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SHORT COMMUNICATION

Colposcopic outcomes for symptomatic patients with a negative oncogenic human papillomavirus test

Georgina Mitchell[1], Jason Phung[1], Elizabeth Holliday[2,3] and Tania Day[1,2]

[1]Maternity and Gynaecology, John Hunter Hospital, New Lambton Heights, New South Wales, Australia

[2]Faculty of Health and Medicine, University of Newcastle, Callaghan, New South Wales, Australia

[3]Hunter Medical Research Institute, New Lambton Heights, New South Wales, Australia

Correspondence: Dr Tania Day, Maternity and Gynaecology, John Hunter Hospital, 2 Lookout Road, New Lambton Heights, NSW 2305, Australia.
Email: tania.day@health.nsw.gov.au

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This study assesses outcomes of colposcopy referrals for post-coital, intermenstrual, or other abnormal bleeding with negative oncogenic human papillomavirus and negative to low-grade cytology. Of 112 cases with median age of 34.5 years, cervical biopsy occurred in 19%, treatment of ectropion in 19%, endometrial sampling in 8%, polypectomy in 4%, and contraceptive change in 2%. No cervical or endometrial neoplasia was detected. Patients with bleeding symptoms and reassuring co-test may instead attend a general gynaecology clinic.

KEYWORDS

coitus, colposcopy, early detection of cancer, papillomavirus infections/diagnosis, uterine cervical neoplasms/diagnosis

INTRODUCTION

Since December 2017, the Australian national cervical screening program (NCSP) guideline recommends primary screening with five-yearly cervical screening test (CST), comprised of oncogenic human papillomavirus (HPV) testing, partial genotyping for HPV types 16 and 18, and reflex liquid-based cytology (LBC).[1] Screening occurs between ages 25 and 74 years in asymptomatic people with a cervix. There is a separate algorithm for management of bleeding symptoms concerning for cervical cancer, defined as persistent post-coital bleeding (PCB), unexplained recurrent intermenstrual bleeding (IMB), and post-menopausal bleeding (PMB). The guideline advises primary care providers investigate symptoms with combined HPV test and LBC, termed the co-test. Additional tests are guided by clinical presentation, such as chlamydia and gonorrhoea testing for PCB or pelvic ultrasound scan (USS) for IMB and PMB. Regardless of results, the guideline recommends referral to a gynaecologist and directs specialists to perform colposcopy during evaluation of PCB.[1]

PCB and IMB are common symptoms with high rates of spontaneous resolution.[2,3] Symptomatic patients comprise up to 20% of referrals to colposcopy.[4,5]

The scant evidence basis for relevant NCSP recommendations includes one systematic review, two prospective and seven retrospective cohort studies, all performed in the era of primary cytology screening.[1] These documented that patients with PCB and nil or negative cytology had detection rates of 2.3–9% for high-grade squamous intraepithelial lesion (HSIL) and 0–3.6% for cancer, representing a three to 15-fold risk of neoplasia compared to asymptomatic patients.[1,2,4–8] These studies have limited generalisability to the current context of co-testing and near-universal vaccination.

The NCSP uses a risk-based strategy to inform algorithms guiding decision for colposcopy vs increased surveillance or routine screening. The colposcopy threshold is set at the age-stratified

20-year cancer risk considered acceptable in pre-2018 NCSP: <1% in patients under 25 with gradual increase to <2.7% in ages ≥65.[1] This framework provides similar management for similar risk, aiming to minimise harms of over-investigation. The USA uses a 4% probability of cervical intraepithelial neoplasia three or worse.[9] A similar risk-based approach might be applied to symptomatic patients once sufficient robust data are available. A Melbourne-based group recently initiated this effort, documenting outcomes of 215 patients with PCB evaluated by co-test, of whom 185 had negative HPV with negative to low-grade squamous intraepithelial lesion (≤LSIL) cytology.[5]

The aim of this study is to describe colposcopic outcomes in patients referred with abnormal bleeding, a negative HPV test, and ≤LSIL cytology.

MATERIALS AND METHODS

The local colposcopy database was interrogated for referrals describing symptoms of PCB, IMB, or other abnormal bleeding with negative oncogenic HPV test and ≤LSIL cytology between October 2018 and September 2019. Exclusion criteria were incomplete records and failure to attend. Data collected included age, identification as Aboriginal or Torres Strait Islander, tobacco use, bleeding pattern, pre-referral investigations, colposcopic impression, biopsy results, colposcopist-initiated procedures, and treatment or follow-up plan. This project gained exemption from review by the Hunter New England Research Ethics and Governance committee (AU201912-13).

