

The outcome of colposcopy in women attending with persistent postcoital bleeding and negative HPV-DNA test

Mehmet Bayrak^{1*}, Hakan Ozan¹

¹ Uludag University Hospital, Dept of Gynecologic Oncology, Bursa, TR

* Corresponding Author: Mehmet Bayrak E-mail: drmehmetbayrak@gmail.com

ABSTRACT

Objective: Women with postcoital bleeding (PCB) are recommended to be evaluated by colposcopy even if cytology is negative. Human papillomavirus (HPV) testing increases the detection of cervical intraepithelial neoplasia or worse compared to the Pap smear test. We aimed to determine the incidence of cervical pathology among women with persistent PCB with a negative Pap smear or HPV-DNA test. Our study, therefore, questions the place of HPV DNA test in women with PCB.

Material and Methods: The clinical data of 212 women with persistent PCB and negative cytology or negative HPV DNA test referred to colposcopy, between January 2010 and June 2019, were retrospectively evaluated.

Results: Among the 212 PCB patients, 161 (75.9%) were cytology negative and 51 (24.1%) were HPV DNA test (n=40) or co-test (n=11) (negative for HPV DNA test and cytology) negative. There were no cases of invasive cancer. The women referred with negative cytology were more likely than those with negative HPV DNA to have CIN (21/161 (13%), 1/51 (1.9%) p=0.042. Seven women (4.3%) were diagnosed with high-grade cervical dysplasia in the negative cytology group. None of the patients in the HPV DNA negative group was diagnosed with high-grade cervical dysplasia.

Conclusion: Our data show that a normal Pap smear cytology in women with PCB does not rule out the possibility of HSIL. HPV DNA testing is a useful triage test to determine if colposcopy referral is required in the context of post-coital bleeding with negative smear test.

Keywords: Postcoital bleeding, colposcopy, HPV-DNA test, cervical smear

INTRODUCTION

Postcoital bleeding (PCB) refers to bleeding that occurs during or immediately after intercourse. The significance of PCB as a potential symptom of cervical cancer has always been emphasized, particularly if it is persistent. On the other hand, it is a common gynecological symptom as the prevalence of PCB is 6% in menstruating women and it is mainly caused by a benign lesion of the cervicovagina such as infection, cervical polyps, ectropion (1). The prevalence of cervical intraepithelial neoplasia (CIN) in women presenting with PCB varied in different studies between 6.8% and 17.8% (2). The management of PCB is inconsistent. Currently, there are no guidelines or evidence from randomized clinical trials to base recommendations on the management of PCB. There is no controversy that women with abnormal high-risk human papillomavirus (HPV) DNA, pap smear test or visible lesion that is highly suspicious for underlying cancer should be referred for colposcopy. However, there is a debate on whether colposcopy should be performed on women who have PCB with a negative pap smear or negative HPV-DNA test. Multiple studies questioned the place of pap smear alone in women with persistent PCB. They reported that a normal pap smear alone would not be regarded as reassuring in a woman with PCB (3). In a retrospective study of 166 women with PCB and negative previous smear history, the rate of cervical cancer and CIN was found to be 3.6% and 9%, respectively (4). The false-negative rate of Pap smears in the presence of invasive cancer is as high as approximately 40-50% (5).

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Limitations of the Pap smear test have led to the development of HPV tests for cervical cancer screening programmes (6). HPV DNA testing is cost-effective as a screening strategy compared to Pap smear (7). On the other hand, HR-HPV testing has a higher false-positive rate than cytology resulting in more women initially being referred for colposcopy (8).

This study was to determine the risk of finding cervical cancer and its precursors among women referred to the colposcopy primarily because of postcoital bleeding with negative cytology or HPV DNA. We aimed to answer whether a negative HPV DNA test excludes significant pathology in women with postcoital bleeding.

MATERIAL AND METHODS

We performed a retrospective study of patients referred to the colposcopy examination with persistent postcoital bleeding at the Gynecologic Oncology Unit, Uludag University Hospital between January 2010 to June 2019. The study protocol was approved by the Uludag University Institutional Ethics Board (2019-17/13).

Inclusion criteria are women with persistent PCB and negative cervical cytology or negative high-risk HPV DNA test. Women excluded from the study were those who presented with PCB and previous abnormal smears or positive high-risk HPV DNA test results, and patients with an obvious cervical lesion were excluded from the study. Persistent PCB is defined as the duration of symptoms for more than six weeks. Identification of these patients was taken from the case notes, and details were extracted from computer records.

National cervical cancer screening program using primary HPV with genotyping and reflex liquid-based cytology (LBC) triage started in 2014 in Turkey. In our institute HPV based testing has been using since 2017, before that primarily Pap smear test was used for follow-up and screening of cervical pre-invasive lesions. In our centre, we use colposcopy to evaluate women with persistent PCB, regardless of cytology or HPV DNA testing results.

Histopathology findings were classified according to the LAST Standardization. High-grade squamous intraepithelial lesion (HSIL) is used to define a group of histologically proven CIN2, CIN3 or carcinoma in situ (9). Patients with positive colposcopic findings underwent a directed biopsy. Standard colposcopic techniques were used, including the application of 3% acetic acid and biopsies were taken from suspicious-looking areas.

