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Post-coital bleeding: What is the incidence of significant gynaecological pathology in women referred for colposcopy?

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ABSTRACT

Objective: To evaluate the incidence of underlying serious gynaecological pathology in women referred to colposcopy with post-coital bleeding.
Main outcome measures.: Incidence of precancer and cancer.
Methods: A retrospective cohort study of women referred to colposcopy at a London hospital from January 2008-March 2015. Inclusion criteria are women with post-coital bleeding and the following cervical cytology history: negative; inadequate; never had. Multinomial logistic regression was used to assess for significant risk factors for cervical dysplasia and cancer.
Results: Overall, 635 women with either negative cytology (n = 436/68.7%), no previous cytology (n = 175/27.6%), or inadequate cytology (n = 24/3.8%) were referred to colposcopy for post-coital bleeding. The median age is 35 years (S.D. = 9.7 years). In 256 (40.3%) women, no cause was detected, and 322 (50.7%) women had a benign cause. Overall, 42 (6.6%) women had low-grade dysplasia, and eleven women had high-grade dysplasia (1.7%). Four women (0.6%) had cervical cancer; clinically evident cancer on speculum examination (n = 3); micro-invasive cancer (n = 1). Current smokers were significantly more likely to have HPV atypia (p = 0.015) or cervical intraepithelial neoplasm grade 1 (CIN1) p = 0.003. Advancing age was a significant risk factor for cervical cancer (p = 0.037).
Conclusion: All women with post-coital bleeding need an urgent speculum examination to rule out frank cervical cancer. Although most women had a benign cause for post-coital bleeding, around 2% had a colposcopy-aided diagnosis of either cervical precancer or cancer; therefore, referral of symptomatic women deserves consideration. HPV testing may reduce referrals to colposcopy for post-coital bleeding due to non-significant pathology in the future.

Introduction

Post-coital bleeding is a concerning symptom for women and remains an important sign of cervical cancer. Overall, 0.7–39% of women with cervical cancer have experienced post-coital bleeding [1]. Evidence from a case series suggests that women presenting with post-coital bleeding have a higher incidence of cervical cancer than the general population [2]. However, post-coital bleeding is a relatively common occurrence in women, with a prevalence ranging from 0.7 to 9% [1,3–5] and is more common in younger, premenopausal women [6]. Benign conditions of the lower genital tract, such as cervical ectropion or cervicitis, are the most common causes of post-coital bleeding [3,7].

There is wide variation in management of women with post-coital bleeding in the U.K., with women reviewed in either gynaecology or colposcopy departments and a survey of the practice of gynaecologists found that 80% had no local guidelines for the management of women with post-coital bleeding [8]. The NHS cervical screening programme guidance [9] advises that women with unexplained cervical symptoms, such as post-coital bleeding, should be referred for further evaluation of the cervix by an experienced gynaecologist; who may refer these women for a further colposcopy examination. However, the management of symptomatic women is outside of the NHS cervical screening programme guidance [9]. The department of health (U.K.) has

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published guidance on the management of women aged 20–24 years presenting with post-coital bleeding, as these women do not fall within the age range for routine cervical cytology screening [10]. The guideline advises women with post-coital bleeding need a speculum examination in primary care to rule out cervical cancer, and if the cervix is suspicious an urgent 2-week wait suspected cancer referral needed. If a benign cause is identified, such as a polyp, then routine referral to gynaecology clinic is required, and if nothing found, then swabs should be taken for cervical infection [10].

It is unknown how useful the symptom of post-coital bleeding is to predict cervical cancer. A systemic review has estimated the probability of a woman aged 20–24 years presenting with post-coital bleeding in the community to have a 1 in 44,000 chance of having cervical cancer, increasing to 1 in 2400 for women aged 45–54 years; based on the frequency of post-coital bleeding and the incidence of cervical cancer per age band [1]. Therefore, if a speculum examination does not reveal a suspicious cervix in primary care, it is uncertain if these women need a referral to gynaecology or colposcopy services. Unnecessary visits to colposcopy services may result in patient anxiety [11] and avoidable interventions [12].

