



## UvA-DARE (Digital Academic Repository)

### Postmenopausal bleeding : studies on the diagnostic work-up

Timmermans, A.

**Publication date**

2009

**Document Version**

Final published version

[Link to publication](#)

**Citation for published version (APA):**

Timmermans, A. (2009). *Postmenopausal bleeding : studies on the diagnostic work-up*. [Thesis, fully internal, Universiteit van Amsterdam].

**General rights**

It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

**Disclaimer/Complaints regulations**

If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: <https://uba.uva.nl/en/contact>, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.

# 9

## **Should endometrial polyps be removed in women with postmenopausal bleeding? An assessment of study designs and report of a failed trial**

A. Timmermans, S. Veersema, T.C. van Kerkvoorde,  
L.F. van der Voet, B.C. Opmeer, M.Y. Bongers, B.W.J. Mol

## Abstract

*Objective:* To assess whether diagnosis and treatment of endometrial polyps in patients with a first episode of postmenopausal bleeding (PMB) is useful.

*Methods:* A single-blinded randomized controlled trial (ISRCTN73825127) was designed. Patients with PMB were scheduled for TVU to measure endometrial thickness. In case the endometrial thickness was  $> 4$  mm, hysteroscopy was scheduled. If during hysteroscopy a benign endometrial polyp was diagnosed, the patient was asked to participate into this trial. After informed consent patients were randomly allocated either to resection of this polyp in the same session or expectant management. Patients were not informed about the result of the randomization (single-blinding). Recurrence of bleeding was determined during a follow-up of six months. We assumed a reduction in recurrent bleeding of 40% and after power calculation showed that we needed 60 patients, 30 patients per arm.

*Results:* The study suffered from lack of recruitment. After 26 months, only four patients had agreed to participate in the trial. Since both patients and clinicians appeared to be reluctant towards randomization when the polyp was already visualized at hysteroscopy, we decided to stop the trial.

*Conclusion:* In our setting a trial, in which patients with PMB and an endometrial polyp at hysteroscopy were randomized to polypectomy or expectant management, turned out not to be feasible. Alternative trial designs may be more successful to answer the question whether removal of benign endometrial polyps in patients with PMB is effective.

## Introduction

Postmenopausal bleeding (PMB) is often caused by abnormalities of the endometrium, being either benign or malignant. At present, transvaginal ultrasound (TVU) measurement of endometrial thickness is used as a first step in the evaluation of patients with PMB.<sup>1-5</sup> Below a cut-off level of 4 mm endometrial sampling is not recommended whereas above this cut-off level endometrium sampling is warranted to rule out malignancy.<sup>3,6,7</sup> This strategy is cost-effective over strategies involving initial evaluation with test combinations or hysteroscopy alone.<sup>8,9</sup> After malignancy has been ruled out, expectant management can be recommended.<sup>4,5</sup> Alternatively, hysteroscopy or Saline Infusion Sonography (SIS) can be used to assess the uterine cavity for the presence of benign pathology, mostly endometrial polyps.<sup>1,4,5,10,11</sup> The Dutch guideline on PMB advocates expectant management once malignancy has been excluded by TVU (i.e. endometrial thickness  $\leq 4$  mm) or office endometrial sampling (e.g. Pipelle).<sup>4</sup> Adherence to this guideline has been shown to be fairly good: 2/3 of women presenting with PMB are managed conform this guideline.<sup>12</sup> Only in 10% of women presenting with PMB hysteroscopy was performed whereas office endometrial sampling would have been sufficient.<sup>12</sup> This adherence study demonstrates that in the Netherlands expectant management in women with PMB after exclusion of malignancy is at present generally accepted.

Premalignant and malignant disorders of the endometrium are found in about 12% of the patients with PMB.<sup>13,14</sup> In contrast, the prevalence of endometrial polyps in patients with PMB and endometrial thickness of more than 4 mm is estimated to be around 40%.<sup>15,16</sup> Such benign lesions can be diagnosed with hysteroscopy or SIS. Hysteroscopy has the advantage of allowing simultaneous removal of polyps at the time of diagnosis. The question is whether it is effective to advise expectant management after exclusion of endometrial malignancy and withhold uterine cavity evaluation until the bleeding recurs or persists.

