Diagnostic workup for postmenopausal bleeding: a randomised controlled trial

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Objective To evaluate the effectiveness of hysteroscopy for the detection and treatment of endometrial polyps versus expectant management in women with postmenopausal bleeding (PMB), a thickened endometrium and benign endometrial sampling.

Design Multicentre, randomised controlled trial.

Setting Three academic hospitals and nine non-academic teaching hospitals in the Netherlands.

Population Women with PMB, an endometrial thickness >4 mm and benign result from endometrial sampling.

Methods Women were randomised to either further diagnostic workup by hysteroscopy (preceded by saline infusion sonography) or expectant management.

Main outcomes The primary outcome measure was recurrence of PMB within a year after randomisation. Secondary outcome measures were time to recurrent bleeding and recurrent bleeding after more than 1 year. In the hysteroscopy group, the presence of polyps and the results of their histology were registered.

Results Between January 2010 and October 2013, 200 women were randomised; 98 to hysteroscopy and 102 to expectant management. Within 1 year a total of 15 women (15.3%) in the hysteroscopy group experienced recurrent bleeding, versus 18 (18.0%) in the expectant management group (relative risk 0.85 (95% CI 0.46–1.59)). In the hysteroscopy group, 50/98 (51%) polyps were diagnosed of which 6/98 (6%) showed evidence of endometrial (pre)malignancy; final pathology results after hysterectomy showed three women with hyperplasia with atypia and three women with endometrial cancer.

Conclusion In women with PMB, a thickened endometrium and benign endometrial sampling, operative hysteroscopy does not reduce recurrent bleeding. Hysteroscopy detected focal endometrial (pre)malignancy in 6% of women who had benign endometrial sampling. This finding indicates that in these women, further diagnostic workup is warranted to detect focal (pre)malignancies, missed by blind endometrial sampling.

Keywords Endometrial carcinoma, endometrial polyp, endometrial sampling, hysteroscopy.
Tweetable abstract In women with PMB, hysteroscopy does not reduce recurrent bleeding but is warranted to detect focal malignancy.

Linked article This article is commented on by TJ Clark, p. 241 in this issue. To view this mini commentary visit http://dx.doi.org/10.1111/1471-0528.14220.

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Introduction

Postmenopausal bleeding (PMB) is a common symptom in gynaecological practice. It signals endometrial cancer in about 10% of women. Transvaginal sonographic measurement of endometrial thickness is used to distinguish between women with a low or high risk of endometrial cancer. If the endometrium is thickened, women are considered at higher risk of endometrial cancer and endometrial sampling is performed.

When endometrial sampling shows a benign result, there is uncertainty whether the workup should be continued to detect benign intracavity pathology. Further evaluation to detect focal intrauterine lesions, which may be missed by blind endometrial sampling, is considered necessary in women who present with recurrent or persistent PMB. However, when a woman does not have persistent bleeding, guidelines leave room for individual women and their doctors to choose between expectant management or further diagnostic workup to detect focal lesions such as polyps. When further diagnostic workup is adopted, testing with saline infusion sonography (SIS) or hysteroscopy is performed because these represent the most accurate tests to diagnose endometrial polyps. Those clinicians choosing further testing do so because undiagnosed endometrial polyps are believed to be responsible for recurrent vaginal PMB although evidence on the effectiveness of polypectomy for preventing recurrent bleeding is lacking. No difference in recurrent bleeding was observed in a cohort study evaluating women investigated for PMB whether they had an endometrial biopsy alone, a hysteroscopy with biopsy or a polypectomy after detection at hysteroscopy.

In view of this lack of knowledge, we performed a multicentre randomised controlled trial in which we investigated the effectiveness of diagnostic workup with hysteroscopy and subsequent polypectomy versus expectant management in women with PMB and a benign endometrial biopsy. As we routinely performed SIS before a hysteroscopy, we were able to evaluate whether an SIS could triage the need for a subsequent hysteroscopy.

Methods

Between January 2010 and October 2013, we performed a multicentre, randomised clinical trial in three academic and nine non-academic teaching hospitals. The trial was performed within the Dutch Consortium for research in Women’s Health, a collaboration of teaching and non-teaching hospitals in the Netherlands. The study was performed by gynaecologists, registrars and research nurses. Full details about the trial protocol can be found at www.studies-obsgyn.nl/upload/protocol_pompoen230908.doc. The trial was registered at the Dutch trial register (NTR2130). Approval for this study was obtained from the Medical Ethical Committee of the Academic Medical Centre, Amsterdam (MEC 2008-177) and from the Central Committee on Research involving Human Subjects (CMO), the Netherlands. The local board of each participating hospital approved the study.

