

## **Question 8:**

For women with postcoital bleeding (PCB) or intermenstrual bleeding (IMB), what is the safety and effectiveness of direct referral to colposcopy compared with HPV testing and cytology?

Non-systematic searches were carried out of Medline, EMBASE and Cochrane Central Register of Controlled Trails from 2005 using (postcoital bleeding OR intermenstrual bleeding OR abnormal vaginal bleeding) AND (cervical cancer/neoplasia OR cervical intraepithelial neoplasia/CIN) AND HPV. A repeat search was performed omitting HPV. Studies from countries without a cervical cancer screening programme were excluded.

No studies were found comparing the safety and effectiveness of direct referral to colposcopy with HPV testing and cytology. Therefore existing guidelines on the management of PCB and IMB are summarised and the results of studies that describe the likelihood a woman with PCB has invasive cervical cancer (ICC) and how this may vary by cytology or HPV test result or age, and the prevalence of PCB and IMB are reported. The details of the included studies with the characteristics and all results are presented.

## **Management of women with postcoital bleeding and intermenstrual bleeding**

### **Results:**

1. Table 1: Existing guidelines on the management of postcoital and intermenstrual bleeding
2. Table 2: Prevalence of postcoital bleeding +/- intermenstrual bleeding
3. Table 3: Postcoital bleeding and risk of invasive cervical cancer
4. Table 4a: Postcoital bleeding, cytology and cervical cancer
5. Table 4b: Postcoital bleeding, HPV testing and cervical cancer
6. Table 4c: Postcoital bleeding, age and cervical cancer
7. Table 5: Characteristics and results of included studies

**Table 1: Existing guidelines on the management of postcoital and intermenstrual bleeding**

| <b>Guideline</b>   | <b>Author/Organisation<br/>Country</b>   | <b>Year</b>   | <b>Evidence base</b>   | <b>Recommendation</b>   |
|--|--|---------------|--|---|
| <b>Colposcopy and Programme Management Guidelines for the NHS Cervical Screening Programme Second edition 2010</b> | NHS Cancer Screening Programmes<br>United Kingdom                                  | 2010          | Unclear if this recommendation is based on evidence or consensus | Women presenting with symptoms of cervical cancer – such as postcoital bleeding (particularly in women over 40 years), intermenstrual bleeding and persistent vaginal discharge – should be referred for gynaecological examination and onward referral for colposcopy if cancer is suspected. Examination should be performed by a gynaecologist experienced in the management of cervical disease (such as a cancer lead gynaecologist). They should be seen urgently, within two weeks of referral.  |
| <b>Clinical Practice Guidance for the Assessment of Young Women aged 20-24 with Abnormal Vaginal Bleeding</b>      | Subgroup of the Advisory Committee for Cervical Screening<br>NHS<br>United Kingdom | 2010          | Unclear  | The cardinal symptom of cervical cancer in this age group is postcoital bleeding, but persistent intermenstrual bleeding, which is more common, also requires attention. The critical intervention in the diagnosis of cervical cancer is an immediate speculum examination...to enable a clear view of the cervix....If the cervix looks abnormal and suspicious, which will be the case in a very small proportion, the correct action is urgent referral to colposcopy under the 'two week wait' rule.   |
| <b>Investigation of intermenstrual and postcoital bleeding</b>   | RANZCOG<br>Australia   | Reviewed 2015 | Consensus based  | Genital tract malignancy is an uncommon cause of abnormal bleeding at any age, is rare in young women, but must be considered in all patients. Women at risk of sexually transmitted infection should have appropriate tests performed. Women with persistent intermenstrual bleeding (IMB) should have a cervical Pap smear, a pelvic ultrasound and referral to a gynaecologist for further assessment.<br>Women complaining of postcoital bleeding (PCB) should have tests to exclude cervical cancer and Chlamydia. It is commonly accepted that a single episode of PCB in a woman who has a normal smear and cervical appearance does not warrant immediate referral, but recurrence or persistence of this symptom mandates colposcopic examination. |

