ÖZGÜN ARAŞTIRMA / ORIGINAL RESEARCH

DOI: 10.17944/mkutfd.1142816
MKÜ Tıp Dergisi 2022;13(47):425-430

The analysis of anal cytology positivity in women with pathological cervical cytology

Mehmet Esat Duymuş[1], Zeynep Bayramoğlu[2], Hülya Ayik Aydın[3], Yusuf Murat Bag[4]

[1]Hatay Mustafa Kemal University Tayfur Ata Sökmen Faculty of Medicine, Department of General Surgery, Hatay, Türkiye
[2]Konya Training and Research Hospital, Department of Pathology, Konya, Türkiye
[3]Hatay Training and Research Hospital, Department of Gynecological Oncology, Hatay Türkiye
[4]Van Training and Research Hospital, Department of Gastroenterology Surgery, Van, Türkiye

Abstract

The analysis of anal cytology positivity in women with pathological cervical cytology

Objective: Cervical cytology (CC) is a routine screening method used to reduce cervical cancer. Although anal cancer and cervical cancer have similar etiological factors the opinion about the anal cancer screening program is unclear. We aimed to determine the features of women with abnormal anal cytology (AC) who had screened via CC for cervical neoplasia.
Method: Two hundred and five females' CC results were investigated. The patients with normal CC were excluded, finally 87 participants were included. The demographics, medical, sexual, and reproductive features, CC and AC results were analyzed.
Results: The study group had a mean age of 40.77 ± 9.50 years. AC was pathological in six patients (6.9%). Four of these (66.7%) were high-grade squamous intraepithelial lesions (HSIL) and two (33.3%) were low-grade squamous intraepithelial lesions (LSIL). The CC results of these patients were all HSIL, all of them were human papillomavirus (HPV) positive, with the most common type being 16 (83.3%).
Conclusion: Women with HSIL in CC (especially with concomitant HPV) may be riskier for AC positivity. The others are most likely to have negative AC results. The use of AC for early diagnosis of risky anal intraepithelial lesions (such as a screening tool) may be considered for this group of patients.
Keywords: Cervical Cytology, Anal Cytology, Human Papillomavirus

Öz

Patolojik servikal sitolojili kadınlardaki anal sitoloji pozitifliğinin analizi

Amaç: Servikal sitoloji (SS) serviks kanserini azaltmak için kullanılan rutin bir tarama yöntemidir. Anal kanser ve serviks kanseri benzer etiyolojik faktörlere sahip olsa da anal kanser tarama programı hakkındaki görüş net değildir. Bizim bu çalışma ile amacımız; SS ile servikal neoplazi taraması yapılan kadınlardan anormal anal sitoloji (AS)'ye sahip olanlarının özelliklerini belirlemektir.
Yöntem: Toplam 205 kadın hastanın SS sonuçları incelendi. Normal SS'li hastalar dışlandı ve sonuçta 87 katılımcı çalışmaya dahil edildi. Demografik özellikleri, tıbbi, cinsel verileri ile reproduktif özellikleri analiz edildi.
Bulgular: Çalışma grubunun yaş ortalaması 40.77 ± 9.50 idi. AS 6 hasta (%6.9)'da patolojikti ve bunlardan 4 (%66.7)'ü yüksek dereceli skuamöz intraepitelyal lezyon (HSIL), 2 (%33.3)'si düşük dereceli skuamöz intraepitelyal lezyon (LSIL) idi. Bu hastaların SS sonuçları HSIL'di ve hepsinde human papillomavirus (HPV) pozitifti. En sık görülen tipi HPV 16 idi.
Sonuç: SS sonucu HSIL çıkan kadınlarda (özellikle eşlik eden HPV varlığında) AS pozitifliği daha riskli olabilir. Diğerlerinin ise AS sonuçlarının negatif çıkması muhtemeldir. AS kullanımı bu hasta grubu için anal intraepitelyal lezyonların erken teşhisinde (bir tarama aracı gibi) kullanılabilir.
Anahtar Kelimeler: Servikal Sitoloji, Anal Sitoloji, Human Papillomavirus

