Original Article

DOI: 10.4274/anajog.galenos.2024.03522

Anat J Obstet Gynecol Res 2024;2:61-65

Could Clinically Suspicious Cervix Predict Cervical Premalignant and Malignant Lesions in Postmenopausal Women?

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ABSTRACT

Purpose: Assessing the role of clinically suspicious cervix in detecting premalignant and malignant lesions in postmenopausal women, ındependent of cervical cytology and human papilloma virus (HPV)-deoxyribonucleic acid (DNA) testing.

Methods: This study retrospectively analyzed 392 postmenopausal women aged 45-86 who underwent colposcopic biopsy at our clinic between 2017 and 2021. Data collected included patient age, parity, cervical cytology results, HPV-DNA test outcomes, and colposcopic biopsy findings. Patients were categorized based on the indication for colposcopy into three groups: clinically suspicious cervix, high-risk group HPV-DNA positivity, and abnormal cytology. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for detecting premalignant and malignant cervical lesions were subsequently calculated.

Results: Among the 174 patients referred for colposcopic biopsy due to a clinically suspicious cervix, 50% were found to have cervical premalignant lesions classified as cervical intraepithelial neoplasia-1 or higher, and 10% were diagnosed with malignancy. In the subset of 30 patients aged 65 and older with a clinically suspicious cervix, 17 were diagnosed with either premalignant or malignant cervical lesions. The sensitivities of clinically suspicious cervix, HPV-DNA positivity, and abnormal cytology for detecting premalignant or malignant lesions were 43%, 80%, and 37%, respectively. The specificities were 53%, 49%, and 73%; accuracies were 47%, 67%, and 51%; PPV were 60%, 68%, and 69%; and NPV were 36%, 64%, and 42%, respectively. Additionally, among the 392 patients, 11 were diagnosed with premalignant or malignant lesions solely through endocervical curettage.

Conclusion: The presence of a clinically suspicious cervix serves as a significant indication for colposcopy, comparable to traditional screening tests, in the detection of cervical premalignant and malignant lesions. The findings from our study indicate that cervical cancer screening should be maintained in women over the age of 65.

Keywords: Clinically suspicious cervix, postmenopause, pap smear, colposcopy, HPV-DNA test

INTRODUCTION

Cervical cancer ranks as the fourth most prevalent malignancy among women globally. Despite a reduction in incidence and mortality rates in developed countries, attributed to the systematic implementation of screening programs, cervical cancer continues to pose a significant public health challenge in developing and underdeveloped regions.[1] Screening methods for cervical cancer include pelvic examination, cervical cytology, human papilloma virus (HPV)-deoxyribonucleic acid (DNA) testing, and co-testing (a combination of cytology and HPV-DNA testing). A key characteristic of cervical cancer is that its premalignant lesions can be detected through screening tests, and these lesions may progress to malignancy over a long period.[2]

Over the past 50 years, the widespread use of cytology in cervical cancer screening has led to a reduction in disease-related mortality by approximately 70%. However, the broad range of false-negative rates, between 5% and 40%, is a major disadvantage of cytological assessment.[2]

HPV 16 is responsible for 50% of cervical cancer cases, while HPV 18 is associated with 20% of cases.[3] HPV-DNA-based

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Received: 31.07.2024 **Accepted:** 25.08.2024

testing is widely regarded as the primary screening method in many countries because of its high sensitivity in detecting cervical cancer. However, the use of these tests is restricted in underdeveloped and developing countries, primarily due to their cost.[4]

Patients referred for colposcopy based on symptoms and lesions suggestive of malignancy, as identified through anamnesis and pelvic examination, are categorized as having a "clinically suspicious cervix".[5] In addition to cytology and HPV-DNA testing, a clinically suspicious cervix is an indication for colposcopy that covers all age groups and does not require additional costs. The existing literature on the colposcopic findings associated with a clinically suspicious cervix is limited, with studies involving relatively small patient cohorts.[5-7]

In this study, we aim to demonstrate the role of a clinically suspicious cervix in detecting premalignant and malignant lesions, particularly in cases where cytology and/or HPV-DNA testing results are negative.