**Table 2: Prevalence of postcoital bleeding +/- intermenstrual bleeding**

| Study                          | Type of study      | Population  | Results   |
|--------------------------------|--------------------|---|---|
| Shapley 2006<br>United Kingdom | Systematic review  | 38 papers identified in which prevalence/incidence of PCB reported or able to be calculated | <p><b>Prevalence/incidence of PCB:</b></p> <ul style="list-style-type: none"> <li>• <u>Community care:</u> point prevalence: 0.7-9% (8 studies)</li> <li>• <u>Primary (1<sup>0</sup>) care:</u> <ul style="list-style-type: none"> <li>○ No studies of women consulting 1<sup>0</sup> care</li> <li>○ Proportion of women in the community who consult 1<sup>0</sup> care not known</li> </ul> </li> <li>• <u>Secondary (2<sup>0</sup>) care:</u> <ul style="list-style-type: none"> <li>○ Prevalence 5% (1 study)</li> <li>○ Proportion of women presenting to 1<sup>0</sup> care with PCB who are referred to 2<sup>0</sup> not reported</li> </ul> </li> </ul> |
| Shapley 2013<br>United Kingdom | Prospective cohort | 2104 naturally menstruating women aged 40-54 years registered with 7 general practices      | <p><b>Prevalence (as a proportion of naturally menstruating women):</b></p> <ul style="list-style-type: none"> <li>• IMB +/- PCB at baseline: 21% (95%CI: 20-23%)</li> <li>• PCB at baseline: 9.5% (95% CI: 8.3-11%)</li> <li>• Frequent PCB at baseline: 2.2% (95%CI: 1.7-3.0%)</li> <li>• Persistent PCB at 12m: 2.2% (95%CI: 1.6-3.2%)</li> <li>• IMB at baseline: 18% (95% CI: 16-20%)</li> <li>• Frequent IMB at baseline: 5.3% (95%CI: 4.4-6.3%)</li> <li>• Persistent IMB at 12m: 7.6% (95%CI: 6.2-9.2%)</li> </ul>  |

**Table 3: Postcoital bleeding and risk of invasive cervical cancer**

| Study                          | Type of Study        | Population   | Results  |
|--------------------------------|----------------------|--|--|
| Khattab 2005<br>United Kingdom | Retrospective cohort | 284 women with PCB seen in colposcopy /gynaecology clinics | <p>Group 1: 166 women with <b>PCB and no/normal referral smear:</b> ICC 6 (3.6%); ICC in women with normal smear history: 2 (1.2% of Group 1)</p> <p>Group 2: 118 women with <b>PCB and abnormal referral cytology:</b> ICC 6 (5%)</p> |
| Abu 2006<br>United Kingdom     | Retrospective cohort | 142 women referred to colposcopy clinic with PCB.          | No ICC   |
| Shapley 2006                   | Systematic review    | 38 papers  | A Finnish mass-screening programme (1975) identified 2648 women with PCB of whom 12 had ICC  |

|                                    |                      |  |  |
|------------------------------------|----------------------|--|--|
| United Kingdom                     |                      | <ul style="list-style-type: none"> <li>○ Cross-sectional PPV of PCB for ICC: 0.5%</li> <li>○ RR for ICC for women with:without PCB: 6.3</li> <li>○ A follow up study on the same cohort (1977) showed that women with PCB and a negative smear had a 15-fold risk of late ICC compared to those without bleeding symptoms (however 93% of all ICC in the cohort were in those without PCB)</li> <li>○ A subsequent Finnish study (1998) reported the risk over intervening 23yrs had dropped to 3-fold</li> </ul> <p>Authors estimated that the probability that a women with PCB in the community has ICC was (in England in 2001) by age was:</p> <ul style="list-style-type: none"> <li>● 20-24yrs: 1 in 44 000</li> <li>● 25-34yrs: 1 in 5600</li> <li>● 35-44yrs: 1 in 2800</li> <li>● 45-54yrs: 1 in 2400</li> </ul> |  |
| Ray<br>2007<br>United Kingdom      | Retrospective cohort | 134 women referred to colposcopy clinic <b>negative cytology</b> and: <ul style="list-style-type: none"> <li>● PCB: 64 (47.8%)</li> <li>● IMB: 12 (9%)</li> <li>● PCB+IMB: 19 (14.2%)</li> </ul>   | PCB: no ICC<br>IMB: no ICC                                   |
| Sahu<br>2007<br>United Kingdom     | Retrospective cohort | 87 women with PCB and <b>negative cytology</b> seen in a colposcopy clinic   | No cases of ICC  |
| Tehrani<br>2009<br>Iran            | Retrospective cohort | 123 women with PCB referred to a colposcopy clinic   | SCC: 1 (0.8%)  |
| Alfhaily<br>2010<br>United Kingdom | Prospective cohort   | 137 women with PCB +/- IMB:  | ICC: 1 (diagnosed clinically) (0.73%)                        |
| See<br>2013<br>United Kingdom      | Retrospective cohort | Women referred to colposcopy clinic with PCB   | SCC: 1 (1.4%)  |
| Gulumser<br>2015<br>Turkey         | Retrospective cohort | 237 women referred to clinic with PCB  | ICC not separately reported (53 (22.4%) of women were CIN2+) |