Nasıl Atıf Yapmalı: Duymuş ME, Bayramoğlu Z, Aydın Ayik H, Bag YM. The analysis of anal cytology positivity in women with pathological cervical cytology. MKÜ Tıp Dergisi. 2022;13(47):425-430. https://doi.org/10.17944/mkutfd.1142816

Sorumlu Yazar/Corresponding Author: Mehmet Esat Duymuş
Email: esatduymus@hotmail.com
ORCID iD: 0000-0002-0372-7999

Geliş/Received: 7 Temmuz 2022
Kabul/Accepted: 24 Ekim 2022

INTRODUCTION

Anal cancer is a rare disease and it is seen in 1-2 per hundred thousand of the entire population (1). But a remarkable increase has been observed in the incidence of anal cancer recently (1, 2). Men who have sex with men (MSM) (2), genital warts (3), anal intercourse (3), multiple sexual partners (3), human immunodeficiency virus (HIV) (3) are the risk factors of anal cancer. In addition, oncogenic types of human papillomavirus (HPV) have been linked with anal cancer as well as cervical cancer (4). Cervical dysplasia (HPV-related) makes women riskier for both anal cancer and anal intraepithelial neoplasms (4, 5).

Anal cancer is rare in healthy individuals and HIV-negative. Moreover, anal cancers are more frequently detected in women than in men (6). Since more than 90 % of anal cancers are caused by high-risk (HR)-HPV infection, possible reasons for the higher risk in women include the history of cervical intraepithelial neoplasia (CIN) and cervical cancer (7-9). In women with CIN, the prevalence of anal HPV infection is greater than in healthy women. Despite the data mentioned above, the relationship between anal cytology (AC) results and cervical cytology (CC) results is unclear in the literature (10). Therefore, in this study, we aimed to determine the features of women with positive AC who had screened via CC for cervical neoplasia.

METHOD

Study Design

This prospective cohort was implemented in the gynecologic oncology division of the obstetrics & gynecology department of our tertiary care center between 01.11.2020-31.05.2021. This study has been approved by the Mustafa Kemal University Invasive Clinical Research Ethics Committee and Helsinki Declaration rules were followed to conduct this study (date: 22.10.2020 / number: 05).The data of 205 patients who had undergone CC, and AC were reviewed. The inclusion criteria were age ≥ 21 years, the presence of abnormal CC result (atypical squamous cells of undetermined significance (ASC-US), atypical squamous cells (cannot rule out high-grade dysplasia; ASC-H), low-grade squamous intraepithelial lesions (LSIL), and high-grade squamous intraepithelial lesions (HSIL), and the presence of no macroscopic anal lesion. Exclusion criteria were the presence of normal CC result, the presence of a sexually transmitted disease, pregnancy, HIV positivity, pharmacological immunosuppression, atypical glandular cells, and prior total hysterectomy with the surgical absence of cervix. Finally, a total of 87 patients were included in the study. The written consent form was signed by all participants for the use of their anonymous data.

The participants filled in a standard questionnaire that included followed items: age, comorbidity, sexual history, medical and reproductive histories, contraceptive methods, smoking history, and history of sexually transmitted diseases. Cytological specimens were obtained from the cervix with a spatula for each participant. Colposcopy procedure was routinely carried out with endocervical curettage and cervical biopsies. All cytological slides underwent evaluation by a trained cytologist in this study. CCs positive for endocervical cells were included in the analysis of cervical cytological results. Standard defined cytological criteria for grading were used in both cervical and anal specimens according to relevant literature (11).

HR-HPV testing was performed uniformly on ASC-US in CC results. In patients with LSIL and HSIL, the cervix was tested for HPV during colposcopy and cytology. Patients with LSIL and HSIL in CC results were tested to identify cervical HPV status during colposcopy using a Dacron swab (12). Anal sampling was performed by an experienced gynecologic oncology specialist who had general surgery rotation for 6 months and who had watched an instructional video on this procedure. Gastroenterology specialists accompanied and supervised the procedure until the specialist was deemed competent. The anal swabs were analyzed similarly to cervical HPV specimens. The swabs were gathered and put in Thin prep fluid media. The specimen was transferred to the laboratory, and AC was performed by pathologists in a fashion similar to that performed for CC and HPV tests.