Our study presents one of the most extensive retrospective cohort studies of women referred to colposcopy with post-coital bleeding whose most recent cervical cytology is either negative, inadequate or never had a cervical smear test. It addresses if women with post-coital bleeding have underlying genital tract precancer or cancer and whether referral to colposcopy is appropriate for these women.

Methods

A retrospective cohort study of women referred to colposcopy for post-coital bleeding, at Newham University Hospital, London was conducted between January 2008 and March 2015. This review of clinical service provision/audit was registered at the hospital's audit department, and formal ethical approval was not needed for this observational study, as defined by the National Research Ethics Service. Newham University Hospital is situated the London Borough of Newham, in east London and referrals to the colposcopy department come from the borough of Newham. The hospital serves a population of approximately 350,000 people.[13] Newham is a deprived area of London, with a poverty rate of 37% and the highest percentage (35.6%) of low-paid workers in London [14]. It is also culturally diverse, with a Caucasian population of 29%, compared to 85.4% for England overall. The main ethnic groups in the borough of Newham include white British 16.7%, Indian 13.8%, Black African 12.3%, Bangladeshi 12.1% and Pakistani 9.8%. English is not the primary language for 24.3% of households in Newham [15].

Hospital 'INFOFLEX' colposcopy database identified all women (n = 677) referred with post-coital bleeding during the study period. Inclusion criteria: the woman's most recent cervical cytology was negative, or the woman was referred with inadequate cervical cytology, or the woman has never had a cervical smear test. Women with concurrent referral cervical cytology of borderline dyskaryosis, mild dyskaryosis, moderate dyskaryosis and severe dyskaryosis were excluded (n = 41). One additional woman was excluded for an incomplete recording of clinical findings at colposcopy. Data included demographics, most recent cervical cytology result, colposcopy opinion, investigations and histology results.

A British Society of Colposcopy and Cervical Pathology accredited colposcopist performed the colposcopy, using the recommended procedure of applying 3% acetic acid first, then Lugol's iodine to determine the presence of cervical or vaginal dysplasia. Cervical cytology was performed in women without an up to date negative smear test. A cervical punch biopsy was taken from areas suggestive of cervical dysplasia on colposcopy examination. Further investigations such as endocervical swabs for infections and endometrial Pipelle biopsies were performed if clinically indicated.

Statistical methods

Data were analysed using IBM SPSS Statistics Version 24.0.0.0 for Macintosh "macOS" (IBM Corp., Armonk, N.Y., USA). Fisher's exact and chi-square test were used for comparisons between categorical variables to assess the potential risk factors of age, results of a previous smear test, contraception and parity on the final outcome.

Multinomial logistic regression analysis has been performed to assess smoking and age as risk factors in the outcome and findings are being presented in the article. Smoking was divided into categories of "non-smokers", "ex-smokers" and "current smokers" while age was considered continuous numerical data in a ratio scale.

The results are presented as absolute numbers and percentages for qualitative variables; means and 95% confidence interval included for quantitative variables. $P < 0.05$ was considered statistically significant in all tests used. (Alpha level 0.05).

Results

Newham colposcopy department saw 5343 new patients between January 2008 and March 2015. Referral for abnormal cervical cytology screening results = 3550 (66.4%) women and 44 (1.2%) had cervical cancer. Referral for other indications (such as abnormal symptoms or appearance of the cervix) = 1793 (33.6%) women, and 13 (0.7%) had cervical cancer.

Overall, 635 women with post-coital bleeding are the focus of the study. The median age of women was 35 years (S.D = 9.7 years). There are 68 women outside of the recommended age of routine cervical screening, with 65 women being below the age of 25 years and three women over the age of 65 years. Table 1 shows the cohort's demographics, including the referral source, menopausal status, parity, contraception, and smoking history.

The population was culturally diverse, with 21.2% of women speaking English as a second language and 27 languages other than English recorded as their preferred language within this cohort of women. In total, 68.7% (n = 436) women's most recent cervical cytology was negative; 27.6% (n = 175) women had never had a smear test, and 3.8% (n = 24) had an inadequate smear test at referral.

