Original Article

The Effect of Random Biopsy and Endo-Cervical Curettage in Diagnosis of Precancerous Cervical Lesions in Women With Normal Colposcopy

Akram Ghahghaei-Nezamabadi; M.D.[1], Afsaneh Tehranian; M.D.[1], Elham Feizabad; M.D.[2], Parvin Nikabadi; M.D.[1]

1 Department of Obstetrics and Gynecology, Arash Women's Hospital, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
2 Department of Obstetrics and Gynecology, Yas Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran

Abstract

Objective: This study aimed to evaluate the effect of random biopsy and endo-cervical curettage (ECC), alone and together, in the diagnosis of high-grade cervical lesions in women with normal colposcopy.

Materials and methods: This cross-sectional study was conducted on 356 women who underwent colposcopy examination in the gynecology-oncology clinic of Roointan-Arash Women's Hospital, affiliated with Tehran University of Medical Sciences. All eligible women underwent colposcopy. In colposcopy examination, up to four biopsy samples were randomly taken for each quartile of the cervix and ECC was performed. Finally, the rate of intraepithelial neoplasia (CIN) and the relation between random biopsy and ECC and CIN diagnosis was determined.

Results: In total, 27 (7.6%) low-grade squamous intraepithelial lesions (LSIL) and 19 (5.3%) high-grade squamous intraepithelial lesions (HSIL) were detected in cases that underwent random biopsy. There was a significant association between the abnormal random biopsy results and having multiple sexual partners (p=0.001), cigarette (p=0.041), and hookah (p=0.033) smoking. Furthermore, 31 (8.7%) LSIL and 42 (11.8%) HSIL were reported in women who underwent ECC. There was a significant relation between the abnormal results of ECC and hookah consumption (p=0.008) and human papillomavirus (HPV) infection (p=0.011). The concordance (p=0.001) between random biopsy and ECC result was 71.2% and only in 28.8% of the cases one of the methods was normal and the other was abnormal.

Conclusion: The present study showed that the simultaneous use of ECC and random biopsy in women with normal colposcopy increases the detection rate of precancerous lesions by up to 28.8%.

Keywords: Colposcopy; Curettage; Uterine Cervical Dysplasia; Early Detection of Cancer

Introduction

Cervical cancer is the fourth most common cancer of women in the world and the second in low- and middle-income countries (1). The diagnosis of high-grade cervical intraepithelial neoplasia (CIN) is undeniably considered a precursor to malignant cervical cancer (2). Colposcopy examination is used as a complementary evaluation for abnormal cervical co-tests (3).

Correspondence:
Dr. Parvin Nikabadi
Email: pnik9095@gmail.com

Colposcopy examination has special visual features in terms of contour, color and vascular pattern that can be detected premalignant and malignant cervical lesions. Common indications for colposcopy are abnormal assessment of the cervix, vagina or vulva, evaluation after abnormal test of cervical neoplasia, follow-up treatment of cervical neoplasia and to detect any other lesions in the surrounding areas, as well as monitoring after treatment (4, 5).

Contraindications to the use of colposcopy are limited, the most important of which are cervicitis, anticoagulant or bleeding diatheses, pregnancy, and immune system suppression. ASCCP recommends targeted biopsies of all white areas and taking at least two to four samples (6).

Some studies have shown that colposcopic biopsy can detect 30 to 50% of the most common high-grade cervical precancers but in some studies, it has been reported that colposcopy-derived biopsies do not detect high-grade CIN2 in 26 to 57% of cases (7, 8).

Although the performance and diagnostic criteria of colposcopy have been standardized, it seems that the location and number of samplings in colposcopy are less standardized.7 To improve the accuracy of the general colposcopy-biopsy examination of the cervix, it has been suggested to take multiple and targeted biopsies of the lesion and perform ECC (9-11).

Hence, this study aimed to evaluate the effect of random biopsy and ECC, alone and together, in the diagnosis of high-grade cervical lesions in women with normal colposcopy.

Materials and methods

This cross-sectional study was conducted on 356 with normal colposcopy who underwent colposcopy examination in the gynecology-oncology clinic of Roointan-Arash Women's Hospital, affiliated with Tehran University of Medical Sciences, between March 2021 and March 2023.

The women with abnormal cervical screening tests (cytology and/or HPV testing), or suspected cervical cancer symptoms such as post-coital bleeding, intermenstrual bleeding or spotting, and vaginal discharge changing were enrolled in the study.