Additionally, we seek to emphasize the importance of cervical examination in guiding the decision for colposcopic biopsy. Given the age range of our study population, we also aim to contribute to the literature on the necessity of continuing cervical cancer screening for women aged 65 and older.

METHODS

In this retrospective observational study, we reviewed the medical records of 2,040 patients who presented to our clinic and were referred for colposcopy between 2017 and 2021. We identified 486 postmenopausal women among these patients. 94 patients were excluded from the study for the following reasons: having a history of premalignant or malignant cervical lesions and currently undergoing follow-up or treatment; receiving exogenous hormone therapy; having undergone hysterectomy; presenting with lesions indicative of obvious invasive cervical cancer who had undergone cervical biopsy without prior colposcopic examination; and possessing incomplete medical records. The remaining 392 postmenopausal women, aged 45-86, were analyzed for age, parity, cervical cytology, HPV-DNA test results, colposcopy indications, and pathology reports. Patients were categorized based on colposcopy indications into clinically suspicious cervix, high-risk group HPV (hr- HPV) positivity, and abnormal cytology. Ethics committee approval for our retrospective observational study was received from the Prof. Dr. Cemil Taşçıoğlu Training and Research Hospital Clinical Research Impact Committee (decision numbered: 248/2021-06-21).

"Clinical suspicion" was defined as postmenopausal bleeding, postcoital bleeding, and treatment-resistant malodorous vaginal discharge. The following criteria were used to diagnose abnormal cervical appearance in postmenopausal patients:

- Presence of ectropion/erosion, markedly hyperemic lesions with contact bleeding,
- Increased abnormal vascularization,
- Presence of leukoplakia or condyloma-like lesions,
- Presence of exophytic millimeter-sized masses.

Patients with lesions indicative of stage 1a[1] or greater cervical cancer, who underwent direct biopsy, were excluded from the study.

Colposcopy Technique in Postmenopausal Patients

The cervix was washed with physiological saline and treated first with a 3-5% acetic acid solution and then with Lugol's solution under colposcopic illumination. The cervix was evaluated for abnormal colposcopic findings, including acetowhite epithelium, mosaic pattern, punctation, and atypical vascularization, and biopsies were taken from areas with detected abnormalities. All postmenopausal patients also underwent endocervical curettage (ECC).

Statictical Analysis

Data analysis was performed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). Normality and homogeneity were assessed using the Kolmogorov-Smirnov and Levene's tests, respectively, and the chi-square test was used to examine the distribution of categorical data between groups. Descriptive statistics were conducted to determine mean and standard deviation values for age and parity. The colposcopic biopsy results for clinically suspicious cervix indications in postmenopausal patients were compared with the results of colposcopy performed due to abnormal cervical cytology and positive high-risk group HPV indications.

Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for detecting premalignant and malignant lesions were calculated. A 95% confidence interval and a significance level of $p=0.05$ were applied for all data evaluations.

RESULTS

Among these patients, 174 were referred for colposcopic evaluation due to clinical suspicion and abnormal cervical appearance, 146 due to HPV-DNA positivity, and 72 due to abnormal cervical cytology.

Age and parity distributions were similar among the three groups. Table 1 provides the descriptive statistics for patients in each group.

As shown in Table 2, 60% of the 174 patients with a clinically suspicious cervix were found to have cervical premalignant or malignant lesions of cervical intraepithelial neoplasia (CIN)-1 or higher, based on pathology results. This percentage was similar to those referred for colposcopy due to positive HPV-DNA testing (63%) and abnormal cytology (58%). Among the

Table 1. Common descriptive characteristics of patients

Patient groups and their numbers	Age Mean ± SD (min.-max.)	Parity Mean
Cervix with clinical suspicion (n=174)	57±9 (45-86)	4
HPV positive (n=146)	54±5 (46-66)	3
Abnormal cytology (n=72)	57±7 (45-70)	3
p-value	0.064	0.091