Table 2 shows the investigations done in colposcopy and the results. Most women had no abnormality found on the cervix (n = 256/40.3%) or had benign findings (n = 322/50.7%); of which cervical ectropion was the most prevalent (n = 108/17.0%) (Fig. 1). Other common benign findings included HPV atypia (n = 97/15.3%), confirmed on cervical biopsies (n = 48) and colposcopy opinion (n = 49). Clinical evidence of cervicitis (n = 74/11.7%) was confirmed on histological biopsy in 48 women, and eight women (n = 8/173) had positive *endo*-cervical swabs for chlamydia and or gonorrhoea. In the women with positive endocervical swabs, seven women were premenopausal (age range 23–37 years), and one woman was postmenopausal (age 55 years). Three women had a colposcopic opinion of cervicitis, and five women had no abnormality seen at colposcopy.

In total, eleven women (1.7%) were diagnosed with high-grade cervical dysplasia (CIN2 n = 7/CIN3 n = 4) and had been referred by their general practitioner (Fig. 1/Table 3). Four women (0.6%) had cervical cancer; three (0.47%) of these women had a clinically evident cervical tumour on speculum examination (Fig. 1/Table 3), and one (0.16%) woman had a micro-invasive adenocarcinoma. All women with high-grade dysplasia and cancer had colposcopy directed cervical punch biopsies that confirmed the diagnosis. Table 3 shows the cytology history for all the precancer and cancer diagnoses. Eight women with precancer or cancer had a negative smear test within the last three years, and three of these women had contemporaneous cytology done at colposcopy, which all came back abnormal. One woman had a negative smear test 36 months previously and was due screening cytology, which showed moderate dyskaryosis.

Chi-square test results

Table 1
Cohort demographics and characteristics.

Demographic	Number (%)
Age range:	635
Range 17-71 years, median 35 years	
Menopausal status:	
Pre-menopausal	592 (93.2)
Post-menopausal	43 (6.8)
Referral source:	
GP	467 (73.5)
GOPD	165 (26.0)
Other	3 (0.5)
Referral category:	
Urgent	75 (11.8)
Routine	546 (86.0)
Abnormal screening result	14 (2.2)
Most recent cytology:	
No smear	175 (27.6)
Negative	436 (68.7)
Inadequate	24 (3.8)
Parity:	
Nulliparous	195 (30.7)
P1	122 (19.2)
P2	157 (24.7)
P3	78 (12.3)
P4 or more	64 (10.1)
Unknown	19 (3.0)
Contraception:	
Combined oral contraceptive pill	88 (13.9)
Condoms	97 (15.3)
Depo-Provera	13 (2.0)
Sterilisation	34 (5.4)
Copper coil	53 (8.3)
Vasectomy	14 (2.2)
Mirena	38 (6.0)
None	234 (36.9)
Other	24 (3.8)
Progesterone only pill	16 (2.5)
Unknown	24 (3.8)
Smoking history:	
Non-smoker	467 (73.5)
< 20 cigarettes a day	101 (15.9)
> 20 cigarettes a day	11 (1.7)
Ex-smoker	40 (6.3)
Unknown	16 (2.5)

Table 2
Investigations done in colposcopy clinic and results.

Investigations and results	**Number (%)**
Cytology taken at colposcopy	
Yes	213 (33.5)
No	422 (66.5)
Results of cytology (n = 213)	
Negative	159
Inadequate	34
Borderline	13
Mild dyskaryosis	3
Moderate dyskaryosis	3
Severe dyskaryosis	1
Cervical biopsy taken at colposcopy	
Yes – single	19 (3.0)
Yes – multiple	195 (30.7)
No	419 (66.0)
LLETZ	4 (0.6)
Results of cervical biopsy (n = 214)	
Cervical cancer	4
CIN1	41
CIN2	6
CIN3	4
HPV	53
Inadequate	4
No CIN/no HPV	57
Cervicitis	48
Unknown	2
Cervical polypectomy (n = 20)	
Benign	16
Adenofibroma	1
Unknown	3
Endometrial pipelle (n = 34)	
Normal endometrium	29
Disordered proliferation	2
Chronic inflammation	1
Benign Polyp	1
Inadequate	1
Endocervical swabs (n = 173)	
Negative	165
Chlamydia	6
Gonorrhoea	1
Chlamydia and gonorrhoea	1