Participants

We studied women with PMB, defined as blood loss occurring after at least 1 year of amenorrhoea over the age of 50 years. Hospitals participating in the study had a workup protocol for these women, based on the Dutch national guideline. First, women underwent transvaginal sonography. The thickness of the endometrium was measured in the sagittal plane, including both layers of endometrium. All measurements were performed with callipers on a frozen ultrasound image. In case the endometrial thickness was ≤4 mm, the woman was reassured, managed expectantly and advised to come back with recurrent bleeding. If the double endometrium thickness was >4 mm or not measurable, endometrial sampling was performed, using Pipelle® (Pipelle de Cornier, Paris, France), an office endometrial sampling device that is generally used in the Netherlands. If the sampling device could not pass the cervical os, or the sampling result was inconclusive, the woman was scheduled for direct hysteroscopy and could not be included in this study.

Inclusion criteria were PMB, an endometrial thickness >4 mm and benign histology. The local pathologist examined the endometrial samples. We defined benign histology of endometrial sampling as the presence of benign endometrial stroma in the histology sample. Hyperplasia without atypia found with endometrial sampling was considered to be a benign result. At trial commencement we considered complex hyperplasia without atypia as a benign result. However, we included one woman with complex hyperplasia without atypia (inclusion number 17) in whom...
hysteroscopy showed an endometrial cancer. After this event, we decided to exclude women with complex hyperplasia. Other exclusion criteria were cervical cytology showing an abnormality which warranted treatment, an endometrial biopsy showing a (pre)malignancy (i.e. atypical endometrial hyperplasia or endometrial cancer) or an insufficient sample or if endometrial sampling had failed due to technical problems. Women using an aromatase-inhibitor or anti-oestrogen medication were also excluded.

**Hypothesis**
We hypothesised that in women with PMB and endometrial thickness of >4 mm, further uterine cavity evaluation to diagnose and resect endometrial polyps would lead to less recurrent bleeding compared with women in whom further testing was not performed.

**Informed consent, randomisation and masking**
The local doctor or research nurse enrolled the participants and assigned them to the randomised intervention. Before randomisation, participating women provided written informed consent, in which they were informed about the possible risks and complications of SIS and hysteroscopy. Women were randomised to receive both SIS and hysteroscopy or expectant management, using a web based program, using block randomisation with a block size of four, an allocation ratio of 1:1 and stratification for hospital. The web-based program generated a unique number with allocation code after entry of the patient’s initials and date of birth. Neither recruiting doctors nor members of the trial project group could access the randomisation sequence. Due to the nature of the intervention the study was open-label, as it meant that masking women and doctors to the assigned intervention was not possible. The statistician doing the analysis (MHZ) was masked to the assigned intervention, but those who collected follow-up data were not.

**Intervention**
Women allocated to diagnostic workup all underwent SIS and hysteroscopy in the same outpatient session, within 6 weeks after randomisation. At SIS, a small volume of saline was inserted into the uterus, which allowed the lining of the endometrium and possible polyps to be clearly seen on an ultrasound scan. During the same visit, regardless of the result, a hysteroscopy was performed, using a vaginoscopic approach with a 4–5.5-mm hysteroscope, according to the local protocol. The hysteroscopy was performed by the local gynaecologist with experience in hysteroscopy. When a polyp was detected, immediate polypectomy was performed using hysteroscopic scissors, a polyp snare or a bipolar electrode (Versapoint®). In a case of thickened or irregular endometrium, a biopsy was taken using a grasping forceps and in case of atrophic endometrium, the doctor could decide on the need for an endometrial biopsy according to the Dutch guideline. When outpatient hysteroscopy was not feasible or a polyp could not be removed completely, the woman underwent hysteroscopy under regional or general anaesthesia. Woman allocated to expectant management did not receive any specific further diagnostic workup or treatment.

**Follow up**
All women received instructions to contact the clinic in case of recurrent PMB. If a woman contacted the clinic because of recurrent bleeding, she was advised to re-attend so that a hysteroscopy could be performed and if an endometrial polyp was detected it could be removed. All women were contacted by telephone after at least 1 year and were specifically asked if they had had recurrent bleeding since study entry. If they had experienced recurrent bleeding, which had not been evaluated they were advised to make an appointment for a hysteroscopy.