Exclusion criteria was a positive history of cervical cancer, chemotherapy and radiotherapy to the cervix, abnormal colposcopy examination, as well as pregnancy.

All eligible women, after obtaining informed consent to participate in the study, underwent colposcopy by an 18-year experience gynecology oncology fellowship. In colposcopy examination, for all participants, up to four biopsy samples were randomly taken for each quartile of the cervix and in case of unsatisfactory colposcopy, ECC was also performed. Pathology evaluation of all samples was done in our hospital laboratory.

Finally, the rate of CIN detection according to the random biopsy and ECC results and the relation between random biopsy and ECC results were determined as the study outcomes.

According to the rate of CIN2 (16.3%) diagnosed by random sampling method reported in Qing Chen et al study (12) and using the formula for determining the sample size in cross-sectional studies, the sample size was calculated at 328. The convenience sampling method was applied for case collection.

Demographic information including age, BMI, smoking habit, first menstruation and first sex age, menstrual pattern, menopause status, history of sexually transmitted diseases, having multiple sexual partners, pregnancy prevention method, gravidity, HPV test, and cytology results were collected.

Descriptive statistics including mean, standard deviation and relative frequency were used to describe the data. For data analysis, the Chi-square test and independent sample T-test were used. All analyzes were performed using SPSS version 24 software at a significant level of $p < 0.05$.

Ethical approval of the study was obtained from the Institutional Review Board of Tehran University of Medical Sciences (IR.TUMS.MEDICINE.REC.1400.762) based on the Declaration of Helsinki. All participants signed written consent before entering the study.

Results

Totally 356 women enrolled the study (Figure 1). The mean age of them was 38.9 ± 9.2 years, their mean BMI was 26.2 ± 2.4 kg/m^2. About 85% of them were married and the average number of their pregnancies was 2.20 ± 1.39. Random biopsy was done for all of them while ECC sample taking was done in 278 women. Normal random biopsy was detected in 310 ones (87.1%) and normal ECC in 205 (73.7%). Demographic and clinical data of the women is shown in Table 1.

In total, 27 (7.6%) low-grade squamous intraepithelial lesion (LSIL) and 19 (5.3%) high grade squamous intraepithelial lesion (HSIL) were detected in cases with abnormal random biopsy.
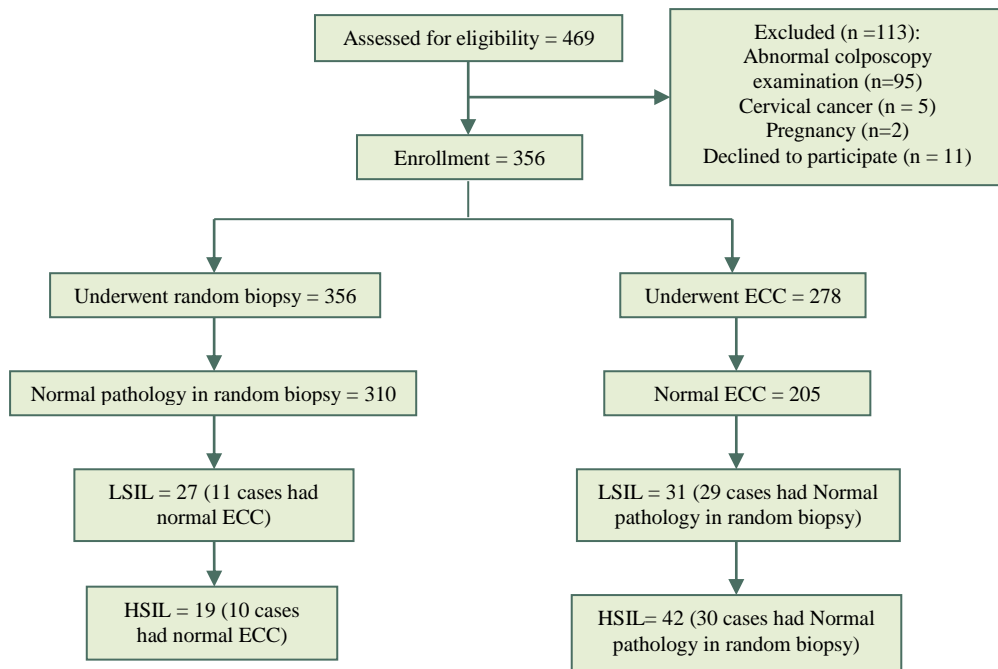
Figure 1: The Consort chart of the study
ECC: Endo-cervical curettage, LSI: Low-grade squamous intraepithelial lesion, HSI: How-grade squamous intraepithelial lesion