**Table 4a: Postcoital bleeding, cytology and cervical cancer**

| Study                           | Type of study        | Population   |   |
|---------------------------------|----------------------|--|---|
| Khattab 2005<br>United Kingdom  | Retrospective cohort | 284 women with PCB seen in colposcopy/gynaecology clinics  | PCB and normal/ no referral cytology: ICC: 3.6% (1.2% of women with normal/ no referral cytology when ICC cases with no referral cytology were excluded)<br>PCB and abnormal referral cytology: ICC: 6%   |
| Tehraniyan 2009<br>Iran         | Retrospective cohort | 123 women with PCB referred to a colposcopy clinic   | Cytology result was abnormal for the one ICC case, however the correlation between cytology and histology results was not reported in detail  |
| Alfhaily 2010<br>United Kingdom | Prospective cohort   | 137 women with PCB;<br>• PCB: 88 (64.2%) PCB+IMB: 49 (35.8%)   | Cervical cytology collected in 132 of 137 women. Details of correlation between cytology and histology were not reported. One case of ICC (0.73%) described as diagnosed clinically.  |
| See 2010<br>United Kingdom      | Retrospective cohort | 73 women referred to colposcopy clinic with PCB; 21 (28.8%) had associated IMB.  | SCC: 1 (1.4%)<br>Cytology had been taken in 43 (58.9%) women; dyskariosis (not further defined) identified in only 1 of these 43 cases with cytology. Correlation with histology results was not reported.  |
| Gulumser 2015<br>Turkey         | Retrospective cohort | 1491 women referred to colposcopy clinic with abnormal cytology, HPV +ve, abnormal biopsy or suspicious looking cervix; 237 women also had PCB | 53 (22.4%) of women were CIN2+ (ICC not separately reported; unclear if any cases were present or not)<br><br>PCB and cytology negative: CIN2+: 7.3%<br>PCB and cytology ASCUS+: CIN2+: 38.6%<br><br>Risk factors for CIN2+ (multiple logistic regression):<br>• Smoking OR 1.7 (95% 1.1 to 2.6)<br>• HPV +ve OR 4.1 (95% CI 2.6 to 6.3)<br>• ASCUS +ve OR 5.8 (95% 2.0 to 16.5)<br>PCB: not associated with increased risk of CIN2+ therefore above ORs are not adjusted for/ stratified by PCB. |

**Table 4b: Postcoital bleeding, HPV testing and cervical cancer**

| Study                | Type of study        | Population   |  |
|----------------------|----------------------|--|--|
| Gulumser 2015 Turkey | Retrospective cohort | 237 women had PCB;<br>65 women had an HPV test<br>HPV testing conducted using PCR (commercial kit Fluorion, Iontek, Turkey) on cervical smear samples.<br>Specific HPV types tested for not described. | Associations were reported in relation to CIN2+ (ICC not separately reported; unclear if any cases were present or not)<br>19/65 (29%) of women with PCB were HPV +ve<br>The number of women with PCB and HPV +ve who had CIN2+ was not reported.<br>Being HPV +ve was associated with increased OR for CIN2+ compared to HPV -ve (OR 4.1 ;95% CI 2.6 to 6.3; adjusted for cigarette use and abnormal vs normal cytology result) |

**Table 4c: Postcoital bleeding, age and cervical cancer**

| Study                       | Type of study        | Population  |   |
|-----------------------------|----------------------|---|---|
| Khattab 2005 United Kingdom | Retrospective cohort | 284 women with PCB seen in colposcopy/gynaecology clinics | No significant difference in the rate of ICC or CIN between women >35yrs with PCB for >4wk and women ≤35yrs with repeated unexplained PCB |