In 2014, researchers checked all case record forms. If recurrent bleeding was mentioned, but the patient had not been evaluated, the research nurse contacted the woman again and asked her to make an appointment at the clinic. To verify that women with recurrent bleeding were not missed in our registration, the researchers checked pathology results for all included women during the study period.

**Outcomes**
The primary objective of this trial was to study the effectiveness of hysteroscopy in preventing recurrent PMB within a year of randomisation in women with PMB and a thickened, benign endometrium. Not only real red-coloured blood loss, but also brown vaginal discharge was considered recurrent bleeding. Secondary outcome measures were time to recurrent bleeding, recurrent bleeding after more than 1 year and the diagnostic accuracy of SIS compared with a hysteroscopic reference standard. Although not described in the original trial protocol as a secondary outcome, the presence of polyps and the results of pathology were also registered. Premalignancy was defined as (simple or complex) hyperplasia with atypia.

**Sample size**
The incidence of recurrent bleeding without hysteroscopy was assumed to be 40% based on the published literature. Our null hypothesis assumed that the performance of hysteroscopy and polypectomy would reduce the chance of recurrent bleeding from 40% to 20%. To show such a difference, we needed to enrol 164 women (two groups of 82) (power 80%, significance level 5%). Anticipating a crossover and dropout rate of 20%, we planned to include 200 women.
Statistical analyses

Statistical analysis was performed according to the intention-to-treat principle. Differences in dichotomous outcomes were analysed with the chi-square test, or Fisher’s exact test when the expected frequencies fell below five. Continuous variables were tested for normal distribution, and since none of the variables were normally distributed, a Mann–Whitney U-test for univariate analysis was used. The primary and secondary outcomes were compared by calculating relative risks (RRs) and their 95% confidence intervals (95% CIs). Women who were lost to follow up were excluded from the analysis. Kaplan–Meier curves were conducted to present the time to recurrent bleeding in both groups and log-rank test was used to test differences in time to recurrent bleeding. Sensitivity and specificity and their 95% CIs were calculated for SIS, with visual hysteroscopy results (polyp yes/no) as reference standard. Women with inconclusive SIS were considered as suspicious for having endometrial pathology and have an indication for a hysteroscopy. Therefore, all women with inconclusive SIS were considered as a positive result and counted as such in the sensitivity calculation. For analysis, the Statistical Package for the Social Sciences (IBM Corp, Armonk, NY, USA) version 20.0 was used. Statistical significance was set at $P < 0.05$.

Results

During the study period 201 women presenting with post-menopausal bleeding, an endometrial thickness of >4 mm and a benign histology result in the 12 participating hospitals, agreed to participate in the study. One woman was excluded because of use of tamoxifen, 98 were randomly allocated to SIS and hysteroscopy and 102 women to expectant management. The baseline characteristics of the participants in the two groups were comparable (Table 1). Of the 98 women in allocated hysteroscopy, 87 underwent the procedure (89%) and 11 women declined further invasive diagnostics and opted for expectant management (Figure 1). SIS was not performed in 6/87 women having a hysteroscopy because of protocol violation, in another two women SIS was not possible due to pain. In the 102 women allocated to expectant management, all women followed the study protocol. Two of these women were lost to follow up; we could not contact them after 1 year and they were excluded from analysis.

Recurrent bleeding within 12 months occurred in 15 women (15.3%) after hysteroscopy and in 18 women (18.0%) after expectant management (RR 0.85; 95% CI 0.4–1.6) (Table 2). Follow up varied between 12 and 56 months, with a median follow up of 14 months in both groups. Figure 2 shows the Kaplan–Meier curve for time to recurrent bleeding. The mean time to recurrent bleeding

<table>
<thead>
<tr>
<th>Age, years; median (IQR)</th>
<th>57 (54–62)</th>
<th>56 (52–61)</th>
</tr>
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<tbody>
<tr>
<td>Age at menopause, years; median (IQR)</td>
<td>51 (48–53)</td>
<td>50 (48–52)</td>
</tr>
<tr>
<td>Years since menopause; median (IQR)</td>
<td>5 (2–12)</td>
<td>5 (2–11)</td>
</tr>
<tr>
<td>BMI, kg/m²; median (IQR)</td>
<td>28.0 (24.3–32.7)</td>
<td>28.7 (25.2–35.0)</td>
</tr>
<tr>
<td>Endometrial thickness, mm; median (IQR)</td>
<td>8 (6–12)</td>
<td>7 (6–10)</td>
</tr>
<tr>
<td>Endometrial thickness measurable (%)</td>
<td>93 (95)</td>
<td>100 (98)</td>
</tr>
</tbody>
</table>