Table 1: Demographic and clinical data of women with normal colposcopy

Variables (N = 356)	Value
Age (years)	38.9 ± 9.2
First menstruation age (years)	12.5 ± 0.9
First sex age (years)	20.2 ± 4.8
Regular menstrual Pattern	339 (95.2)
Menopause	45 (12.6)
History of sexually transmitted diseases	71 (19.9)
Having multiple sexual partners	40 (11.2)
Pregnancy prevention method	
None	256 (71.9)
OCP	21 (5.9)
Withdrawal	1 (0.3)
IUD	16 (4.5)
Condom	62 (17.4)
Pap smear result	
Normal	313 (87.9)
LSIL	2 (0.6)
HSIL	5 (1.4)
ASCUS	36 (10.1)
Positive HPV test	161 (45.2)

OCP: Oral contraceptive pills, IUD: Intrauterine device, LSIL: Low-grade squamous intraepithelial lesion, HSIL: High-grade squamous intraepithelial lesion, ASCUS: Atypical squamous cells of undetermined significance, HPV: Human papillomavirus, P value is significant at p< 0.05.

There was a significant association between the abnormal random biopsy results and having multiple sexual partners, hookah, and cigarette smoking (Table 2).

Furthermore, in women who underwent ECC, 31 (8.7%) LSIL and 42 (11.8%) HSIL were reported. There was a significant relation between the abnormal results of ECC and hookah consumption and positive HPV test (Table 3).

The concordance between random biopsy and ECC result was evaluated. The results showed that 71.2% of the test results were the same in the two methods and only in 28.8% of the cases one of the methods was normal and the other was abnormal, which shows that the simultaneous use of the above two methods can be related significantly (p=0.001) with increasing the detection of CIN lesions.

Discussion

The results of the present study showed that the simultaneous use of biopsy and ECC in women with normal colposcopy increases the possibility of precancerous cervical lesion detection rate up to 28.8% of cases. It was also found that the diagnosis of cervical lesions by random biopsy method has a significant relation with multiple sexual partners, hookah, and cigarette smoking, and the diagnosis of these lesions with the help of ECC has a significant relationship with having high-risk HPV infection and hookah consumption.

Table 2: Demographic and clinical data of women with normal colposcopy

Variables	Random biopsy results		P value
	Normal (N = 310)	Abnormal (N = 46)	
Age (years)	39.3±9.4	36.6±6.9	0.109
First sex age (years)	20.2±5.1	20.6±3.4	0.314
Cigarette smoking history	27 (8.7)	9 (19.5)	0.041
Hookah smoking history	48 (15.4)	22 (47.8)	0.033
Gravidity < 2 times	223 (71.9)	37 (80.4)	0.100
Having multiple sexual partners	26 (8.3)	14 (30.4)	0.001
Pap smear result[#]			0.081
Normal	271 (87.4)	42 (91.3)	
LSIL	2 (0.6)	0 (0)	
HSIL	4 (1.2)	1 (2.1)	
Positive HPV test	127 (40.6)	34 (79.1)	0.063

[#]Missing data was in 36 cases, LSIL: Low-grade squamous intraepithelial lesion, HSIL: High-grade squamous intraepithelial lesion, HPV: Human papillomavirus, P value is significant at p< 0.05.

These findings are in complete agreement with the results of Pretorius and Goksedef's studies, but it is contradictory to the study of Liu, the most important possible reasons for this dissimilarity can be the difference in the time of performing ECC and the difference in the experience of gynecologists performing ECC (11, 13, 14).

ECC allows sampling of the endocervical canal, and approximately 5 to 15% of patients with high-grade CIN are diagnosed based on ECC sampling alone (15). Some data have shown that ECC increases the sensitivity of the examination, especially in older patients, ECC may even detect nonadjacent lesions that are representative of glandular neoplasia (11, 16). However, not all women benefit from the ECC method in the same way and the debate about its effectiveness is still high (18). Colposcopists usually perform ECC according to the personal experience, rather than scientific evidence, which is likely to result in higher adverse events for patients (16, 17).