HPV Detection and Genotyping

Exfoliated cervical cell samples were obtained for HPV detection. A brush was utilized to achieve smear from the entire ectocervix and endocervix, including the entire transformation zone and anal transformation zone.

Each sample was taken separately into the PreservCyt transport medium with maximal care to avoid contamination. The Linear Array Genotyping HPV test was used for all samples following the instructions of the manufacturer (Roche Molecular Systems, Inc., Branchburg, NJ, USA).

The Linear Array Genotyping HPV test was performed to identify 37 HPV genotypes that included 13 HR and 24 low-risk types. The strips were interpreted using the provided reference guide (13).

Cytology and Histology

CC results were classified as normal, ASC-US, ASC-H, LSIL, and HSIL according to the 2001 Bethesda system (14). An additional follow-up list was scheduled for participants who met the colposcopy referral criteria. Specifically, this included concomitant infection with ASC-US and HR-HPV type, or detection of atypical glandular cells or

carcinoma in E6/E7 mRNA, LSIL, ASC-H, and HSIL on CC. Cervicovaginal abnormalities were identified and biopsied for histopathological analysis during a colposcopy.

Statistical Analysis

The Shapiro-Wilk test was performed to determine the normality of the distribution of numerical variables. Normally distributed numerical variables were defined as mean ± standard deviation, while non-normally distributed numerical variables were defined as median (minimum-maximum). Categorical variables were defined as frequency (percentage). IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, N.Y., USA) was used for statistical analyses.

RESULTS

The demographics, medical, sexual, and reproductive data of the study group are summarized in Table 1.

The study group had a mean age of 40.77 ± 9.50 years. While the median gravidity was 4 (0-9), the median parity was 3 (0-8). Seventeen of the patients (19.5%) had comorbidity, and the most common was primary hypertension. About one-third of the patients were smokers, and about half of them were using at least one method of contraception. The vast majority of patients were in the postmenopausal period, and two-thirds were HPV positive. The CC results of the study group are shown in Table 2.

Table 1. The demographics, medical, sexual, and reproductive data of the study group

Study group (n=87)		
Age (years), mean±SD	40.77	9.50
BMI (kg/m²), median (min-max)	25.4	18.2-46.9
Gravidity, median (min-max)	4	0-9
Parity, median (min-max)	3	0-8
Abortion, median (min-max)	0	0-4
	n	%
Comorbidity (yes)*	17	19.5
Primary hypertension	6	6.9
Hypothyroidism	3	3.4
Asthma	2	2.3
Chronic kidney disease	1	1.1
Cardiovascular disease	2	2.3
Diabetes mellitus	4	4.6
Smoking (yes)	27	31
Contraception (yes)	49	56.3
Multiple sexual partners (yes)	6	6.9
Menopausal status		
Premenopausal	70	80.5
Postmenopausal	17	19.5
Postcoital bleeding (yes)	18	20.7
Condyloma acuminatum (yes)	3	3.4
Vaccination (yes)	2	2.3
HPV (yes)	56	64.4

BMI: Body mass index, HPV: Human papillomavirus
* One patient had more than one comorbidities

The most common pathology in CC was ASC-US (63.2%), followed by LSIL (24.1%). Ten patients (11.5%) were diagnosed with HSIL via CC. Histopathological images are shown in Figures 1 and 2.