**Table 5: Characteristics and results of included studies**

| Author       | Country        | Type of study        | Objective(s) of relevance   | Population   | Results   |
|--------------|----------------|----------------------|---|--|---|
| Khattab 2005 | United Kingdom | Retrospective cohort | Measure the frequency of abnormal findings in women referred with PCB | 284 women with PCB seen in colposcopy/gynaecology clinics<br><br>166 women referred with PCB and <b>no or normal smear</b> .<br><ul style="list-style-type: none"> <li>• 2 subgroups: <ol style="list-style-type: none"> <li>1. 72 women &gt;35yrs with PCB for &gt;4wks</li> <li>2. 94 women ≤35yrs with repeated unexplained PCB</li> </ol> </li> <li>• PCB+IMB: 60 (36%)</li> </ul> | <b>Normal or no referral smear:</b> <ul style="list-style-type: none"> <li>• Cervix examination: normal 42%, ectropion 23%, contact bleeding 21%, cervical polyp 8%, cervical ulceration 4%</li> <li>• No pathology detected in approx. 50% women</li> <li>• ICC in group 1: 6 (3.6%) <ul style="list-style-type: none"> <li>○ 3 women had no previous smear</li> <li>○ 1 woman had negative smear 8 years prior</li> </ul> </li> <li>• ICC in group 1 excluding cases in women with no smear history: 2 (1.2% of group 1)</li> <li>• CIN: 9%</li> <li>• No endometrial Ca</li> </ul> |

|              |                |                      |  |  |   |
|--------------|----------------|----------------------|--|--|---|
|              |                |                      |  | <ul style="list-style-type: none"> <li>• PCB+dyspareunia: 34 (21%)</li> <li>• PCB+pelvic pain: 18 (11%)</li> </ul> <p>118 women referred with PCB and <b>abnormal cytology</b></p> <ul style="list-style-type: none"> <li>• PCB+IMB: 37 (31%)</li> <li>• PCB+dyspareunia: 5 (4%)</li> <li>• PCB+pelvic pain: 2 (1.7%)</li> </ul>   | <ul style="list-style-type: none"> <li>• No significant difference in the rate of ICC or CIN between women aged &gt;35 with PCB for more than 4 weeks and women aged &lt;= 35 with repeated unexplained PCB</li> </ul> <p><b>Abnormal referral smear:</b></p> <ul style="list-style-type: none"> <li>• Cervix examination: normal 86%, ectropion 5%, contact bleeding 5%, cervical polyp 3%, cervical ulceration 2%</li> <li>• No pathology detected in 17% of women</li> <li>• ICC: 6 (5%)</li> <li>• CIN: 66%</li> <li>• No endometrial Ca</li> </ul>   |
| Abu 2006     | United Kingdom | Retrospective cohort | Determine the risk of significant cervical pathology abnormality in women referred to colposcopy clinic with PCB. Evaluate cervical smear history of these women and correlated this with any colposcopic or pathological abnormality. | <p>142 women referred to colposcopy clinic with PCB.</p> <p>Age range: 16-61yrs (mean 34.1yrs)</p> <p>113 (79.6%) had smear in last 3yrs; 4 had smear &gt;3yrs ago.</p> <p>Of the 117 smears:</p> <ul style="list-style-type: none"> <li>• 102 (87.2%) negative smear</li> <li>• 5 borderline changes</li> <li>• 2 mild dyskaryosis</li> <li>• 1 moderate dyskaryosis</li> <li>• 1 severe dyskaryosis</li> <li>• 6 unsatisfactory</li> </ul> | <p>Diagnosis following investigations carried out in the colposcopy clinic in 142 women with PCB:</p> <ul style="list-style-type: none"> <li>• Normal 56 (39.4%)</li> <li>• Cervical ectopy 44 (31.0%)</li> <li>• Benign cervical polyp 7 (4.9%)</li> <li>• Cervical inflammation 1 (0.7%)</li> <li>• Nabothian cyst 1 (0.7%)</li> <li>• CIN1: 12 (8.5%)</li> <li>• CIN2: 11 (7.7%)</li> <li>• CIN3: 4 (2.8%)</li> </ul> <p><b>Referral cytology and histology:</b></p> <p>102 women with negative smear prior to referral:</p> <ul style="list-style-type: none"> <li>• CIN1: 10</li> <li>• CIN2: 8</li> <li>• CIN3: 2</li> </ul> <p>1 borderline changes: CIN1<br/> 2 mild dyskaryosis: CIN1: 1; CIN2: 1<br/> 1 moderate dyskaryosis: CIN2<br/> 1 severe dyskaryosis: CIN3<br/> 2 no cervical smear: CIN2: 1; CIN3: 1</p> |
| Shapley 2006 | United Kingdom | Systematic review    | Estimate PPV of PCB for cervical cancer to aid decision making in primary care about whom to   | 38 papers identified in which prevalence/incidence of PCB reported or able to be calculated  | <p><b>Prevalence/incidence of PCB:</b></p> <ul style="list-style-type: none"> <li>• <u>Community care</u>: point prevalence: 0.7-9% (8 studies)</li> <li>• <u>Primary (1<sup>0</sup>) care</u>: <ul style="list-style-type: none"> <li>○ No studies of women consulting 1<sup>0</sup> care</li> <li>○ Proportion of women in the community who consult 1<sup>0</sup> care not known</li> </ul> </li> </ul>  |