Table 1. Baseline characteristics

BMI, body mass index; IQR, interquartile range.
Figure 1. Trial flowchart.
after hysteroscopy was 34.5 weeks (95% CI 30–39) versus 30.1 weeks (95% CI 26–34) after expectant management (log-rank test $P = 0.20$). The hazard ratio for the difference between treatment arms is 1.44 (95% CI 0.82–2.53, $P$-value 0.2). Table 2 shows no statistical differences in the number of polyps and carcinomas found at recurrent bleeding between the women in the hysteroscopy group or the women in the expectant management group.

In 25/51 women (49%) with recurrent bleeding the study protocol was followed and they underwent immediate hysteroscopy. The other 17 women were contacted again after the study was finished and were offered to undergo a hysteroscopy. Finally, four women did not receive further diagnostic workup: three women refused hysteroscopy and one woman had died due to heart failure 2 years after randomisation. Further details on the women with recurrent bleeding are provided in the Supporting information (Table S1 and Table S2).

Figure 1 and Table 3 show the findings of SIS compared with hysteroscopy. In two women SIS was not possible due to pain. SIS showed a polyp in 40 women, no polyp in 33 women and was inconclusive in six women. Among these six women, hysteroscopy showed a benign polyp in five and one of these showed atypical hyperplasia at pathology. In the other 73 women, hysteroscopy failed in one, while a polyp was found in 41/72 (57%) of the women. The sensitivity of SIS to diagnose an endometrial polyp was 93% (95% CI 0.81–0.98) for a specificity of 94% (95% CI 0.78–0.99).18 In two of 87 women who underwent hysteroscopy, the cavity could not be reached by hysteroscopy because of pain and they refused hysteroscopy under general anaesthesia. In these two women a polyp could be seen in the cervical canal. Biopsy showed benign result in both cases.

Out of 85 women who underwent hysteroscopy successfully, 50 were diagnosed with an endometrial polyp (Table 4). In two women, the polyp was not sent for pathology. The pathology results of the other 48 polyps showed hyperplasia with atypia in five women and endometrial cancer in one woman, all six presenting as a focal lesion inside the polyp. Five of the six women in whom the Pipelle® had missed a (pre)malignancy, had SIS and in four women the polyp had been visualised, whereas in one woman the SIS had been inconclusive due to bad visibility. All six women with (pre)malignancies were treated with hysterectomy and bilateral salpingo-oophorectomy. The

<table>
<thead>
<tr>
<th>Table 2. Primary and secondary outcomes</th>
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<tbody>
<tr>
<td><strong>Diagnostic workup (n = 98)</strong></td>
</tr>
<tr>
<td>Findings at randomisation</td>
</tr>
<tr>
<td>Polyps found with hysteroscopy</td>
</tr>
<tr>
<td>Hyperplasia and atypia</td>
</tr>
<tr>
<td>Endometrial cancer</td>
</tr>
<tr>
<td>Recurrent bleeding &lt;1 year</td>
</tr>
<tr>
<td>Polyps found with recurrent bleeding &lt;1 year</td>
</tr>
<tr>
<td>Endometrial cancer in recurrent bleeding &lt;1 year</td>
</tr>
<tr>
<td>Total recurrent bleeding during follow up</td>
</tr>
<tr>
<td>Polyps found with recurrent bleeding</td>
</tr>
<tr>
<td>Endometrial cancer in recurrent bleeding</td>
</tr>
</tbody>
</table>

Data are n (%), unless otherwise indicated.
final pathology result in two of the women with hyperplasia with atypia showed an endometrial cancer adding up to three women having endometrial cancer and three women having hyperplasia with atypia. All three women diagnosed with carcinoma had International Federation of Gynecology and Obstetrics (FIGO) stage I endometroid adenocarcinoma and did not need adjuvant treatment.

Women with a missed diagnosis of a (pre)malignancy after endometrial sampling had a significantly thicker endometrium (12 mm versus 8 mm; \( P = 0.02 \)) and a higher BMI (35.9 versus 27.5; \( P = 0.008 \)) compared with women with a true negative result of endometrial biopsy. The patient characteristics of these women are detailed in the Supporting information (Appendix S1 and Table S3).