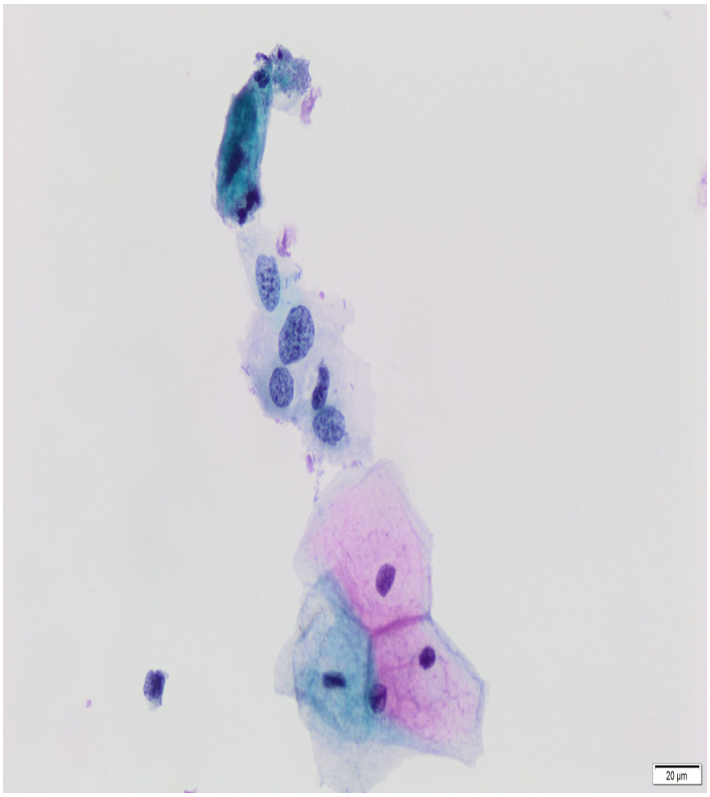

Figure 1. Low grade squamous intraepithelial lesion (Papanicolaou stain 400x)

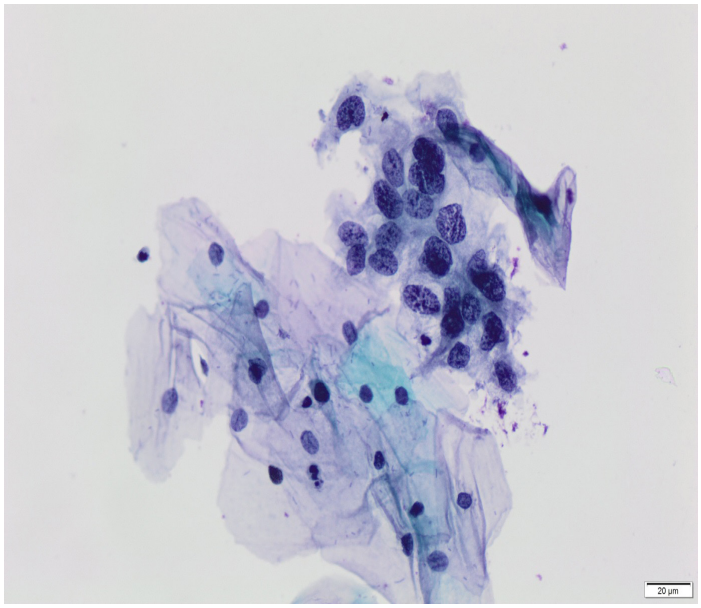

Figure 2. High grade squamous intraepithelial lesion (Papanicolaou stain 400x)

Table 2. Cervical cytology findings of whole study group (n=87)

	Cervical cytology								
	ASC-US		ASC-H		HSIL		LSIL		Total
	n	%	n	%	n	%	n	%	
Total	55	63.2	1	1.1	10	11.5	21	24.1	87

ASC-US: Atypical squamous cells of undetermined significance, ASC-H: Abnormal squamous cells in the tissue that lines the outer part of the cervix, HSIL: High-grade squamous intraepithelial lesion, LSIL: Low-grade squamous intraepithelial lesion

The features of the patients with positive AC are presented in Table 3. AC was pathological in six patients (6.9%), four of these (66.7%) were HSIL and two (33.3%) were LSIL. None of the patients with positive AC had multiple sexual partners and none of them were vaccinated. The rates of smoking and contraceptive use were 33.3%. All patients were HPV positive, and the most common type was 16 (83.3%). CC results were HSIL for all patients. No pathological AC was found in any of the patients with normal, ASCUS, ASC-H, or LSIL in CC results. But, this rate was 60% for patients with HSIL in CC. Anoscopy was performed for 6 patients with HSIL on follow-up period but no change was observed.