One could hypothesize that the removal of endometrial polyps reduces the probability of recurrent bleeding.<sup>17</sup> From that point of view, it would be important to diagnose endometrial polyps, which can then be removed hysteroscopically. At present, high-quality evidence on this subject is lacking, as no studies prospectively compared polypectomy to expectant management. Simple polypectomy is known to lead to subjective improvement in symptoms of bleeding and high satisfaction rates.<sup>17-19</sup> The question that remains to be answered is whether endometrial polyps in patients with PMB should be removed when malignancy has been excluded, in view of recurrent bleeding symptoms. On the one hand, this will depend on the prevalence of benign endometrial polyps in patients with PMB, and whether such polyps can be diagnosed accurately, for example with TVU or with SIS. On the other hand, this depends on whether removal of a benign endometrial polyp improves outcome. To answer this question, we set up a prospective cohort study with an embedded randomized clinical trial comparing

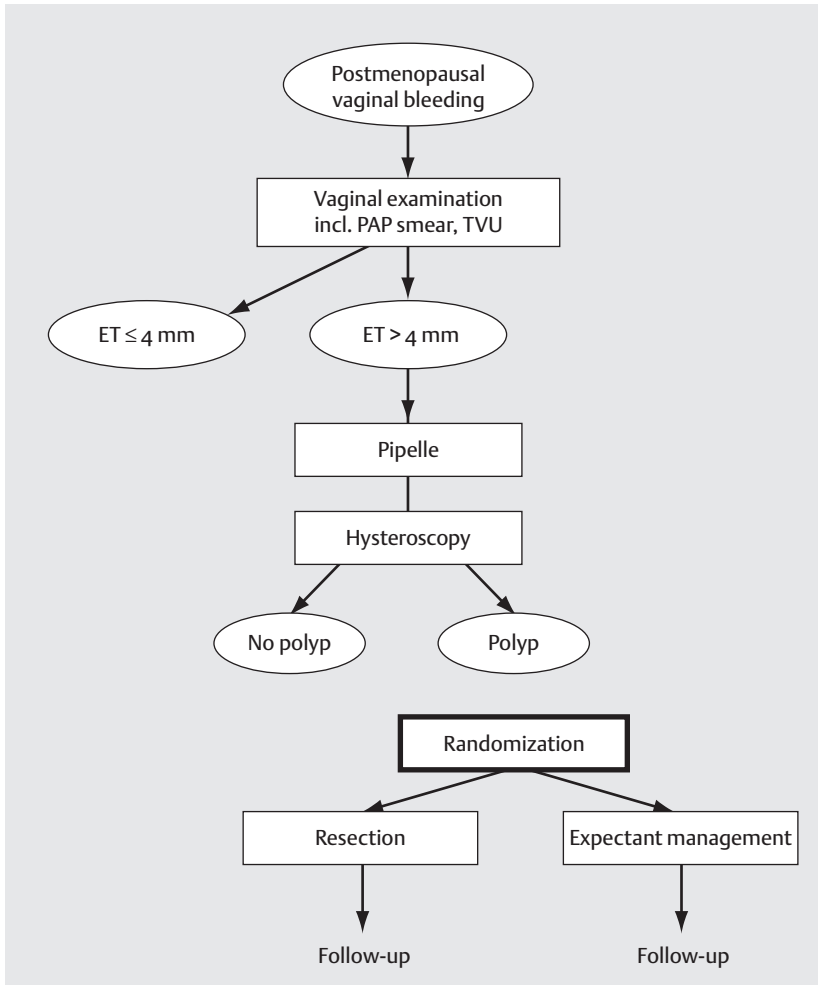
polypectomy and expectant management. The trial was stopped due to lack of recruitment after 26 months. With respect to efficacy of polypectomy in women with abnormal uterine bleeding, randomized clinical trials are advocated.<sup>17</sup> Our trial on this subject failed by lack of recruitment and to avoid other investigators who might encounter the same problems, we report the study design and inclusion until discontinuation, discuss explanatory factors for this failure and propose a possible alternative study design.