investigate for ICC

- Secondary (2<sup>0</sup>) care:
  - Prevalence 5% (1 study)
  - Proportion of women presenting to 1<sup>0</sup> care with PCB who are referred to 2<sup>0</sup> not reported

**Proportion of women with ICC who report PCB:** 11% (estimate calculated to be relevant to British general practice population)

**Proportion of women with PCB who on screening/investigation have cancer:**

- Community care: (1 study, 1975) Finnish mass-screening programme identified 2648 women with PCB of whom 12 had ICC
  - Cross-sectional PPV of PCB for ICC: 0.5%
  - RR for ICC for women with:without PCB: 6.3
  - A follow up study on the same cohort (1977) showed that women with PCB and a negative smear had a 15-fold risk of late ICC compared to those without bleeding symptoms (however 93% of all ICC in the cohort were in those without PCB)
  - A subsequent Finnish study using same methodology (1998) reported the risk over intervening 23yrs had dropped to 3-fold
- Primary care: no studies
- Secondary care: (8 studies):
  - ICC: 2%
  - Gynaecological malignancy: 3%

**Predictive value of PCB for ICC:**

The Finnish mass-screening study (1975) gave a PPV of 1 in 220 for Ca. However Shapley et al discuss how epidemiology of PCB and ICC has changed with bleeding symptoms becoming more frequent and the incidence of ICC decreasing. They estimated that the probability that a women with PCB in the community has ICC was (in England in 2001) by age was:

- 20-24yrs: 1 in 44 000
- 25-34yrs: 1 in 5600
- 35-44yrs: 1 in 2800
- 45-54yrs: 1 in 2400

Direct estimates of PPV in 1<sup>0</sup> and 2<sup>0</sup> care could not be calculated due to the lack of information re incidence of PCB in 1<sup>0</sup> and referred populations.