During follow up two women in the hysteroscopy group and one woman in the expectant management group were diagnosed with endometrial cancer. Details can be found in the Supporting information (Appendix S1).

Discussion

Main findings

The results from this multicentre, open label, randomised controlled trial suggest that in women with PMB, a thickened endometrium on ultrasound and a benign result on endometrial sampling, there is no strict indication for hysteroscopy and/or polypectomy to reduce the risk of recurrent bleeding within 1 year after randomisation. The rate of (pre)malignancy in women presenting with recurrent bleeding was comparable in both groups. However, we found a (pre)malignancy rate of 6% in women undergoing hysteroscopy, after an initially benign result of endometrial biopsy. Additional testing with hysteroscopy would detect focal endometrial pre-cancers or cancers initially missed by ultrasound combined with endometrial biopsy alone. Alternatively, SIS could be used to select women for hysteroscopic polypectomy because we found that it had a sensitivity of 93% to detect focal pathology.

Strengths and limitations

Important strengths of this study are that loss to follow up was limited both by contacting all women after 1 year and by requesting the pathology results of all included women. By doing this we reduced the percentage of women without any diagnostic workup from 33% to 8%. An important weakness is that the study protocol (and national guideline) had not been followed in all women with recurrent bleeding.8 We found that women and also doctors were sometimes reluctant to perform hysteroscopy and that some general practitioners did not refer women with recurrent bleeding, although this is a recommendation in the national guideline.

A potential limitation of our study is its power. When we started this study we assumed a percentage of recurrent bleeding of 40%, to be reduced to 20% after hysteroscopy, which was based on only three available studies.14,16,17 However, the percentage of recurrent bleeding in the untreated group in this study was only 18%. Another limitation is that we were not able to perform a thorough evaluation of the women in the expectant management group. It is to be expected, due to the nature of randomisation, that a similar number of women would have endometrial (pre)cancer in the expectant management group. However, because this study was not funded, we were not able to call back these women for further evaluation.

Table 3. Diagnostic accuracy of saline infusion sonography (SIS) compared with the reference standard hysteroscopy

<table>
<thead>
<tr>
<th>SIS</th>
<th>Polyp</th>
<th>No polyp</th>
<th>No result</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyp</td>
<td>38</td>
<td>1</td>
<td>1</td>
<td>40</td>
</tr>
<tr>
<td>No polyp</td>
<td>3</td>
<td>30</td>
<td>–</td>
<td>33</td>
</tr>
<tr>
<td>Inconclusive</td>
<td>5</td>
<td>1</td>
<td>–</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>46</td>
<td>32</td>
<td>1</td>
<td>79</td>
</tr>
</tbody>
</table>

Sensitivity for SIS to diagnose an endometrial polyp 93% for a specificity.

Table 4. Pathology results after hysteroscopy (and hysterectomy) in diagnostic workup group (n = 87)

<table>
<thead>
<tr>
<th>Polypectomy (n = 45)</th>
<th>Biopsy (n = 5)</th>
<th>No polyp (n = 35)</th>
<th>Biopsy (n = 6)</th>
<th>Hysteroscopy not possible (n = 2)</th>
<th>Biopsy (n = 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No result</td>
<td>2 (2.3)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Benign</td>
<td>35 (39.1)</td>
<td>5 (5.8)</td>
<td>6 (6.9)</td>
<td>2 (2.3)</td>
<td>–</td>
</tr>
<tr>
<td>Hyperplasia without atypia</td>
<td>2 (2.3)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Hyperplasia with atypia</td>
<td>3 (3.5)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>3 (3.5)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
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</tbody>
</table>

Numbers (percentages) of total hysteroscopies.
Interpretation

To our knowledge this is the first randomised clinical trial that studies the effectiveness of hysteroscopy and polypectomy in women with postmenopausal bleeding. In literature there is a lack of studies on the removal of endometrial polyps, highlighting the need for randomised trials on this subject.²⁰ Our initial question was whether hysteroscopy and polypectomy would reduce the probability of recurrent bleeding. A previous trial, in which we aimed to randomise women for polypectomy or not after a polyp was detected by hysteroscopy, failed as after 26 months only four women were randomised. Apparently, women as well as their doctors did not want to be exposed to no intervention once a polyp was diagnosed.²¹ The present study design was based on the failed previous study.