HPV: Human papilloma virus, min.-max.: Minimum-maximum

patients referred for colposcopy due to clinical suspicion, 10% (n=18) had detected malignancies, while only one patient each in the HPV-DNA positive and abnormal cytology groups exhibited malignancies. Among 43 patients aged 65-86, 27 (62.7%) had pathological results indicating pre-malignant/malignant cervical lesions. Specifically, 11 patients had CIN1, 2 patients had CIN2, 3 patients had CIN3 and 11 (25.5%) patients had malignancy. In contrast, among 349 patients aged 45-65, malignancy was found in 2% (n=7). Malignacy detection in cases of clinically suspicious cervix was significantly more frequent in elderly postmenopausal patients aged 65 and greater compared to postmenopausal patients younger than age 65 (p=0.0001).

Among patients with abnormal cytology (n=72), the distribution was as follows: 70% (n=50) had an atypical squamous cells of undetermined significance, 14% (n=10) had a low-grade squamous intraepithelial lesion or, 8% (n=6) had an atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion, and 7% (n=5) had a high-grade squamous intraepithelial lesion. One patient had an atypical glandular cells.

In the classification of HPV-DNA positive cases (n=146) based on oncogenic risk potential, 125 cases were identified as high-risk types, while 21 cases were categorized as having unknown types.

The primary indications for referral to colposcopy due to clinically suspicious cervix were exophytic mass (28%), postcoital bleeding (17%), postmenopausal bleeding (20%), and increased cervical vascularity (11%) (Table 3). We observed a higher detection rate of CIN1 or more severe lesions in cases presenting with postcoital and postmenopausal bleeding which are among the most significant symptoms of cervical cancer. In instances where malignancy was identified, postmenopausal and postcoital bleeding, along with exophytic mass, were the predominant clinical suspicions.

Table 4 shows that the PPV among the three groups were nearly equivalent. HPV positivity had the highest sensitivity, while clinically suspicious cervix had higher sensitivity compared to abnormal cytology, but lower specificity.

Among the 392 patients, 11 who had negative colposcopic biopsies were diagnosed solely through ECC. Pathology results for these patients included CIN3 in 5 patients, CIN2 in 1 patient, CIN1 in 3 patients, and invasive cancer in 2 patients (Table 5).

DISCUSSION

Contemporary indications for colposcopy predominantly include high-risk HPV positivity and abnormal cytology.[8] The American Society for Colposcopy and Cervical Pathology risk-

Table 2. Pathology results distribution based on colposcopy indications

Biopsy result	Benign	CIN1	CIN2	CIN3	Malign
Cervix with clinical suspicion (n=174) n (%)	69 (40%)	66 (38%)	9 (5%)	12 (7%)	18 (10%)
HPV positive (n=146) n (%)	54 (37%)	64 (44%)	12 (8%)	15 (10%)	1 (1%)
Abnormal cytology (n=72) n (%)	30 (42%)	34 (47%)	5 (7%)	2 (3%)	1 (1%)
Total	**153**	**164**	**26**	**29**	**20**

HPV: Human papilloma virus, CIN: Cervical intraepithelial neoplasia

Table 3. Distribution of pathology results by clinical suspicious cervix diagnostic criteria

Colposcopic biopsy result	Normal	CIN1	CIN2	CIN3	Malignite	Total
Exophytic mass	20 (40.8%)	20 (40.8%)	0	3 (6%)	6 (12%)	49 (28%)
Erosion/Ectropion	11 (45.8%)	7 (29%)	4 (16.6%)	0	2 (8.3%)	24 (13.7%)
Postmenopausal bleeding	12 (36%)	9 (27%)	1 (3%)	5 (15%)	6 (18%)	33 (20%)
Increased vascularity	9 (45%)	9 (45%)	1 (5%)	0	1 (5%)	20 (11.4%)
Postcoital bleeding	10 (33%)	13 (43%)	1 (3%)	3 (10%)	3 (10%)	30 (17%)
Abnormal vaginal discharge	4 (36.3%)	5 (45.4%)	1 (9%)	1 (9%)	0	11 (6%)
Leukoplakia	3 (43%)	4 (57%)	0	0	0	7 (4%)
Total	**69 (40%)**	**66 (38%)**	**9 (5%)**	**12 (7%)**	**18 (10%)**	**174 (100%)**