Table 3. Data of patients with positive anal cytology (n=6)

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age (years)	39	39	60	32	39	35
BMI (kg/m²)	20.8	21.9	37.8	24.03	26.7	22
Comorbidity (yes)	-	-	-	-	-	-
Gravidity	3	1	9	0	2	3
Parity	3	1	8	0	2	3
Abortion	0	0	1	0	0	0
Smoking (yes)	-	+	+	-	-	-
Contraception (yes)	-	+	-	-	-	+
Multiple sexual partners (yes)	-	-	-	-	-	-
Menopausal status	Pre	Pre	Post	Pre	Pre	Pre
Postcoital bleeding (yes)	-	-	-	-	+	-
Condyloma acuminatum (yes)	-	-	-	-	-	-
Vaccination (yes)	-	-	-	-	-	-
HPV (yes)	+	+	+	+	+	+
HPV type	16	18	16	16,18	16	16
Cervical cytology	HSIL	HSIL	HSIL	HSIL	HSIL	HSIL
Anal cytology	HSIL	HSIL	LSIL	HSIL	LSIL	HSIL

BMI: Body mass index, HPV: Human papillomavirus, HSIL: High-grade squamous intraepithelial lesion, LSIL: Low-grade squamous intraepithelial lesion, ASC-H: Abnormal squamous cells in the tissue that lines the outer part of the cervix

DISCUSSION

In this study, we found a 6.9% rate of positive AC for patients with abnormal CC This rate was highest in patients with HSIL in CC, with 60%. The common characteristics for patients with positive AC were that the presence of HSIL in CC, HPV positivity, single sexual partner, and no vaccination.

In a study by Calore et al. (15) they found an AC positivity rate of 59.2% in patients with abnormal CC. In addition, this rate was 61.5% for patients with cervical HSIL. They also found a significantly higher abnormal AC in patients with cervical HSIL. Compared to this study, our positive AC rate was similar for patients with cervical HSIL, while it was extremely lower for all patients with abnormal CC. We think that this difference is due to the fact that in our study cervical HSIL/LSIL rate was 34.5% in CC, while this was about 94% for the study of Calore et al. In another recently study on brazilian women, the abnormal AC rate was found as 10.1% (16).

One hundred and fifty-three women with abnormal Pap smear, CIN, cervical cancer, and HR-HPV were evaluated via AC in a study by Hosseini et al. (17). They revealed that multiple sexual partners, smoking, genital warts, and anal intercourse were the risk factors for abnormal AC in these women. Although we didn't examine the risk factors, we saw that none of the patients with abnormal AC had multiple sexual partners. And also, the smokers were only 33.3%.

It is well-known that HPV has an oncogenic potential and a remarkable role in the occurrence of both CIN and invasive cancer. Women with high-grade cervical dysplasia are at higher risk for cervical cancer as well as anal cancer (12). Besides anal intraepithelial neoplasia (AIN) and anal cancer are both common in women with HPV-related cervical dysplasia (5). The presences of HPV 16, 18, 31, 35, 23, 24, and 33 were detected in anal squamous cell carcinoma, reminding that they have similar biological behavior with cervical cancer (18). These findings remind us that HPV may have a central role in both CIN and AIN. In concordance with these data, we found HPV positivity in all patients with abnormal AC.

For the screening of anal cancer in women, no guidelines have yet been published. Slama et al. (13) concluded that anal HPV testing and anal Pap smear screening can be suitable for cases with severe cervical lesions caused by HPV 16 and a history of anal sex, and heavy smoking. In another study, it was emphasized that anal cancers may be detected in women with HPV-related gynecologic cancers, and effective strategies for screening are necessary for early diagnosis and appropriate treatment without delay (19). Bräutigam at al. (20) investigated the distribution of HPV subtypes in the different areas. They reported HPV 53 was the second most

common after HPV 16 on the anal and oral areas.