An unexpected finding of our study is the relatively high rate of (pre)malignancy after a benign endometrial sampling. Two previous meta-analyses showed the sensitivity of Pipelle⁶⁰ to be 97% and 99.6%, respectively.²²,²³ Although both meta-analyses included premenopausal and postmenopausal women, the number of women with postmenopausal bleeding was limited (Clark et al.²² described 314 postmenopausal women, of whom 14 had endometrial cancer and Dijkhuizen et al.²³ described 319 postmenopausal women, of whom 52 had endometrial cancer). All included studies used dilatation and curettage as the reference standard,²⁴–²⁸ and therefore would be expected to miss 50–85% of all focal intracavitary pathology.²⁹,³⁰ At present, hysteroscopy with guided biopsies is the gold standard to diagnose endometrial abnormalities.¹¹

Of major importance is the clinical relevance of the diagnosis of endometrial cancer. Mingels et al. recently performed histological assessment of the whole endometrium in a cohort of 48 postmenopausal women without bleeding who had hysterectomy because of a prolapse.³¹ Four (8.3%) of 48 women had atypical hyperplasia while two women (3%) had a small focal endometrial cancer and in 27% an endometrial polyp was found. This suggests a higher prevalence of endometrial pathology in (asymptomatic) postmenopausal women than assumed.³² This underscores that the relation between intracavitary pathology and postmenopausal bleeding is debatable. Although the women in our study diagnosed with atypical hyperplasia or carcinoma had hysterectomy with bilateral salpingo-oophorectomy, the clinical course of these cancers, when left untreated, is unclear. The fact that overall in this study eight women in the hysteroscopy group and one woman in the expectant group were diagnosed with a (pre)malignancy, suggests that due to randomisation, we missed a few (pre)malignancies in the expectant management group. This strengthens the indication for further diagnostic workup in women with a benign result of endometrial sampling to exclude focal (pre)malignancies, because these can be missed by endometrial sampling.

Conclusion

In women with PMB, a thickened endometrium and benign endometrial sampling, we did not find a significant reduction in recurrent bleeding after operative hysteroscopy. This might be explained due to a lack of power of our study. However, the finding of a 6% prevalence of (pre)malignancy in an endometrial polyp, not diagnosed by blind endometrial sampling, indicates that intracavity diagnostics should become a standard procedure in these women. In alignment with other studies,³³,³⁴ we found SIS to be accurate in the diagnosis of endometrial polyps, indicating that a strategy starting with SIS triaging for hysteroscopy or not would be reasonable although the cost-effectiveness of different testing strategies will depend greatly on the healthcare setting, available resources and clinical expertise.

Disclosure of interests

Full disclosure of interests available to view online as supporting information.

Contribution to authorship

All authors: NH, MCB, SS, MHZ, PG, RC, JP, LV, FD, GH, NRP, SV, MH, PK, JH, BO, MYB, BWM and AT provided the data from the participating centres, provided critical discussion, and contributed in the preparation of the manuscript. BWM, AT, BO and MCB conceived the idea for the study. NH and MCB wrote the manuscript with input from all other co-authors. MHZ and NH had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. SS completed the data and was responsible for follow up. MYB, AT and BWM participated in the analysis, manuscript drafting, and supervision of the work. BWM is the guarantor. NH, MCB, SS, MZ, PG, RC, JP, LV, FD, GH, NRP, SV, MH, PK, JH, BO, MYB, BWM and AT participated in drafting of the article and approved the final version of the article.

Details of ethics approval

The study protocol was approved by the Medical Ethical Committee of the Academic Medical Centre in Amsterdam (26 November 2008, MEC 2008-177) and the boards of directors of each participating centre. All participating women provided written informed consent.

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Acknowledgements
We thank all the women who participated in this study. We also thank all the members of the Dutch Consortium (www.studies-obsgyn.nl) and especially the research nurses, for all their hard work and dedication.

Supporting Information
Additional Supporting Information may be found in the online version of this article:
Table S1. Diagnostic work up in women with recurrent bleeding, during total follow up Numbers (percentages of women with recurrent bleeding).
Table S2. Patient characteristics of women with recurrent bleeding within the first year after randomisation.
Table S3. Patient characteristics of women with a missed diagnosis of atypical hyperplasia or endometrial carcinoma with Pipelle®.
Appendix S1. Women with endometrial carcinoma during follow up.

References
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