CIN: Cervical intraepithelial neoplasia

Table 4. Predictive value of clinically suspicious cervix, HPV positivity and abnormal cytology in cervical premalignant and malignant lesions

	Sensitivity	Specificity	Confirmation rate	PPV	NPV
Cervix with clinical suspicion	43%	53%	47%	60%	36%
HPV positive	80%	49%	67%	68%	64%
Abnormal cytology	37%	73%	51%	69%	42%

HPV: Human papilloma virus, PPV: Positive predictive value, NPV: Negative predictive value

Table 5. Comparison of colposcopic biopsy and ECC results

Colposcopic biopsy + ECC			
Colposcopic biopsy	**Negative**	**Positive**	**Total**
Negative	141	11	152
Positive	0	240	240
Total	141	251	392

ECC: Endocervical curettage

based management algorithm also utilizes these two screening methods to calculate and manage the risk of developing cervical pre-invasive lesions.[8] Other indications for colposcopy include clinical suspicion and abnormal cervical appearance. However, the boundaries and objective criteria for defining clinically suspicious cervixes for identifying pre-malignant and malignant lesions are unclear. Cervical examination, whether performed visually or via colposcopy, remains a subjective assessment.

There is limited information on clinical suspicion in evaluating the cervix and the definition of abnormal cervical appearance. In a guide published by Casey et al.,[9] abnormal-looking cervical lesions were categorized as cervical polyps and fibroids, cervical ectropion, cervical endometriosis, cervicitis, lesions associated with postcoital bleeding, and in utero dietilstilbestrol exposure. In another study, cervical ectopy/ectropion, suspicious masses, ulcers, hypertrophy, leukoplakia, and cervical warts were additionally included among these lesions.[10] In our study, under the heading of the clinically suspicious cervix, we aggregated cases of exophytic masses, erosion/ectropion, increased vascularization, contact bleeding lesions, abnormal chronic vaginal discharge, leukoplakia, condyloma, and postmenopausal/postcoital bleeding.

In our study, among the 174 patients referred for clinically suspicious cervix, colposcopic biopsy results revealed CIN1 or higher cervical pre-malignant or malignant lesions in 60% of cases. Reviewing similar studies in the literature, a 60% positive result rate for cervical dysplasia in cases of clinically suspicious cervix was reported.[5] However, other studies have shown this rate to be between 20% and 30%.[6,7] We hypothesize that these difference in the literature may be attributed to limited number of patients, subjective definitions of clinically suspicious cervix, and differences in background risk of the populations the studies were conducted.

During the postmenopausal period, the squamocolumnar junction typically shifts towards the endocervical canal. Cervical ectropion and erosion are not expected to be seen during this period. Since it is not possible to definitively differentiate cervical ectropion from CIN and cervical cancer using macroscopic imaging in postmenopausal patients, it is necessary to distinguish between cervical pre-malignant and malignant lesions using cytology and/or colposcopy in suspicious cases.[11] In our study, half of the 24 postmenopausal patients who were evaluated colposcopically for cervical erosion or ectropion had abnormal pathology findings.

In a study examining 314 women presenting with postcoital bleeding, colposcopy results revealed invasive cancer in 4% of cases and CIN in 17%.[12] Our study identified postcoital bleeding as a significant symptom indicative of cervical lesions. Among the 14 postmenopausal patients who underwent colposcopic biopsy due to this symptom, CIN1 or higher pre-malignant/malignant lesions were detected in 10 cases. A study examining 148 patients with cervical cancer found that 70% of the cases were symptomatic, with postmenopausal bleeding being the most common symptom at a rate of 33%.[13] In our study, among the 21 patients with postmenopausal bleeding, 2/3 had pre-malignant or malignant pathology on colposcopy. Specifically, 6 patients had CIN1, 4 patients had CIN3 and 4 patients had invasive cancer. These data suggest that postmenopausal bleeding is a significant indicator of cervical cancer.