## Methods

The study was performed between July 2005 and September 2007. All patients visiting the outpatient clinic with postmenopausal vaginal bleeding were included in a cohort study. A history was taken to determine the nature of the bleeding (i.e. vaginal bleeding and not rectal bleeding) and to establish whether there had been a single bleeding episode, whether the bleeding persisted or whether the bleeding had occurred more than once. Subsequently, a gynaecological examination was performed including a cervical smear and a TVU.

The thickness of the endometrium was measured from a longitudinal sonogram through the thickest area of the endometrium, and from the outermost border of the endometrium on one side to that on the other side. All measurements were done with callipers on a frozen image. The measurements of endometrial thickness included both layers and any expansive process or fluid in the endometrial cavity. The endometrial measurement was classified in full millimetres. In case the endometrial thickness was  $\leq 4$  mm the patient was reassured and discharged in accordance with the Dutch guideline.<sup>4</sup> In case the endometrial thickness was  $> 4$  mm or if the endometrial thickness was not clearly measurable, an office endometrial sampling (e.g. Pipelle biopsy) was taken to ensure histology, and subsequently in all patients a hysteroscopy was scheduled (Figure 1). Office endometrial sampling has been shown to have a sensitivity of 99.6% in excluding endometrial cancer.<sup>20</sup> In those patients in whom office endometrial sampling is unsuccessful or histology shows insufficient material for diagnosis, hysteroscopy is at present advocated. Therefore the trial design reflects current practice with respect to diagnosis of endometrial cancer or hyperplasia.

Figure 1. Flow chart of study design



Patients were informed that at present the Dutch guideline advocates exclusion of malignancy by office endometrial sampling.<sup>4</sup> They were informed that the diagnostic work-up of women with PMB does not in general include a hysteroscopy. Furthermore, they were informed that for this trial a hysteroscopy was performed, which was additional to office endometrial sampling in their diagnostic work-up. Patients were then scheduled for hysteroscopy and received information regarding the possible presence of an endometrial polyp. They received written information about the ongoing trial and were asked to consider participation in case an endometrial polyp was detected at hysteroscopy. Before the hysteroscopy patients were asked whether they would agree to participate in the trial if during hysteroscopy an endometrial

polyp would be diagnosed, a principle for consent was asked prior to the hysteroscopy. At hysteroscopy, the uterine cavity was systematically assessed. A polyp was defined as a benign, localized overgrowth of endometrial tissue covered by epithelium. Patients with a lesion suspect for malignancy were excluded, as were patients using Tamoxifen (Nolvadex®). If, during hysteroscopy a polyp was diagnosed, the patient was again asked to confirm consent for randomization. Patients who confirmed their consent were randomized to immediate resection of the polyp or expectant management (Figure 1). Assisting operating nurse performed the randomization which took place by a computer through block-randomizations, stratified for one or multiple polyps. Patients were not informed about the result of the randomization (single-blinding). Resection of the endometrial polyp was performed in the same session in which the polyp was diagnosed. Resection was performed following standard procedures: smaller polyps (< 5 mm) were resected using endoscopic forceps and/or scissors; larger polyps (> 5 mm) were resected using a monopolar polyp snare.<sup>21</sup> In patients that were randomized for expectant management a sham resection procedure was performed for five minutes.

The primary outcome measure was recurrence of PMB. Patients were asked to record bleeding on a bleeding chart. We planned to assess time to recurrence of PMB using Kaplan-Meier analysis and to test for significance with the log-rank statistic. Beforehand we assumed the recurrence of PMB in case of an endometrial polyp to be 60% after 6 months. In case a polyp was resected, we expected the probability of recurrence of bleeding to be 20%. In view of these assumptions, and using a two-sided test with conventional characteristics (alpha-error 5%, beta-error 20%), we needed 60 patients to be randomized to the two arms of the study (i.e. 30 patients per arm).