An unusually high risk of anal cancer development in patients with a history of cervical pre-cancerous lesions may be recognized as a reason for AC screening, especially for HPV-positive cases. Although concurrent anal and cervical HPV infection is a common occurrence, the predicted risk of AIN or anal malignancies in this group is still low. As a result, screening all women in this cohort would not be appropriate or cost-effective. Further stratification of this group according to the presence of other risk factors can be useful (13).

This study has some limitations. First, this was a descriptive study, therefore no comparative analysis, as well as risk factor analysis, was performed. Second, it had a relatively small sample size. Third, there was a lack of data on the natural course of anal dysplasia in association with cervical dysplasia. Fourth, only anal cytology was used for screening tool but anal HPV testing was not used.

CONCLUSION

Women with HSIL in CC (especially with concomitant HPV) may be riskier for AC positivity. The others are most likely to have negative AC results. Further studies are needed to identify the benefits of AC, especially for risky women. Only after that, the use of AC for early diagnosis of risky anal intraepithelial lesions (such as a screening tool) may be considered for this group of patients.

ACKNOWLEDGEMENT

Peer-Review

Both externally and internally peer reviewed.

Conflict of Interest

Authors declare that there is no conflict of interest in this article.

Support Resources

The authors report no financial support regarding content of this article.

Ethical Declaration

This study has been approved by the Mustafa Kemal University Invasive Clinical Research Ethics Committee date: 22.10.2020 and number: 05 and Helsinki Declaration rules were followed to conduct this study

Authorship Contributions

Concept: MED, HAA, Design: MED, ZB, HAA, Supervising: MED, Data Collection and entry: MED, YMB, HAA, Analysis or Interpretation: MED, Literature Search: ZB, YMB, Writing: MED, YMB, Critical review: MED, HAA

Thanks

The authors are grateful to the participants for their collaboration.

REFERENCES

1. Shiels MS, Kreimer AR, Coghill AE, Darragh TM, Devesa SS. Anal Cancer Incidence in the United States, 1977-2011: Distinct Patterns by Histology and Behavior. Cancer Epidemiol Biomarkers Prev 2015;24(10):1548–56. https://doi.org/10.1158/1055-9965.EPI-15-0044
2. Palefsky JM. Anal human papillomavirus infection and anal cancer in HIV-positive individuals: an emerging problem. AIDS 1994;8(3):283-95. https://doi.org/10.1097/00002030-199403000-00001.
3. Tseng HF, Morgenstern H, Mack TM, Peters RK. Risk factors for anal cancer: results of a population-based case–control study. Cancer Causes Control 2003;14(9):837-46. https://doi.org/10.1023/b:caco.0000003837.10664.7f
4. Moscicki AB, Schiffman M, Kjaer S, Villa LL. Updating the natural history of HPV and anogenital cancer. Vaccine 2006;24:S3/42–5 https://doi.org/10.1016/j.vaccine.2006.06.018.
5. Valari O, Koliopoulos G, Karakitsos P, Valasoulis G, Founta C, Godevenos G, et al. Human papillomavirus DNA and mRNA positivity of the anal canal in women with lower genital tract HPV lesions, Predictors and Clinical Implications. Gynecol Oncol 2011;122(3):505-8. https://doi.org/10.1016/j.ygyno.2011.05.033.
6. Joseph DA, Miller JW, Wu X, Chen VW, Morris CR, Goodman MT, et al. Understanding the burden of human papillomavirus associated anal cancers in the US. Cancer 2008;113(S10):2892-900. https://doi.org/10.1002/cncr.23744.
7. Daling JR, Madeleine MM, Johnson LG, Schwartz SM, Shera KA, Wurscher MA, et al. Human papillomavirus, smoking, and sexual practices in the etiology of anal cancer. Cancer 2004;101(2):270-80. https://doi.org/10.1002/cncr.20365.
8. Frisch M, Glimelius B, Van den Brule AJ, Wohlfahrt J, Meijer CJ, Walboomers JM, et al. Sexually transmitted infection as a cause of anal cancer. N Engl J Med 1997;337(19):1350-8. https://doi.org/10.1056/NEJM199711063371904.
9. Holly EA, Ralston ML, Darragh TM, Greenblatt RM, Jay N, Palefsky JM. Prevalence and risk factors for anal squamous intraepithelial lesions in women. J Natl Cancer Inst 2001;93(11):843-9. https://doi.org/10.1093/jnci/93.11.843.
10. do Socorro NM, Jacyntho CM, Eleutério JJr, Giraldo PC, Gonçalves AK. Abnormal anal cytology risk in women with known genital squamous intraepithelial lesion. Braz J Infect Dis 2016;20(3):294-7. https://doi.org/10.1016/j.bjid.2016.01.008.
11. Williams AB, Darragh TM, Vranizan K, Ochia C, Moss AR, Palefsky JM. Anal and cervical human papillomavirus infection and risk of anal and cervical epithelial abnormalities in human immunodeficiency virus-infected women. Obstet Gynecol 1994;83(2):205-11.
12. Lammé J, Pattaratornkosohn T, Mercado-Abadie J, Alkhas A, Robinson A, Lanneau G. Concurrent anal human papillomavirus and abnormal anal cytology in women with