A history of negative or no previous or inadequate cervical cytology had no significant correlation with the clinical outcome of high-grade dysplasia or cancer (p = 0.245). Parity (p = 0.469) and the type of contraception used (p = 0.872) did not show any significant correlation with cervical dysplasia or cancer.

Logistics regression results (Table 4)

Advancing age increases the probability of cancer by 1.097 times for every year of age (CI 95% 1.006–1.197). Being a current smoker increases the probability of HPV atypia 1.952 times (CI 95% 1.141–3.338) and increases the probability of CIN1 2.947 times (CI 95% 1.455–5.969) compared to non-smokers. No significance was found between current smoking and CIN2, CIN3 or cancer. Ex-smokers had no significant increased risk of HPV atypia, cervical dysplasia or cancer (Table 4).

Discussion

Post-coital bleeding is a troubling symptom for women and usually prompts consultation with a general practitioner. Our retrospective study shows that most women (97.7%) referred with post-coital bleeding will not have an underlying precancer or cancer of the genital tract if their smear history is never had, negative or inadequate. However, post-coital bleeding remains a symptom that requires investigation and immediate speculum examination to rule out frank cervical cancer.

The incidence of cancer (0.6%) and high-grade dysplasia (1.7%) in our cohort is lower than previously reported by Rosenthal et al. (2001) of 4% and 12% respectively [2]. This may reflect the general decline in cervical cancer diagnoses over the last two decades, as Rosenthal data is from 1988 to 1994. The incidence of cervical cancer has fallen by 24% since 1993 and 2015[16] because of the comprehensive national cervical screening programme to identify and treat the precancer of the cervix. Our data is in keeping with recent evidence of 6.8% of 248 women with post-coital bleeding had cervical dysplasia and no cancers found [17]. Another article found one case of cervical cancer in 137 women referred for post-coital bleeding (0.7%), [18] again comparable to our study. In our study three of the four women with cervical cancer had a clinically evident cervical tumour on speculum examination, and examination in the community could have directed these patients more appropriately to see a gynaecological oncologist within two weeks.