Currently, cervical cancer screening programs enable the detection of cervical lesions in the pre-invasive stage, allowing for monitoring and treatment to prevent progression to invasive lesions. Guidelines for cervical screening methods and their management are continuously updated with emerging studies. According to international guidelines, cervical screening programs are recommended to be terminated at age 65.[14-16] In our study, malignacy detection in cases of clinically suspicious cervix was significantly more frequent in elderly postmenopausal patients aged 65 and greater compared to postmenopausal patients younger than age 65.

Based on the pathological results of the 43 patients aged 65 and over in our study, the cumulative risk for cervical cancer continues, continuing screening beyond age 65 appears reasonable as the life expectancy in the world is increasing. Additionally, these data indicate that in developing countries like ours, the risk of cervical malignancy persists in older age, and continued screening could significantly prevent malignancy. Supporting studies in the literature include Rustagi et al.,[17] who reported that HPV infection risk persists in older women, and cervical cancer screening programs should include women aged 65 and over. Another study involving 2,753 women with invasive cervical cancer found that approximately 20% of cervical cancer cases were in the 55-69 age group, and 19% were in those aged 70 and over. This suggests that the risk of cervical cancer continues with age, most cancer cases still occur in women over 65, and screening should continue at older ages.[18]

In a study by Gage et al.,[19] among 13,115 colposcopic biopsies detecting CIN2 and above, approximately 1% of cases had a positive ECC only, and they recommended the addition of ECC to colposcopic procedures, especially in older women. In our study, among 392 patients, 11 had normal colposcopic cervical biopsy results but had pathological diagnoses identified only through ECC. ECC alone detected CIN1 in 3 patients, CIN2 in 1 patient, CIN3 in 5 patients, and invasive cancer in 2 patients. Our results support that ECC should be performed routinely with colposcopic biopsy, particularly in postmenopausal patients.

In our study, HPV positivity exhibited the highest sensitivity at 80%, whereas colposcopic biopsy conducted in the presence of a clinically suspicious cervix demonstrated greater sensitivity (43%) compared to cytology results (37%). The positive PPV for all three groups we examined were similar.

This indicates that a clinically suspicious cervix is at least as effective as screening tests in identifying actual cases of cervical pathology.

Study Limitations

The limitations of our study include the restricted sample size and the fact that it was conducted on a cross-sectional subset of the population. This does not address whether similar results would be obtained in premenopausal patients. Additionally, the subjective nature of defining a clinically suspicious cervix represents another limitation of our study. On the other hand, our study could contribute to establishing standard criteria for the definition of a clinically suspicious cervix. Given that it includes data from the postmenopausal patient group outside of screening programs, it highlights the importance of gynecological examinations and the necessity for continued screening in this group of patients.

CONCLUSION

The gold standard method for the diagnosis of cervical lesions is colposcopy-guided cervical biopsy and histopathologic examination. Currently, the majority of patients referred for colposcopy are those with positive cervical cytology and/or high-risk group HPV-DNA test results. Nevertheless, our study identified a clinically suspicious cervix as a significant indicator for detecting pre-malignant and malignant lesions, comparable to screening tests. The importance of clinical suspicion increases particularly when considering the age group and menopausal status examined in our study. In the postmenopausal patient group, we concluded that directing patients to immediate colposcopic biopsy after evaluating cervical examination and symptoms by a clinician is at least as effective as screening tests in detecting pre-malignant and malignant lesions. This suggests that cytological screening should be continued in the postmenopausal patient group.

Footnote

Ethics Committee Approval: Prof. Dr. Cemil Taşçıoğlu Training and Research Hospital Clinical Research Impact Committee (decision numbered: 248/2021-06-21).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: T.Ö.A., Y.C., Concept: T.Ö.A., H.G., Design: T.Ö.A., H.G., Data Collection or Processing: D.E.A., Ö.D.S., Analysis or Interpretation: T.Ö.A., Y.C., H.G., Literature Search: D.E.A., Ö.D.S., Writing: T.Ö.A., Y.C.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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