The trial was registered in the clinical trial register (ISRCTN73825127) and approved by the institutional review board of the St. Antonius Hospital in Nieuwegein, The Netherlands (registration number TME/C.04.08, date of approval 17<sup>th</sup> December 2004). All gynaecologists working in the outpatient department expressed their willingness to participate in this trial. During several meetings they were informed about the trial and instructed on how to counsel eligible patients at the outpatient clinic. All hysteroscopies were performed by three gynaecologists who were all members of the scientific committee of this trial.

## Results

The trial started on July 15<sup>th</sup> 2005. On September 15<sup>th</sup> 2007 the trial was stopped due to lack of recruitment. From the start onwards, the study suffered from lack of recruitment. In the study period, 361 patients visited the outpatient clinic with PMB (Figure 2). We performed 255 outpatient hysteroscopies in patients with PMB. Two patients met the exclusion criteria and seven patients were not found suitable by their doctor. Of the remaining 246 patients, 105 patients were informed about the trial before hysteroscopy. Hysteroscopy showed an endometrial polyp in 94 patients. Of these, 43 (46%) patients were informed about the trial and 4 out of these 43 (9%) patients gave informed consent (Table 1). These four patients were all randomized to resection. Of the 94 patients with endometrial polyp(s), 67 patients underwent immediate resection of the polyp in the same session, in the remaining 27 the endometrial polyp was not resected in that session.

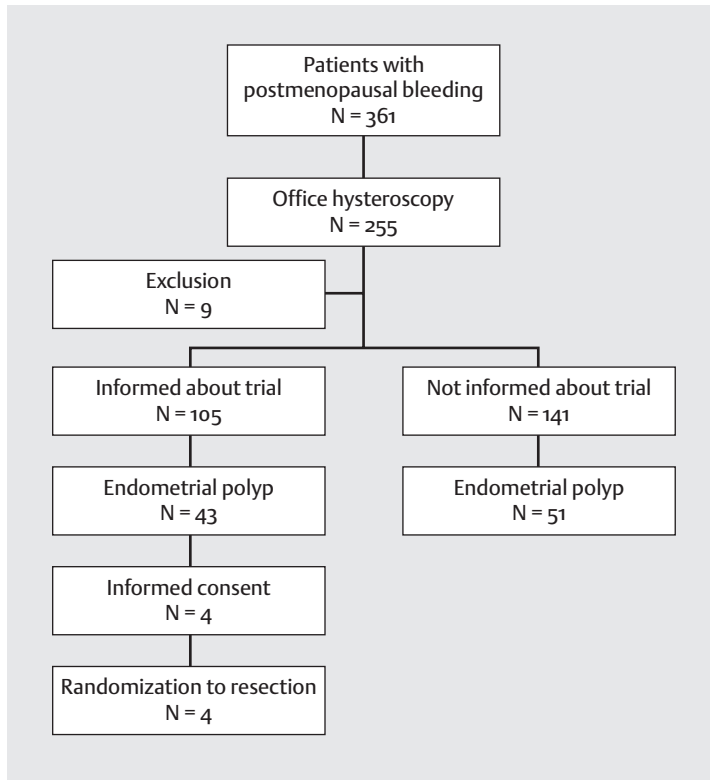
Table 1. Findings at hysteroscopy related to informed consent for randomization

Findings at hysteroscopy	No.	Asked	Informed consent	Randomization
No intracavitary pathology	77	41 (53%)	13 (32%)	NA
Atrophy	18	6 (33%)	1 (17%)	NA
Hypertrophy	4	0 (0%)	0 (0%)	NA
Endometrial polyp	94	43 (46%)	4 (9%)	4
Myoma	12	2 (17%)	2 (100%)	NA
Endometrial carcinoma	14	2 (14%)	1 (50%)	NA
Synecchia	1	1 (100%)	0 (0%)	NA
Procedure stopped	35	10 (29%)	2 (20%)	NA

NA: not applicable



Figure 2. Flow chart of patients eligible for RCT



## Discussion

In this paper, we reported on a randomized trial that was discontinued due to a lack of recruitment. In our study design, we performed a complete diagnostic work-up of patients presenting with PMB including a hysteroscopy. Since a large majority of patients did not give informed consent once the polyp was diagnosed, we could only include four patients in 26 months. Based on this low recruitment we decided to stop the trial after 26 months. With respect to efficacy of polypectomy in women with abnormal uterine bleeding, randomized clinical trials are advocated.<sup>17</sup> Our trial on this subject failed by lack of recruitment and to advise other investigators who might encounter the same problems, we report this trial and explore possible explanatory factors for this.