All calculations were performed using IBM SPSS 23.0 (IBM SPSS Inc., Armonk, NY, IBM Corp.). A descriptive analysis of the data was undertaken. Statistical significance for differences was analyzed using the t-test and χ^2 test as appropriate. All P-values were tested as two-tailed and considered significant at <0.05 .

RESULTS

A total of 212 women with PCB and negative cytology or negative HPV DNA testing were examined with colposcopy during the study period. Among the 212 PCB patients, 161 (75.9%) were cytology negative and 51 (24.1%) were HPV DNA (n=40) or co-test (n=11) negative (negative for HPV and cytology). The characteristics of the 212 women included are shown in Table 1.

Of the 161 women who had PCB and negative cytology, 78 (48.4%) had normal colposcopic appearances, hence had not histology. The remaining 83 (51.6%) had a punch biopsy. Of these, 62 (74.7%) had normal histology. Of the 51 women who had PCB and negative HPV DNA testing, only one woman had cervical pathology. Table 2 presents the details of management. The women referred with negative cytology were more likely than those with negative HPV DNA to have CIN (21/161 (13%), 1/51 (1.9%) $p=0.042$). There were no cases of invasive cancer.

In total, seven women (4.3%) were diagnosed with HSIL in the negative cytology group. However, none of the patients in the HPV DNA negative group was diagnosed with HSIL, but this finding did not reach statistical significance. ($p=0.199$).

Table 1. Main characteristics of the study population

	Negative cytology group (n=161)	Negative HPV-DNA group (n=51)	p
Age (Median, min-max)	38 (20-66)	41 (25-60)	0.126
Parity			
Nuliparous	15 (9.3%)	5 (9.8%)	0.927
Primiparous	33 (20.5%)	8 (15.7%)	0.544
Multiparous	113(70.2 %)	38 (74.5%)	0.599

Table 2. Colposcopic and histopathologic findings of patients

	Negative cytology group (n=161)	Negative HPV-DNA group (n=51)	p
Macroscopic appearance of cervix			
Normal	106 (65.8%)	31 (60.8%)	0.507
Cervical ectopy	35 (21.7%)	16 (31.4%)	0.189
Cervical polyp	20 (12.4%)	4 (7.8%)	0.455
Colposcopy findings			
Unsatisfactory	38 (23.6%)	14 (27.4%)	0.579
Normal appearance	78 (48.4%)	31 (60.8%)	0.149
Abnormal	45 (28%)	6 (11.8%)	0.023
Histopathology			
LSIL	14 (8.7%)	1 (1.9%)	0.042
HSIL (CIN2/CIN3)	7 (4.3%)	0	0.199

DISCUSSION

PCB is a concern for women because of its association with cervical cancer risk. Pap smear is the cornerstone of the screening and prevention of cervical cancer; however, due to high false negativity, the reliability of negative smear remains a topic of debate in the management of PCB. Although patients referred with negative cytology, have a lower incidence of CIN than those with no cytology (10). Women with PCB are recommended to be evaluated by colposcopy even if cytology is negative (11). HPV testing has been replacing cytology in many regions as a primary screening tool for cervical cancer in recently years. HPV testing increases the detection of CIN3 or worse by approximately 40% compared to cytology (12). HPV testing is cost-effective as a screening strategy compared to conventional cytology. On the other hand, it has a higher false-positive rate than pap smear resulting in more women initially being referred for colposcopy (8). Our study, therefore, questions the place of HPV DNA testing in women with PCB.

There were no cases of invasive cervical cancer in our study. This result is a contrast to previous studies, which showed an incidence of 0.6 and 3% (8, 13). This can be due to the exclusion of patients who have suspected mass in our study group.

In the current study, 4.3% of women with postcoital bleeding had HSIL even though they had normal smears. These rates are consistent with other studies. Khattab et al. analyzed the data of 166 women referred with PCB and negative cytology history and reported that the rate of cervical cancer and CIN to be 3.6% and 9%, respectively (4). Sahu et al. reported that women with negative cytology and PCB had a 3.45% risk of severe than CIN2 histopathology (11).

In the last ASCCP Risk-Based Management Consensus Guidelines stated that when patients have an estimated immediate risk of a diagnosis of CIN 3+ of 4.0% or greater based on history and current results, referral to colposcopy is recommended (14). The immediate risk of HSIL as 4.3 %, which our study reported would lead to colposcopy.

None of the patients who had PCB with negative HPV DNA testing was diagnosed with HSIL. This consistent with a previous single study that reported no cancer or HSIL in 83 women with PCB and negative HPV testing (15).

The major limitation of the current study is the inherent drawbacks from its retrospective design. Also, the number of HPV negative patients was small because HPV testing had not been considered beforehand for all cases. Despite these limitations, our study does add supportive evidence to the management of PCB.

CONCLUSION

Our data show that a normal pap smear in women with postcoital bleeding does not rule out the possibility of HSIL. Consequently, HPV DNA testing is a useful triage test to determine if colposcopy referral is required in the context of postcoital bleeding with negative cytology. A negative HPV DNA testing record is able to be regarded as reassuring in a woman with PCB. In situations where the HPV test cannot be performed, women with PCB should be evaluated with

colposcopy whether or not they have negative cervical cytology.

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Ethical issues: All authors declare originality of research.

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