|              |                   |                         |  |   |  |
|--------------|-------------------|-------------------------|--|---|--|
| Ray<br>2007  | United<br>Kingdom | Retrospective<br>cohort | Evaluate patients referred to colposcopy clinic with PCB and/or IMB with <i>negative cytology</i> to establish incidence of underlying HSIL                    | 134 women referred to colposcopy clinic for clinical indication and negative cytology:<br><ul style="list-style-type: none"> <li>• PCB: 64 (47.8%)</li> <li>• IMB: 12 (9%)</li> <li>• PCB+IMB: 19 (14.2%)</li> </ul>  | <p>PCB:</p> <ul style="list-style-type: none"> <li>• Colposcopy (64 women): <ul style="list-style-type: none"> <li>○ Normal: 18 (28.1%)</li> <li>○ Ectropion: 16 (25%)</li> <li>○ Cervical polyp: 7 (10.9%)</li> <li>○ LSIL 4 (6.25%)</li> <li>○ HSIL 2 (3.1%)</li> </ul> </li> <li>• Biopsy (37 women): <ul style="list-style-type: none"> <li>○ Inflammation 17 (45.9%)</li> <li>○ Metaplasia 6 (16.2%)</li> <li>○ Polyp 1 (2.7%)</li> <li>○ HPV 9 (24.3%)</li> <li>○ LSIL 2 (5.4%)</li> <li>○ HSIL: 1 (2.7%)</li> <li>○ VAIN: 1 (2.7%)</li> </ul> </li> </ul> <p>IMB:</p> <ul style="list-style-type: none"> <li>• Colposcopy (12 women) <ul style="list-style-type: none"> <li>○ Normal 8 (60%)</li> <li>○ Ectropion: 1 (8.3%)</li> </ul> </li> <li>• Biopsy (7 women): <ul style="list-style-type: none"> <li>○ Metaplasia 2 (28.6%)</li> <li>○ Polyp 3 (42.8%)</li> <li>○ HPV 2 (28.6%)</li> </ul> </li> </ul> |
| Sahu<br>2007 | United<br>Kingdom | Retrospective<br>cohort | Determine the frequency of cervical pathology and the incidence of cervical neoplasia in women with PCB at the colposcopy clinic with <i>negative cytology</i> | 87 women with PCB and negative cytology seen in a colposcopy clinic;<br><br>Age:<br><25yrs: 6 (6.9%)<br>26-35yrs: 31 (35.6%)<br>36-45yrs: 32 (36.8%)<br>46-55yrs: 17 (19.5%)<br>>55yrs: 1 (1.2%)<br><br>Associated symptoms:<br><ul style="list-style-type: none"> <li>• IMB: 13 (14.9%)</li> <li>• Dyspareunia: 3 (3.2%)</li> <li>• Vaginal discharge: 2 (2.3%)</li> </ul> | <p>Clinical examination:</p> <ul style="list-style-type: none"> <li>• Normal looking cervix: 47 (52.4%)</li> <li>• Cervical ectopy: 29 (33.6%)</li> <li>• Cervical polyp: 11 (12.5%)</li> </ul> <p>Infection screen performed in 51 (58.6%) women:</p> <ul style="list-style-type: none"> <li>• Chlamydia: 2 (2.3%)</li> <li>• Bacterial vaginosis: 5 (5.8%)</li> </ul> <p>Colposcopy:</p> <ul style="list-style-type: none"> <li>• 62 (71.5%) normal colposcopic appearance</li> <li>• 25 (28.5%) abnormal appearance on colposcopy and had a biopsy</li> <li>• 6/25 women who underwent diagnostic biopsies had histological abnormalities: <ul style="list-style-type: none"> <li>○ CIN1: n=3 (3.5%)</li> </ul> </li> </ul>   |

|                 |                |                      |   |   |  |
|-----------------|----------------|----------------------|---|---|--|
|                 |                |                      |   |   | <ul style="list-style-type: none"> <li>○ CIN2: n=1 (1.2%)</li> <li>○ CIN3: n= 2 (2.3%)</li> <li>○ No cases of ICC</li> </ul>   |
| Tehrani<br>2009 | Iran           | Retrospective cohort | Evaluate PCB by clinical examination, cytology, colposcopy and histopathology         | <p>123 women with PCB referred to a colposcopy clinic</p> <p>If colposcopy:</p> <ul style="list-style-type: none"> <li>• Normal: 4 biopsies were taken</li> <li>• Abnormal: biopsies were taken from abnormal area</li> </ul>                         | <p>Clinical examination:</p> <ul style="list-style-type: none"> <li>• Normal: 91 (74.0%)</li> <li>• Cervical polyp: 18 (14.6%)</li> <li>• Cervical ectropion: 14 (11.4%)</li> </ul> <p>Cytology:</p> <ul style="list-style-type: none"> <li>• Normal: 78 (82.1%)</li> <li>• Inflammatory: 23 (18.7%)</li> <li>• ASCUS: 13 (10.6%)</li> <li>• AGC: 2 (1.6%)</li> <li>• LSIL: 4 (3.3%)</li> <li>• HSIL: 3 (2.4%)</li> </ul> <p>Colposcopy:</p> <ul style="list-style-type: none"> <li>• Unsatisfactory: 26 (21.1%)</li> <li>• Normal: 49 (39.8%)</li> <li>• Atypical TZ grade 1: 41 (33.3%)</li> <li>• Atypical TZ grade 2: 6 (4.9%)</li> <li>• Suspect invasive carcinoma: 1 (0.8%)</li> </ul> <p>Pathology:</p> <ul style="list-style-type: none"> <li>• LG glandular neoplasia: 1 (0.8%)</li> <li>• CIN1: 9 (7.3%)</li> <li>• CIN2: 2 (1.6%)</li> <li>• CIN3 1 (0.8%)</li> <li>• SCC: 1 (0.8%)</li> </ul> <p>Cytology missed 7/14 (50%) biopsy-proven abnormalities: 6 CIN1; 1 LG glandular neoplasia</p> <p>Colposcopy missed 3/14 (21.4%): 2 CIN1; 1 CIN2</p> |
| Alfaily<br>2010 | United Kingdom | Prospective cohort   | Review the management and identify the diagnostic outcome in women referred with PCB. | <p>137 women with PCB;</p> <ul style="list-style-type: none"> <li>• PCB: 88 (64.2%) PCB+IMB: 49 (35.8%)</li> <li>• 48 (35.0%) met criteria for endometrial investigation</li> <li>• 124/137 (90.5%) had PCB for &gt;4weeks at presentation</li> </ul> | <p>Examination:</p> <ul style="list-style-type: none"> <li>• Normal: 39 (28.5%)</li> <li>• Ectropion: 62 (45.2)</li> <li>• Contact bleeding: 39 (28.5%)</li> <li>• Cervical polyp: 15 (10.9%)</li> </ul> <p>63/137 (46%) had a colposcopy</p>  |