The low recruitment in this trial was probably related both to the doctors at the outpatient clinic as well as the patients. Several factors can affect the granting of consent to participate

in a clinical trial. Patients can expect some therapeutic benefit from participation in a trial.<sup>22</sup> In our trial, participation led to the possibility of expectant management after randomization, with a possible disadvantage of recurrent bleeding and the burden of an extra hysteroscopy at the end of the follow-up period. Furthermore, placebo-controlled studies are known to induce patient's unwillingness to participate, especially if placebo means "no treatment".<sup>22</sup> Therefore the design of the trial itself incurs less willingness to participate. Extra attention to communication and reduction of uncertainty in these trials is known to lead to improvement of participation.<sup>22</sup> The relationship between the person asking for informed consent and the patient is also a known factor to influence trial participation. Some patients are more willing to participate if their own doctor advises them to participate or if they know to please their doctor.<sup>22</sup> If the informed-consent seeker has moral or ethical objections against the trial or has insufficient knowledge about the trial, this could obstruct recruitment.<sup>22</sup> In our trial there was not one single informed-consent seeker. Although all doctors at the outpatient clinic were informed about the details of the trial so that they could inform patients about the trial, trial specific training was not given. Lack of this training and lack of time at the outpatient department might have led to insufficient communication about the trial and therefore lack of recruitment.

Furthermore, the ethics of clinical research requires equipoise. Equipoise is defined as a state of genuine uncertainty on the part of the clinical investigator regarding the comparative therapeutic merits of each arm in a trial, which entails that the investigator has no "treatment preference".<sup>23</sup> It is possible that individual doctors did have a treatment preference and that their beliefs have led to less recruitment of patients. An alternative concept of equipoise would be "clinical equipoise" in which controversy exists in the clinical community over the preferred treatment.<sup>23</sup> It is known that patients do not fully understand or accept the theoretical concept of equipoise, even when given explicit information about the fact that one treatment is not better than the other.<sup>24</sup> Even if they have some understanding of the concept of equipoise the majority of the patients would ask their doctor about his opinion about the best treatment option.<sup>24</sup>

Finally, a patients' preference study was performed alongside this trial.<sup>25</sup> With respect to the diagnostic work-up of endometrial polyps women were more likely to accept expectant management, but only if the risk of recurrent bleeding did not exceed 25%. This suggests that patients are willing to accept expectant management, however the risk of recurrent bleeding was not known during the trial, since this was subject of the trial. Recent literature has shown that the risk of recurrent bleeding probably lies around this 25%.<sup>26</sup> This implicates that patients might be less willing to participate in this trial with expectant management. Furthermore, the preference study demonstrated that most women deemed office hysteroscopy a rather easy and minimal invasive procedure and are willing to undergo invasive procedures.