In HU et al.'s study, 3217 women with a positive screening test and a negative colposcopy, who received 4-quartile random sampling, was analyzed from 17 population-based cervical cancer screening studies conducted in China from 1999 to 2008. The results showed that if random sampling was done without ECC, 9.3% of CIN2+ and 18.5% of CIN3+ would not be diagnosed, and it is necessary to perform ECC along with random biopsy. This finding is completely consistent with the results of the present study, which found the use of two methods of random biopsy and ECC to be more effective at the same time for the diagnosis of cervical pre-cancerous lesions (18).

Table 3: Investigating the correlation of endo-cervical curettage results according to demographic and clinical variables

Variables	Endo-cervical curettage results		P value
	Normal (N = 205)	Abnormal (N = 73)	
Mean women age (years)	38.1±8.8	40.1±10.7	0.211
Mean age of first sex (years)	20.7±4.9	19.4±4.1	0.288
Cigarette smoking history	20 (9.7)	9 (12.3)	0.117
Hookah smoking history	32 (15.6)	24 (32.8)	0.008
Gravidity less than 2 times	143 (69.7)	49 (67.1)	0.100
Having multiple sexual partners	24 (11.7)	10 (13.6)	0.612
Pap smear result[#]			0.121
Normal	187 (91.2)	65 (89)	
LSIL	0 (0.0)	2 (2.7)	
HSIL	2 (0.9)	2 (2.7)	
Positive HPV test	87 (42.4)	39 (53.4)	0.011

[#]Missing data was in 20 cases, LSIL: Low-grade squamous intraepithelial lesion, HSIL: High-grade squamous intraepithelial lesion, HPV: Human papillomavirus, P value is significant at p< 0.05.

The study of Pretorius et al., showed that the diagnosis of CIN2+ in colposcopic biopsy is about 57.1%, in random biopsy about 37.4%, and in ECC about 5.5% (19). Cagle et al. study showed that the use of expanded diagnostic criteria compared to the routine diagnostic exams increased the CIN and cancer detection from 3.2% to 4.2% (20).

Jach et al. investigated the usefulness of random cervical biopsy and ECC in a low-risk population with the aim of determining the increase in the detection efficiency of CIN3 or cancer through random cervical biopsy in four quadrants without visible lesions and comparing it with ECC. The results showed that random sampling in the cervical quadrant without visible lesions along with ECC will increase the detection of CIN3 in women with low-risk colposcopy (21).

In Yilmaza et al.'s study, 296 patients underwent colposcopic biopsy and ECC simultaneously. In 125 patients, premalignant/malignant lesions of the cervix were diagnosed by random biopsy, and in the rest 42 patients, by ECC. This study showed that simultaneous ECC with random biopsy can increase the accuracy of colposcopy (22).

All the above three studies show the importance and necessity of performing ECC with random biopsy in order to increase the accuracy in the diagnosis of precancerous lesions of cervical masses, which has been done in different communities, which is consistent with the results of the present study (20-22).

In the study of Zhao et al., (23) which was conducted with the aim of evaluating the effect of random biopsy in the diagnosis of squamous intraepithelial lesions or high-grade carcinoma of the cervix (HSIL+), it was determined that random biopsy was not effective in women with positive colposcopy and should be performed in women with cytologically positive HSIL. However, it should be performed in those with cytological LSIL or HGSL+, HPV-positive, and normal colposcopy. In Wentzensen et al.'s study, it was stated that random sampling in 4 quadrants of the cervix is only recommended for HPV positive women with HSIL cytology (24). These studies differ from our study in terms of their objectives and implementation method, and therefore cannot be fully compared.

The results of some studies have shown that negative random biopsies with positive ECC have a clear added value and can identify a significant number of women with positive and negative colposcopy results with curable cervical dysplasia (25, 26).

Huh et al. showed that age, cytology type, lesion size, HPV type and viral load of HPV are possible indicators of the severity of the lesion detected using random biopsy and the diagnosis of CIN 2+, especially high cytology abnormalities; which it can be raised by further random sampling. This finding is somewhat consistent with the results of the present study, especially regarding the type of HPV and its severity (27).

Jespersen et al. also reported that in colposcopy-negative cases, performing a random biopsy will be associated with an increase in the diagnosis of CIN2+ (28).

Considering that the detection of cervical cancer is very important and the sensitivity of colposcopy is low; future studies seem necessary to evaluate methods to increase the sensitivity and accuracy of cervical cancer screening.

One of the most important strengths of this study is the combination of two common methods of diagnosing cervical lesions and the overlap of their weak points in diagnosing cervical lesions.