|              |                |                      |  |   |  |
|--------------|----------------|----------------------|--|---|--|
|              |                |                      | <p>All women:</p> <ul style="list-style-type: none"> <li>examination</li> <li>cytology if none in previous 3 months</li> <li>triple swabs (chlamydial, endocervical and high vaginal)</li> <li>colposcopy</li> </ul> <p>Postmenopausal and women &gt;35yrs with PCB+IMB:</p> <ul style="list-style-type: none"> <li>pelvic ultrasound</li> <li>endometrial sampling</li> </ul> | <ul style="list-style-type: none"> <li>14/28 women (50%) were &lt;35 years of age</li> <li>7/28 women (25%) had severe episodes of PCB</li> </ul>   | <p>28 women (20.4%) had significant pathology:</p> <ul style="list-style-type: none"> <li>ICC: n=1 (diagnosed clinically)</li> <li>AIS: n=1</li> <li>HG CIN: n=6</li> <li>LG CIN: n=12</li> <li>Chlamydial cervicitis: n=3</li> <li>Bacterial vaginosis: n=9</li> </ul> <p>The AIS and 5/6 of HG CIN cases had a negative smear history and the sixth had a negative smear history except one borderline smear 10 years prior to the episode of PCB</p> <p>No endometrial hyperplasia/cancer; benign endometrial pathology in 4 women with PCB+IMB</p> |
| See 2013     | United Kingdom | Retrospective cohort | Determine the frequency of pathology in women with PCB   | <p>Women referred to colposcopy clinic with PCB</p> <ul style="list-style-type: none"> <li>PCB+IMB: 21 (28.8%)</li> <li>PCB duration: 1 episode to 2yrs</li> <li>Age: <ul style="list-style-type: none"> <li>&lt;25yrs: 17 (23.3%)</li> <li>25-49yrs: 52 (71.2%)</li> <li>≥50yrs: 4 (5.5%)</li> </ul> </li> </ul> | <p>No cause of PCB was found in 35 (47.9%) women</p> <p>Pathology present in 38 (52.1%) women:</p> <ul style="list-style-type: none"> <li>SCC: 1 (1.4%)</li> <li>CIN: 11 (15.1%)</li> <li>Infection: 7 (9.6%)</li> <li>Cervical polyp: 2 (2.7%)</li> <li>Cervical ectropion: 14 (19.2%)</li> <li>HPV changes: 3 (4.1%)</li> </ul>  |
| Shapley 2013 | United Kingdom | Prospective cohort   | Obtain estimates of the rates of occurrence and spontaneous resolution of IMB and PCB and investigate any association with underlying  | <p>2104 naturally menstruating women aged 40-54 years registered with 7 general practices</p> <ul style="list-style-type: none"> <li>Questionnaires at baseline, 6m, 12m, 18m and 24m</li> <li>Frequent = ≥3 times in previous 6m</li> <li>Persistent=on 2 consecutive questionnaires</li> </ul>                  | <p>Prevalence (as a proportion of naturally menstruating women):</p> <ul style="list-style-type: none"> <li>IMB +/-or PCB at baseline: 21% (95%CI: 20-23%)</li> <li>PCB at baseline: 9.5% (95% CI: 8.3-11%)</li> <li>Frequent PCB at baseline: 2.2% (95%CI: 1.7-3.0%)</li> <li>Persistent PCB at 12m: 2.2% (95%CI: 1.6-3.2%)</li> <li>IMB at baseline: 18% (95% CI: 16-20%)</li> <li>Frequent IMB at baseline: 5.3% (95%CI: 4.4-6.3%)</li> <li>Persistent IMB at 12m: 7.6% (95%CI: 6.2-9.2%)</li> </ul>  |