Logistic regression calculation shows that current cigarette smokers

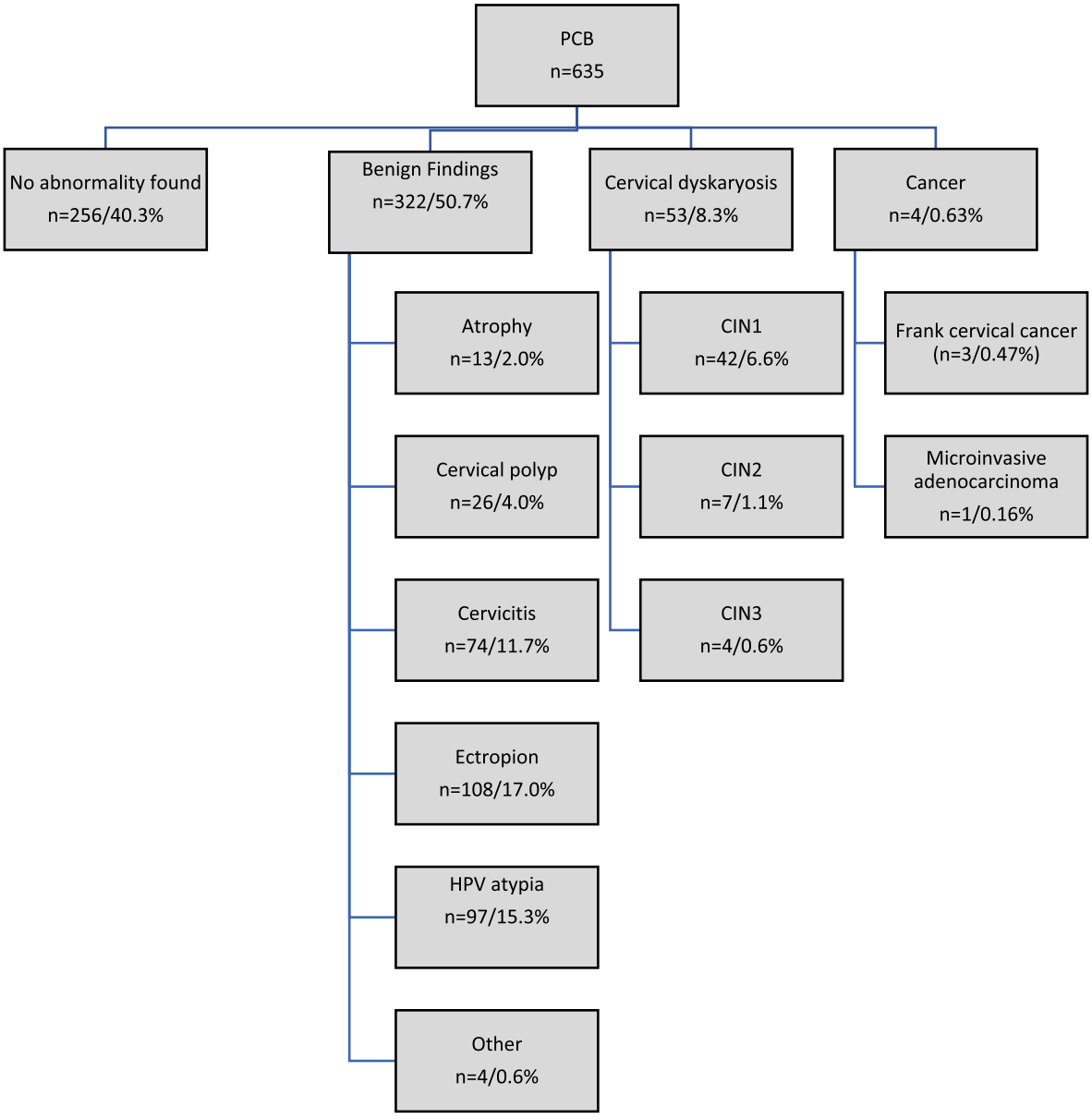

Fig. 1. Study flow chart of the 365 women referred with postcoital bleeding with most recent smear test of negative/inadequate/no previous smear. Final clinical outcome based on colposcopy findings and investigation results.

Table 3
Age and cytology history of all women diagnosed with high-grade dysplasia (n = 11) or cervical cancer (n = 4) at colposcopy.

Patient (age in years)	Last cytology result	Time since last cytology (months)	Colposcopy diagnosis	Cytology done at colposcopy
1 (35)	Never had	NA	CIN2	Moderate dyskaryosis
2 (25)	Never had	NA	CIN2	Not done as menstruating
3 (40)	Negative	10	CIN2	Borderline dyskaryosis
4 (44)	Negative	36	CIN2	Moderate dyskaryosis
5 (26)	Negative	18	CIN2	Not done
6 (34)	Negative	4	CIN2	Not done
7 (31)	Inadequate	2	CIN2	Not done
8 (21)	Never had	NA	CIN3	Not done – below screening age
9 (30)	Negative	9	CIN3	Severe dyskaryosis
10 (28)	Negative	33	CIN3	Moderate dyskaryosis
11 (37)	Negative	1	CIN3	Not done
12 (35)	Negative	26	Microinvasive cervical adenocarcinoma	Not done
13 (71)	Never had	NA	Cervical cancer	Not done – clinically evident cervical tumour
14 (38)	Negative	< 1	Cervical cancer	Not done – clinically evident cervical tumour
15 (42)	Inadequate	< 1	Cervical cancer	Not done – clinically evident cervical tumour

Table 4
Multinomial logistic regression analysis for age and smoking history for HPV atypia, cervical dysplasia and cervical cancer.