known cervical dysplasia. Obstet Gynecol 2014;124(2pt1):242-8. https://doi.org/10.1097/AOG.0000000000000370.

13. Slama J, Sehnal B, Dusek L, Zima T, Cibula D. Impact of risk factors on prevalence of anal HPV infection in women with simultaneous cervical lesion. Neoplasma 2015; 62(2):308-14. https://doi.org/10.4149/neo_2015_037.
14. Luff R, Kurman R, Solomon D. The Bethesda system for reporting cervical/vaginal cytologic diagnoses. J Fam PracT 1992;35(1):98-101. PMID:1613480
15. Calore EE, Giaccio CM, Nadal SR. Prevalence of anal cytological abnormalities in women with positive cervical cytology. Diagn Cytopathol 2011;39(5):323-7. https://doi.org/10.1002/dc.21386.
16. Brum VDOR, Tricoti ADSO, Pannain GD, Drumond DG, Leite ICG. Cytology-based Screening for Anal Intraepithelial Neoplasia in Immunocompetent Brazilian Women with a History of High-Grade Cervical Intraepithelial Neoplasia or Cancer. Rev Bras de Ginecol Obstet 2022;44(7):678-85. https://doi.org/10.1055/s-0042-1743163.
17. Hosseini MS, Khosravi D, Farzaneh F, Ebrahimi A, Arab M, Ganjoie TA, et al. Evaluation of Anal Cytology in Women with History of Abnormal Pap Smear, Cervical Intraepithelial Neoplasia, Cervical Cancer and High Risk HPV for Anogenital Dysplasia. Asian Pac J Cancer Prev 2018;19(11):3071-5. https://doi.org/10.31557/APJCP.2018.19.11.3071.
18. Melbye M, Smith E, Wohlfahrt J, Osterlind A, Orholm M, Bergmann OJ, et al. Anal and cervical abnormality in women-prediction by human papillomavirus tests. Int J Cancer 1996;68(5):559-64. https://doi.org/10.1002/(SICI)1097-0215(19961127)68:5<559::AID-IJC1>3.0.CO;2-Y.
19. Edgren G, Sparén P. Risk of anogenital cancer after diagnosis of cervical intraepithelial neoplasia: a prospective population-based study. Lancet Oncol 2007;8(4):311-16. https://doi.org/10.1016/S1470-2045(07)70043-8.
20. Bräutigam K, Meier S, Meneder S, Proppe L, Stroschein K, Polack S, et al. Distribution of HPV Subtypes in Diverse Anogenital and Oral Samples from Women and Correlation of Infections with Neoplasia of the Cervix. Cancers 2022;14(13):3136. https://doi.org/: 10.3390/cancers14133136.