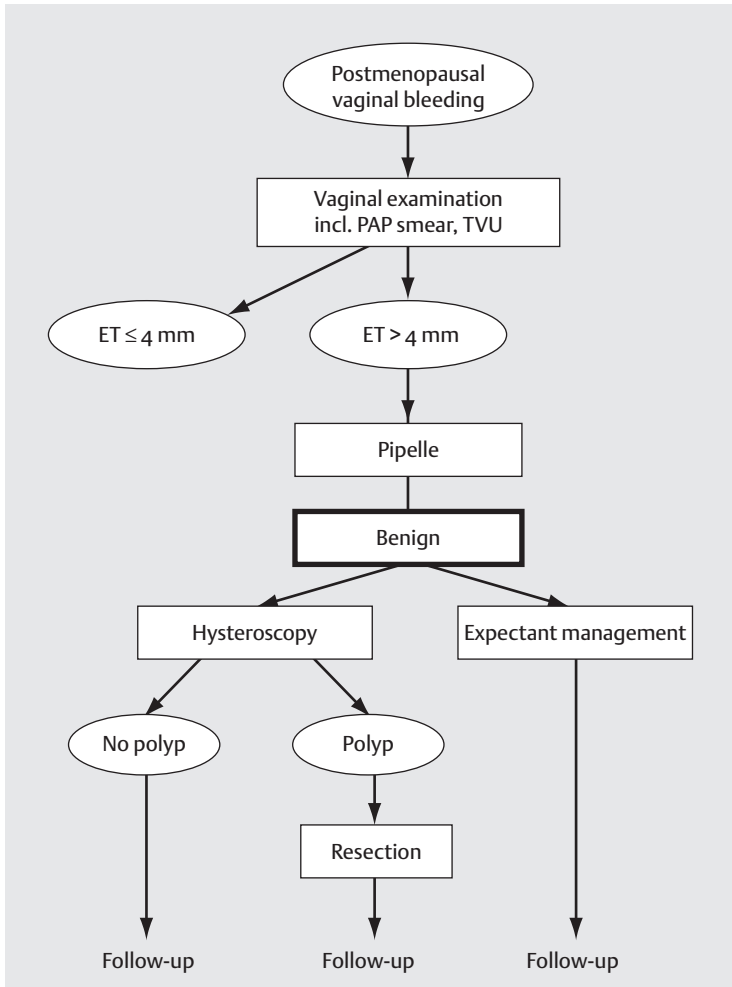
At present no universal algorithm exists in the diagnostic management of women with PMB. Guidelines in different countries advocate evaluation of the uterine cavity and removal of benign endometrial polyps.<sup>1,4,5,10,11</sup> However, high-quality evidence on this subject is lacking.<sup>17</sup> Endometrial polyps are highly prevalent in women with PMB and as such may be responsible for significant morbidity and high resource use.<sup>15,16</sup> Alternatively, we may be subjecting women to unnecessary interventions, risks and wasting valuable health care resources. No studies exist that included a control group when reporting on the efficacy of polypectomy. A systematic review advocated RCT's on this subject.<sup>17</sup> It is therefore important to report this trial, since it's failure due to lack of recruitment adds valuable information to the discussion on efficacy of polypectomy. Although an RCT should be undertaken to fully answer the question if polypectomy is beneficial to patients, the present design does not seem to be feasible. It is important for clinicians to realize this.

The design of RCTs that evaluate diagnostic tests, has been subject to debate.<sup>27</sup> Although trials are often undertaken for issues in therapy and prevention, there is no a-priori reason why they should not be used to resolve difficulties in diagnosis and monitoring. Yet, one should keep in mind how diagnostic tests affect patient outcome. Hysteroscopy itself does not influence patient outcome. A woman suffering from PMB, in whom hysteroscopy does not show any abnormalities, does not have a decreased probability of recurrent bleeding after hysteroscopy. In contrast, the woman in whom a polyp is diagnosed at hysteroscopy might benefit from the hysteroscopy, but only if removal of the polyp reduces the probability of recurrent bleeding. The latter question was addressed in our unsuccessful trial.

We can distinguish two types of trials that evaluate diagnostic tests. We applied a design in which all patients were scheduled for hysteroscopy after which only those patients in whom the hysteroscopy showed a polyp were eligible for the study (Figure 2). In this so-called discordance design, patients with a polyp at hysteroscopy were randomized to either resection or expectant management. The effectiveness of hysteroscopy as a test can then be evaluated by integrating the effectiveness of removing the polyp and data on the prevalence of polyps.

An alternative design is a trial in which patients are allocated to undergo the test or not to undergo the test. In our case this would imply that patients are randomized either to hysteroscopy or to expectant management without hysteroscopy (Figure 3).

