DS, Peterson D, Kamineni A, Weinmann S, Ross T, et al. Follow-up and clinical significance of unsatisfactory liquid-based Papanicolaou tests. Cancer Cytopathol. 2015;123(1):59-65.

15. Perkins RB, Guido RS, Castle PE, Chelmow D, Einstein MH, Garcia F, et al. 2019 ASCCP Risk-Based Management Consensus Guidelines for Abnormal Cervical Cancer Screening Tests and Cancer Precursors. J Low Genit Tract Dis. 2020;24(2):102-31.