The bleeding pattern was categorised as PCB or non-PCB to include IMB, PMB, and unspecified abnormal bleeding. The cohort was also stratified by age under or over 25 years, reflecting the point at which routine screening commences. Descriptive statistics comprised mean with standard deviation (SD), median with interquartile range (IQR), and frequency with percent. Group comparisons used *t*-tests, Wilcoxon rank sum test, and Fisher's exact test.

RESULTS

Median age was 34.5 years with a range of 18–72; 22% were under age 25. The sample represented 7% of colposcopy referrals, filling ten appointments per month. There were 137 referrals with an 18% failure to attend despite two or more reminders, hence 112 patients were included.

Compared to other bleeding patterns, patients with PCB were less likely to smoke tobacco (15/94 (16%) vs 7/18 (39%), $P = 0.05$) (Table 1). There was no difference in HPV vaccination when stratified by bleeding pattern, but 28% of non-PCB and 12% of PCB patients had unknown status due to non-documentation or patient unawareness. Pre-referral investigations demonstrated one case of chlamydia in the PCB group, treated prior to referral.

TABLE 1 Pre-referral characteristics of symptomatic patients with a negative oncogenic HPV test referred to colposcopy, stratified by bleeding pattern

	Postcoital bleeding *N* = 94	Other bleeding pattern *N* = 18
Age, years; median (LIQR, UIQR)	34 (26, 45)	41 (29.5, 48)
<25 years old	22 (23)	3 (17)
25–50 years old	61 (65)	12 (67)
>50 years old	11 (12)	3 (17)
Aboriginal and Torres Strait Islander, *n* (%)	7 (7)	1 (5.5)
Tobacco use, *n* (%)*	15 (16)	7 (39)
Cervical surgery, *n* (%)	14 (15)	6 (33)
Received HPV vaccination, *n* (%)	36 (38)	7 (39)
Cytology, *n* (%)		
Negative	74 (79)	12 (67)
pLSIL/LSIL	20 (21)	6 (33)
Chlamydia and gonorrhoea screen completed, *n* (%)	58 (62)	8 (44)
Pelvic ultrasound completed, *n* (%)	52 (55)	13 (72)

HPV, human papillomavirus; LIQR, lower interquartile range; LSIL, low-grade squamous intraepithelial lesion; pLSIL, possible low-grade squamous intraepithelial lesion; UIQR, upper interquartile range.
*$P \leq 0.05$.

Pre-referral USS showed structural abnormality in 11.5% (6/52) with PCB and 30% (4/13) with other patterns; findings included polyps, fibroids, cervical varices, and adenomyosis.

All patients underwent a colposcopy. Colposcopic-directed biopsy occurred in 19% and resulted as normal or LSIL (Table 2). Biopsy occurred in all 16 patients with impression of LSIL or HSIL. Colposcopic impression was normal in 42%, ectropion in 36%, polyp in 4%, LSIL in 9%, and HSIL in 5%. Among the 94 patients with PCB, 32% (30/94) had minor procedures to investigate or treat presumed aetiologies of symptoms. Gynaecologic follow-up was arranged in 13% (12/94) of patients with PCB. The follow-up visits resulted in change of contraceptive for 8% (1/12), infertility investigation in 17% (2/12), surgical management of abnormal bleeding in 33% (4/12), no intervention in 17% (2/12), and non-attendance in 25% (3/12). One-third (6/18) with non-PCB patterns had minor procedures, of whom 33% had gynaecologic follow-up. All cases of endometrial sampling and polypectomy yielded benign histopathology. Discharge to the general practitioner (GP) after a single visit occurred in 84%.

Among patients under age 25, 68% had pre-referral testing for chlamydia and gonorrhoea and 56% had USS; no structural abnormalities were identified. Specialists obtained negative testing for chlamydia and gonorrhoea in four patients and none were booked

TABLE 2 Outcomes of patients referred to colposcopy for symptoms and a negative oncogenic HPV test

	Postcoital bleeding *N* = 94	Other bleeding pattern *N* = 18
Colposcopic impression, *n* (%)		
Normal†	82 (87)	14 (78)
LSIL	6 (6)	4 (22)
HSIL	6 (6)	0
Biopsy result, *n* (%)		
Normal†	14 (78)	2 (67)
LSIL	4 (22)	1 (33)
Endometrial sampling, *n* (%)		
Office biopsy	4 (4)	1 (6)
Hysteroscopy	3 (3)	1 (6)
Management, *n* (%)		
Ectropion treatment	17 (18)	4 (22)
Polypectomy	4 (4.3)	0
IUD insertion or removal	2 (2.1)	0
Follow-up, *n* (%)		
Discharged to primary care	82 (87)	12 (67)
Specialist	12 (13)	6 (33)

HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; IUD, intrauterine device; LSIL, low-grade squamous intraepithelial lesion.
†A normal impression and normal biopsy result encompassed normal, ectropion, other benign.

for gynaecologic follow-up. No age-related differences were detected in other demographic factors or colposcopic outcomes.