Figure 3. Alternative study design



Both designs have their advantages and disadvantages. In the discordance design, the impact of random error on the outcomes in the study stays limited, as patients without abnormalities can cause random error due to coincidental PMB. Second, the number of patients that is asked informed consent for randomization, which is in itself a time consuming and therefore costly procedure, will be limited. This advantage could not be applied in our study as we tried to inform patients prior to the hysteroscopy. Finally, when only the patients with a polyp are randomized, the follow up can be limited to those patients, whereas patients without an abnormality do not need follow-up, also increasing the efficiency of the trial.

An alternative design (Figure 2) that addresses the effectiveness of hysteroscopy and subsequent polypectomy in patients with PMB would be to randomize patients with benign histology results at office endometrial sampling to office hysteroscopy or to expectant management. Patients in whom office endometrial sampling is not successful, or shows insufficient material for diagnosis or patients with malignancy are excluded. In patients scheduled for office hysteroscopy in whom a polyp is visualized, the polyp can be removed during this procedure. The primary outcome measure would be similar to our trial, i.e. the recurrence of PMB. An obvious disadvantage of this study design is that patients can not be blinded for the treatment arm. The analysis would be performed in a similar way, i.e. with the construction of Kaplan-Meier curves demonstrating time to recurrent bleeding. We expect the probability of recurrence of PMB without hysteroscopy to be 36%. A strategy with hysteroscopy is thought to reduce this percentage to 20%.<sup>26</sup> We need 270 patients randomized to two groups of 135 patients to show such a difference.

In summary, the limited evidence that is available suggests that hysteroscopic polypectomy is a technical successful procedure that might improve abnormal uterine bleeding symptoms. However, there is lack of high clinical evidence to reliably inform clinical practice regarding the efficacy of endometrial polyp removal in patients with abnormal bleeding in pre- and postmenopausal patients.<sup>17</sup> We conducted a RCT in which patients with PMB in whom hysteroscopy showed an endometrial polyp, but our effort failed as a result of insufficient recruitment. A RCT on the subject is still warranted and an alternative trial design might be more feasible to fill this gap in evidence.

## References

1. Epstein E. Management of postmenopausal bleeding in Sweden: a need for increased use of hydrososonography and hysteroscopy. *Acta Obstet Gynecol Scand* 2004;83:89-95.
2. Goldstein RB, Bree RL, Benson CB, *et al*. Evaluation of the woman with postmenopausal bleeding: Society of Radiologists in Ultrasound-Sponsored Consensus Conference statement. *J Ultrasound Med* 2001;20:1025-36.
3. Gupta JK, Chien PF, Voit D, Clark TJ, Khan KS. Ultrasonographic endometrial thickness for diagnosing endometrial pathology in women with postmenopausal bleeding: a meta-analysis. *Acta Obstet Gynecol Scand* 2002;81:799-816.
4. NVOG (Dutch Society of Obstetrics and Gynaecology). NVOG-Richtlijn Abnormaal vaginaal bloedverlies in de menopauze [in Dutch]. (NVOG Guideline: Abnormal vaginal bleeding during menopause). 2003.
5. Scottish Intercollegiate Guidelines Network. *Investigation of postmenopausal bleeding*. 1st edn Edinburgh, UK: Scottish Intercollegiate Guidelines Network, Royal College of Physicians 2002; ([www.sign.ac.uk](http://www.sign.ac.uk)).
6. Smith-Bindman R, Kerlikowske K, Feldstein VA, *et al*. Endovaginal ultrasound to exclude endometrial cancer and other endometrial abnormalities. *JAMA* 1998;280:1510-7.
7. Tabor A, Watt HC, Wald NJ. Endometrial thickness as a test for endometrial cancer in women with postmenopausal vaginal bleeding. *Obstet Gynecol* 2002;99:663-70.
8. Clark TJ, Barton PM, Coomarasamy A, Gupta JK, Khan KS. Investigating postmenopausal bleeding for endometrial cancer: cost-effectiveness of initial diagnostic strategies. *BJOG* 2006;113:502-10.
9. Dijkhuizen FP, Mol BW, Brolmann HA, Heintz AP. Cost-effectiveness of the use of transvaginal sonography in the evaluation of postmenopausal bleeding. *Maturitas* 2003;45:275-82.
10. Clark TJ. Outpatient hysteroscopy and ultrasonography in the management of endometrial disease. *Curr Opin Obstet Gynecol* 2004;16:305-11.
11. Epstein E, Ramirez A, Skoog L, Valentin L. Transvaginal sonography, saline contrast sonohysteroscopy and hysteroscopy for the investigation of women with postmenopausal bleeding and endometrium > 5 mm. *Ultrasound Obstet Gynecol* 2001;18:157-62.
12. Werkgroep Dutch Study in Postmenopausal B. [Gynaecological diagnosis of postmenopausal women with abnormal vaginal bleeding: a comparison with the guideline] Diagnostiek door gynaecologen bij vrouwen met abnormaal vaginaal bloedverlies in de menopauze; vergelijking met de richtlijn [in Dutch]. *Ned Tijdschr Geneesk* 2005;149:2676-82.
13. Dijkhuizen FP, Brolmann HA, Potters AE, Bongers MY, Heinz AP. The accuracy of transvaginal ultrasonography in the diagnosis of endometrial abnormalities. *Obstet Gynecol* 1996;87:345-9.
14. Emanuel MH, Verdel MJ, Wamsteker K, Lammes FB. An audit of true prevalence of intrauterine pathology: the hysteroscopic findings, controlled for patient selection in 1,202 patients with abnormal uterine bleeding. *Gynaecol Endosc* 1995;4:237-41.