One of the most important limitations of this research is absence of HPV results in a large percentage of the patients, since in our country women, the colposcopic evaluation is less expensive and more accessible rather than HPV test (29). The other limitations were lack of full cooperation of some patients, and unicentric study hospital. In addition, it is necessary to carry out extensive studies in different parts of the world with different physiological, social and genetic characteristics for the long-term follow-up of the effect of this method in tracking the occurrence and progress of CIN.

Conclusion

The results of the present study showed that the simultaneous use of ECC and random biopsy in women with normal colposcopy increases the detection rate of precancerous lesions. Therefore, in cases of negative colposcopy, it is recommended to use both random biopsy and ECC.

Conflict of Interests

Authors declare no conflict of interests.

Acknowledgments

References

1. Tehranian A, Ghahghaei-Nezamabadi A, Motiei Langeroudi M, Aghajani R. Comparison of Visual Inspection Methods Using Either Acetic Acid Solution or Lugol's Iodine Solution with Colposcopy in Screening of Cervical Cancer: A Cross Sectional Study. Journal of Obstetrics, Gynecology and Cancer Research. 2023;8(1):53-6.

2. Smith HJ, Leath CA 3rd, Huh WK, Erickson BK. See-and-Treat for High-Grade Cytology: Do Young Women Have Different Rates of High-Grade Histology? J Low Genit Tract Dis. 2016;20(3):243-6.

3. Cantor SB, Cárdenas-Turanzas M, Cox DD, Atkinson EN, Nogueras-Gonzalez GM, Beck JR, et al. Accuracy of colposcopy in the diagnostic setting compared with the screening setting. Obstet Gynecol. 2008;111(1):7-14.

4. Carwile JL, Feldman S, Johnson NR. Use of a simple visual distraction to reduce pain and anxiety in patients undergoing colposcopy. J Low Genit Tract Dis. 2014;18(4):317-21.

5. Schmid BC, Pils S, Heinze G, Hefler L, Reinthaller A, Speiser P. Forced coughing versus local anesthesia and pain associated with cervical biopsy: a randomized trial. Am J Obstet Gynecol. 2008;199(6):641.e1-3.

6. Perkins RB, Guido RS, Castle PE, Chelmow D, Einstein MH, Garcia F, et al.; 2019 ASCCP Risk-Based Management Consensus Guidelines Committee. 2019 ASCCP Risk-Based Management Consensus Guidelines for Abnormal Cervical Cancer Screening Tests and Cancer Precursors. J Low Genit Tract Dis. 2020;24(2):102-131.

7. Baasland I, Hagen B, Vogt C, Valla M, Romundstad PR. Colposcopy and additive diagnostic value of biopsies from colposcopy-negative areas to detect cervical dysplasia. Acta Obstet Gynecol Scand. 2016 Nov;95(11):1258-1263.

8. Davey DD, Neal MH, Wilbur DC, Colgan TJ, Styer PE, Mody DR. Bethesda 2001 implementation and reporting rates: 2003 practices of participants in the College of American Pathologists Interlaboratory Comparison Program in Cervicovaginal Cytology. Arch Pathol Lab Med. 2004;128(11):1224-9.

9. Gage JC, Hanson VW, Abbey K, Dippery S, Gardner S, Kubota J, et al; ASCUS LSIL Triage Study (ALTS) Group. Number of cervical biopsies and sensitivity of colposcopy. Obstet Gynecol. 2006;108(2):264-72.

10. Massad LS. Selecting Patients for Endocervical Curettage. J Low Genit Tract Dis. 2015;19(4):271-2.

11. Pretorius RG, Zhang WH, Belinson JL, Huang MN, Wu LY, Zhang X, et al. Colposcopically directed biopsy, random cervical biopsy, and endocervical curettage in the diagnosis of cervical intraepithelial neoplasia II or worse. Am J Obstet Gynecol. 2004;191(2):430-4.

12. Chen Q, Du H, Pretorius RG, Wang C, Yang B, Wang G, et al. High-Grade Cervical Intraepithelial Neoplasia Detected by Colposcopy-Directed or Random Biopsy Relative to Age, Cytology, Human Papillomavirus 16, and Lesion Size. J Low Genit Tract Dis. 2016;20(3):207-12.

13. Goksedef BP, Akbayir O, Numanoglu C, Corbacioglu A, Guraslan H, Bakir LV, et al. Evaluation of endocervical canal in women with minimal cervical cytological abnormalities. J Low Genit Tract Dis. 2013;17(3):261-6.