DISCUSSION

There was a 0% detection rate of HSIL, cervical cancer, and endometrial neoplasia at colposcopy of 112 symptomatic patients with negative HPV and ≤LSIL cytology. Tan and colleagues identified one case of HSIL among 185 patients with the same co-test results as this study.[5] Combining cases from both, the detection rate for ≥HSIL was 0.03% (1/297), well below the risk-based threshold for colposcopy in Australia and the USA.[1,9]

Aetiologies of bleeding were identified as ectropion in 36% and polyps in 3.6%, similar to previously published rates of ectropion in 2–34%, polyps in 4–15%, cervicitis in 33%, and no cause identified in >50%.[6–8,10–12] The NCSP and Royal Australian and New Zealand College of Obstetricians and Gynaecologists recommend GPs investigate symptomatic patients for reversible causes.[13] Despite this, 41% (46/112) overall and 32% under age 25 did not have pre-referral chlamydia and gonorrhoea testing. Likewise, there was no pre-referral USS in 28% with IMB and other bleeding patterns. This highlights opportunities for improvement in referral submission systems, triaging by gynaecology departments, and delivery of educational content to GPs.

The nil detection rate for serious pathology elevates consideration of potential harms of colposcopy: psychological distress, travel time and cost to attend specialist review, risk of overtreatment of LSIL or ectropion, and misallocation of resources away from patients with higher risk of HPV-related neoplasia. The traditional teaching that PCB is 'a cardinal symptom of cervical cancer' provokes anxiety in patients and GPs, potentially augmenting the 21% rate of significant distress encountered at normal colposcopy.[13,14] Colposcopy workload attributable to symptomatic patients with negative HPV and ≤LSIL cytology was 7% locally and 5% in Melbourne, representing over 100 visits or 50 colposcopy-hours per site per year. The 2020 NCSP monitoring report found 21.8% of people with HPV16/18 and 32.6% with two consecutive non-16/18 HPV positive tests did not have colposcopy within six months of CST.[15] The report did not explore the cause, but it may indicate an overburdened system.[16]

An alternative approach to current guidance would be GP-led investigation and treatment of reversible causes followed by reassessment for symptom resolution. This strategy would be appropriate only for patients with a normal appearing cervix, negative oncogenic HPV, and ≤LSIL cytology. Gynaecologic referral would occur for persistent symptoms or structural abnormalities. Colposcopy would be reserved for cervical appearance worrisome for neoplasia and persistent possible LSIL or LSIL cytology. Uncoupling the long-held association between PCB and cancer would require NCSP revision accompanied by educational outreach to GPs, women's health nurses, and non-colposcopist specialists. Patients would benefit if culture shift resulted in enhanced GP-led management of common bleeding complaints, rather than referral to lengthy outpatient waitlists for invasive diagnostic procedures.

The study's main strength is access to detailed clinical records held in interlinked multi-site electronic databases. Weakness are those inherent to retrospective design: practice variation, missing variables, and possibility that referrals did not contain copies of pertinent investigations. Sample size was inadequate to identify differences across age groups and bleeding patterns. Results are most generalisable to urban public hospitals with distinct clinicians, facilities, nursing support, and appointment templates for colposcopy vs general gynaecology. In that setting, allocation of a service inconsistent with the chief complaint may result in care delays, provider discontinuity, and additional encounters with the health service. However, permanent change to national practice guidelines requires larger datasets from multiple jurisdictions.

In conclusion, the nil detection rate for HSIL or cancer in 112 referrals to colposcopy for symptoms and negative HPV with ≤LSIL cytology suggests these cases may instead be reviewed in general gynaecology clinics if symptoms persist after GP-led evaluation and management. As data accumulates about symptomatic

patients in settings of near-universal vaccination and oncogenic HPV testing, the NCSP and other national guidelines may elect to remove recommendations for colposcopy in groups not meeting a set risk threshold for neoplasia.

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