		B	Std. Error	Wald	df	Sig.	Exp(B)	95% Confidence Interval for Exp(B)	
								Lower Bound	Upper Bound
HPV atypia	Age at referral	−0.017	0.012	2.044	1	0.153	0.983	0.959	1.007
	Current smoker	**0.669**	**0.274**	**5.963**	**1**	**0.015**	**1.952**	**1.141**	**3.338**
CIN1	Age at referral	−0.021	0.018	1.412	1	0.235	0.979	0.946	1.014
	Current smoker	**1.081**	**0.360**	**9.008**	**1**	**0.003**	**2.947**	**1.455**	**5.969**
CIN2	Age at referral	−0.038	0.044	0.769	1	0.380	0.963	0.884	1.048
	Current smoker	0.029	1.105	0.001	1	0.979	1.030	0.118	8.990
CIN3	Age at referral	−0.091	0.068	1.775	1	0.183	0.913	0.799	1.044
	Current smoker	1.565	1.017	2.370	1	0.124	4.784	0.652	35.084
Cancer	Age at referral	**0.093**	**0.045**	**4.356**	**1**	**0.037**	**1.097**	**1.006**	**1.197**
	Current smoker	0.663	1.6	0.318	1	0.573	1.941	0.194	19.454

Advancing age increases the probability of cancer by 1.097 times for every year of age (p = 0.037). Being a current smoker increases the probability of HPV atypia 1.952 times (p = 0.015) and increases the probability of CIN1 2.947 times compared to non-smokers (p = 0.003). No significance was found between current smoking and CIN2, CIN3 or cancer. The reference category is: No abnormality/Other benign.

are at significantly higher risk of having HPV atypia and CIN1 than non-smokers or ex-smokers. The link between smoking and CIN2 and CIN3 and cervical cancer is established in several studies, [19,20] and it is likely due to the small numbers of high-grade dysplasia and carcinoma in our cohort that no significance was found. Current cigarette smokers with post-coital bleeding may warrant colposcopy as per our study results, whereas it may be argued that non-smokers with negative cytology and clinical examination do not require colposcopy.

Increasing age was also a significant risk factor for finding cervical cancer in our cohort with post-coital bleeding, with no cancers found under the age of 35 years. A recent study has shown that increasing age is a risk factor for post-LLETZ recurrence of high-grade dysplasia, and that clearance of HPV decreased with age [21], which may explain why increasing age is a risk factor for cervical cancer. Age may also be a suitable way to triage the necessity of referral for colposcopy, with the likelihood of finding significant disease in women in their twenties to be very unlikely, if the clinical examination and cytology are normal. We found no significant associations between cervical dysplasia or cancer and parity or type of contraception used in keeping with a recent study of women presenting with post-coital bleeding in Tehran [22].

There was a low incidence of confirmed cervical infection on swabs, despite a higher rate of clinically evident cervicitis on colposcopy and biopsy result. Nongonococcal nonchlamydial cervicitis has an unknown prevalence and aetiology and can be treated empirically with antibiotics in symptomatic women [23]. Although there is a low incidence of gonorrhoea and chlamydia in our cohort, endocervical swabs should be offered to allow for appropriate treatment and contact tracing if results are positive.

Referral to colposcopy may cause unnecessary anxiety in women [11,24]. Attendance to colposcopy clinics may result in unnecessary interventions, with 57 (26%) cervical biopsies in our study having no histological abnormality. A previous study reported doing 66 biopsies in women with post-coital bleeding and negative cytology to identify three women with high-grade dysplasia; therefore, potentially needless biopsies are frequent in these women [12].

The group of women that need further consideration are the 11 (1.7%) women diagnosed with high-grade dysplasia and the one (0.16%) woman found to have a micro-invasive adenocarcinoma. The background incidence of high-grade cervical dysplasia in the U.K. screened population is approximately 2% [25]; therefore, it is unsurprising to find a similar prevalence within our cohort. On reviewing these 12 (1.9%) women's recent cytology, seven women had negative cytology within the last three years, including the woman with a micro-invasive adenocarcinoma; which may reflect the relative lack of sensitivity of cytology [26]. Three of these women had contemporaneous cytology at colposcopy, which was not due in terms of screening interval, and all came back abnormal. It is likely some of these 12 women would have had abnormal screening results and referral to colposcopy at their next routine cytology recall, had they not presented with post-coital bleeding.