14. Liu AH, Walker J, Gage JC, Gold MA, Zuna R, Dunn ST, et al. Diagnosis of Cervical Precancers by Endocervical Curettage at Colposcopy of Women With Abnormal Cervical Cytology. Obstet Gynecol. 2017;130(6):1218-1225.

15. Gage JC, Duggan MA, Nation JG, Gao S, Castle PE. Detection of cervical cancer and its precursors by endocervical curettage in 13,115 colposcopically guided biopsy examinations. Am J Obstet Gynecol. 2010;203(5):481.e1-9.

16. Chen Q, Du H, Pretorius RG, Wang C, Yang B, Wang G, et al. High-Grade Cervical Intraepithelial Neoplasia Detected by Colposcopy-Directed or Random Biopsy Relative to Age, Cytology, Human Papillomavirus 16, and Lesion Size. J Low Genit Tract Dis. 2016;20(3):207-12.

17. Song Y, Zhao YQ, Zhang X, Liu XY, Li L, Pan QJ, et al. Random biopsy in colposcopy-negative quadrant is not effective in women with positive colposcopy in practice. Cancer Epidemiol. 2015;39(2):237-41.

18. Hu SY, Zhang WH, Li SM, Li N, Huang MN, Pan QJ, et al. Pooled analysis on the necessity of random 4-quadrant cervical biopsies and endocervical curettage in women with positive screening but negative colposcopy. Medicine (Baltimore). 2017;96(17):e6689.

19. Pretorius RG, Belinson JL, Azizi F, Peterson PC, Belinson S. Utility of random cervical biopsy and endocervical curettage in a low-risk population. J Low Genit Tract Dis. 2012;16(4):333-8.

20. Cagle AJ, Hu SY, Sellors JW, Bao YP, Lim JM, Li SM, et al. Use of an expanded gold standard to estimate the accuracy of colposcopy and visual inspection with acetic acid. Int J Cancer. 2010;126(1):156-61.

21. Jach R, Mazurec M, Trzeszcz M, Bartosinska-Dyc A, Galarowicz B, Kedzia W, et al. COLPOSCOPY 2020 - Colposcopy Protocols: A Summary of the Clinical Experts Consensus Guidelines of the Polish Society of Colposcopy and Cervical Pathophysiology and the

Polish Society of Gynaecologists and Obstetricians. Ginekol Pol. 2020;91(6):362371.

22. Yilmaza F, Kilincb AN, Baymanc MG, Ünlub Y, Özturk EN. Prognostic Value of Endocervical Curettage at the Time of Colposcopic Assessment of the Uterine Cervix. Journal of Clinical Obstetrics & Gynecology 2023;33(1):22-6.

23. Zhao Y, Zhao F, Hu S, Zhang X, Zhang W, Pan Q, et al. Value of multi-quadrants biopsy: Pooled analysis of 11 population-based cervical cancer screening studies. Chin J Cancer Res. 2020;32(3):383-394.

24. Wentzensen N, Walker JL, Gold MA, Smith KM, Zuna RE, Mathews C, et al. Multiple biopsies and detection of cervical cancer precursors at colposcopy. J Clin Oncol. 2015;33(1):83-9.

25. Kishi Y, Inui S, Sakamoto Y, Mori T. Colposcopy for postmenopausal women. Gynecol Oncol. 1985;20(1):62-70.

26. Li Y, Luo H, Zhang X, Chang J, Zhao Y, Li J, et al. Development and validation of a clinical prediction model for endocervical curettage decision-making in cervical lesions. BMC Cancer. 2021;21(1):804.

27. Huh WK, Sideri M, Stoler M, Zhang G, Feldman R, Behrens CM. Relevance of random biopsy at the transformation zone when colposcopy is negative. Obstet Gynecol. 2014;124(4):670-678.

28. Jespersen MM, Booth BB, Petersen LK. Can biopsies be omitted after normal colposcopy in women referred with low-grade cervical cytology? A prospective cohort study. BMC Womens Health. 2021;21(1):394.

29. Yarandi F, Shirali E, Feizabad E, Ramhormoziyan S, Sarmadi S, SadrAmeli M, Arshadi E. Cervical intraepithelial neoplasia in non-16/18 high-risk human papilloma virus positive/cytology negative women: An alternative approach in poor resource areas. Taiwan J Obstet Gynecol. 2023;62(2):299-303.