|               |        |                      |  |  |  |
|---------------|--------|----------------------|--|--|--|
|               |        |                      | malignancy   | <ul style="list-style-type: none"> <li>1771 (93%) women had their medical records reviewed for a further 2yrs</li> </ul>   | <p>Over 4yrs: 3 women developed "uterine cancer":</p> <ul style="list-style-type: none"> <li>ICC: diagnosed at 18m; reported frequent IMB at baseline and 12m (6m and 18m questionnaires not returned)</li> <li>Ca body of uterus: diagnosed by 31m; no PCB/IMB or vaginal bleeding once amenorrhoeic</li> <li>Ca body of uterus: diagnosed at 18m; no PCB/IMB or vaginal bleeding once amenorrhoeic</li> </ul>  |
| Gulumser 2015 | Turkey | Retrospective cohort | Evaluate to what extent PCB is an indicator of CIN2+ | <p>1491 women referred to clinic with abnormal cytology, HPV +ve, abnormal biopsy or suspicious looking cervix (excluded if abnormal looking cervix at baseline speculum examination)</p> <ul style="list-style-type: none"> <li>237 women had PCB</li> <li>Conventional cytology and colposcopic guided biopsy performed on all women with PCB</li> </ul> | <ul style="list-style-type: none"> <li>406/1491 (27%) women were CIN2+</li> <li>53/406 (13.1%) of women with CIN2+ had PCB</li> <li>53/237 (22.4%) of women with PCB were CIN2+ (calculated)</li> <li>509/1491 women had an HPV test of which 215/509 (42%) were +ve</li> <li>65/237 women with PCB had an HPV test</li> <li>19/65 (29%) of women with PCB were HPV +ve</li> <li>1092/1491 women were ASCUS +ve</li> <li>114/237 women with PCB had ASCUS +</li> <li>384/1092 (35.2%) of women with ASCUS+ were CIN2+</li> <li>44/144 (38.5%) women with PCB and ASCUS+ had CIN2+</li> </ul> <p>Histology results by cytology grade in women with PCB:</p> <ul style="list-style-type: none"> <li>Cytology negative (123 women): <ul style="list-style-type: none"> <li>Normal: 108 (87.8%)</li> <li>CIN1: 6 (4.9%)</li> <li>CIN2+: 9 (7.3%)</li> </ul> </li> <li>Cytology ASCUS+ (114 women): <ul style="list-style-type: none"> <li>Normal: 53 (46.5%)</li> <li>CIN1: 17 (14.9%)</li> <li>CIN2+: 44 (38.6%)</li> </ul> </li> </ul> <p>Risk factors for CIN2+ (multiple logistic regression across women with and without PCB):</p> <ul style="list-style-type: none"> <li>Smoking OR 1.7 (95% 1.1 to 2.6)</li> <li>HPV +ve OR 4.1 (95% CI 2.6 to 6.3)</li> <li>ASCUS +ve OR 5.8 (95% 2.0 to 16.5)</li> <li>PCB: not associated with increased risk of CIN2+</li> </ul> |

PCB: postcoital bleeding; IMB: intermenstrual bleeding; LSIL: low-grade squamous intraepithelial neoplasia; HSIL: high-grade squamous intraepithelial neoplasia; CIN: cervical intraepithelial neoplasia; AIS: adenocarcinoma in situ; ICC: invasive cervical cancer; SCC: squamous cell carcinoma; Ca: cancer; LG: low-grade; HG: high-grade; TZ: transition zone; VAIN: vaginal intraepithelial neoplasia

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