A recent Cochrane review gave a pooled sensitivity of 72.9% of cervical smear tests for the detection of CIN2 + lesions in asymptomatic women [26]. Cervical cytology to detect glandular dysplasia and prevent adenocarcinoma of the cervix is inferior compared to squamous cell carcinoma of the cervix [27,28]. A Swedish population-based study evaluating cervical screening found a risk reduction of 89% for squamous cell carcinoma in women with negative cytology compared to only 60% for adenocarcinoma [28]. In this study, 16% of all women diagnosed with cervical cancer had negative cervical screening results, and this increased to 24% of women diagnosed with adenocarcinoma of the cervix [28]. Therefore, the incidence of high-grade dysplasia found within this cohort may be independent and unrelated to the symptom of post-coital bleeding, as cervical precancer is usually asymptomatic, and mostly detection relies on accurate cervical screening.

Most women in this cohort had a healthy cervix, questioning the cost-effectiveness of referring all women with post-coital bleeding to colposcopy. HPV testing has an improved sensitivity of 89.9% compared to cytology to detect CIN2 + lesions [26] and would be a useful test in the community to determine if colposcopy referral is required in the context of post-coital bleeding. HPV testing has been evaluated as a primary screening tool by several studies, and randomised trials, [29–33] and HPV testing increases the detection of CIN3 or worse by approximately 40% compared to cytology [25]. A negative HPV test has a predictive value approaching 100% [26] and is associated with a very low risk of cervical cancer for up to five years [32,34]. HPV testing also improves the diagnosis of glandular precancer and adenocarcinoma of the cervix [35]. For these reasons, HPV testing is replacing cytology in the U.K. as a primary screening tool for cervical cancer from 2019. HPV testing is cost-effective as a screening strategy compared to conventional cytology [36] despite having a higher false positive rate than cytology resulting in more women initially being referred for colposcopy. Colposcopy would be an unnecessary investigation in most women with post-coital bleeding, a routine clinical examination and a negative HPV test. Some clinical dilemma remains whether to refer all women to colposcopy with post-coital bleeding and an unremarkable clinical examination if cytology is the only test available. The screening performance of cytology improves with repeat testing, [28] therefore, contemporaneous cytology may be helpful for women presenting with post-coital bleeding, even if the woman has had a negative smear test within the last three years. Individual risk factors for cervical cancer such as smoking, poor compliance with cervical screening and previous abnormal cytology are also relevant in deciding whether to refer a woman with post-coital bleeding to colposcopy. Women that miss screening or have previous abnormal cytology, even if followed by a negative result remain at a higher risk of cervical cancer [28].

There are some limitations to our study. We did not collect data on

the duration or frequency of post-coital bleeding, which may be important. However, previous studies did not find a link between the length of post-coital bleeding and pathology [7]. Only cytology results were available as per the previous cervical screening guidelines, and there was no high-risk HPV testing performed in this cohort of women. Future U.K. studies will be able to provide this data with the changing cervical screening guidelines to primary HPV screening, and cytology if the high-risk HPV test is positive. Cost-analysis comparison of the number of colposcopy visits for benign pathology and the potential to miss an easy to treat precancer or early-stage cervical cancer if all women with post-coital bleeding do not have colposcopy was beyond the scope of this paper but would be of great interest.

In conclusion, all women with post-coital bleeding need an urgent speculum examination to rule out frank cervical cancer. Although most women had a benign cause for post-coital bleeding, around 2% had a colposcopy-aided diagnosis of either cervical precancer or cancer. Cytology alone may miss this small number of women; therefore, referral of symptomatic women deserves consideration; particularly if additional risk factors for cervical cancer are present. Primary HPV testing may be a useful tool to reduce the number of women with post-coital bleeding referred to colposcopy for non-significant pathology in the future.

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