15. Epstein E, Ramirez A, Skoog L, Valentin L. Dilatation and curettage fails to detect most focal lesions in the uterine cavity in women with postmenopausal bleeding. *Acta Obstet Gynecol Scand* 2001;80:1131-6.
16. Timmermans A, Veersema S. Office hysteroscopy in women with postmenopausal bleeding: see and treat of endometrial polyps using a Duckbill polyp snare. *Gynecol Surg* 2004;1:189-90.
17. Nathani F, Clark TJ. Uterine polypectomy in the management of abnormal uterine bleeding: A systematic review. *J Minim Invasive Gynecol* 2006;13:260-8.
18. Cravello L, D'Ercole C, Azoulay P, Boubli L, Blanc B. [Hysteroscopic treatment of uterine fibromas] Le traitement hysteroscopique des fibromes uterins. *J Gynecol Obstet Biol Reprod (Paris)* 1995;24:374-80.
19. Tjarks M, Van Voorhis BJ. Treatment of endometrial polyps. *Obstet Gynecol* 2000;96:886-9.
20. Dijkhuizen FP, Mol BW, Brolmann HA, Heintz AP. The accuracy of endometrial sampling in the diagnosis of patients with endometrial carcinoma and hyperplasia: a meta-analysis. *Cancer* 2000;89:1765-72.
21. Timmermans A, Veersema S. Ambulatory transcervical resection of polyps with the Duckbill polyp snare: a modality for treatment of endometrial polyps. *J Minim Invasive Gynecol* 2005;12:37-9.
22. Nievaard MA, de Vos R, de Haes JC, Levi M. [Reasons why patients do or do not participate in clinical trials; a systemic review of the literature]  
Redenen voor patienten om (niet) te participeren in klinische trials; een systematisch literatuur-overzicht. *Ned Tijdschr Geneesk* 2004;148:186-90.
23. Freedman B. Equipoise and the ethics of clinical research. *N Engl J Med* 1987;317:141-5.
24. Robinson EJ, Kerr CE, Stevens AJ, *et al.* Lay public's understanding of equipoise and randomisation in randomised controlled trials. *Health Technol Assess* 2005;9:1-192, iii-iv.
25. Timmermans A, Opmeer BC, Veersema S, Mol BW. Patients' preferences in the evaluation of postmenopausal bleeding. *BJOG* 2007;114:1146-9.
26. Timmermans A, van Doorn LC, Opmeer BC, *et al.* Follow-up of women after a first episode of postmenopausal bleeding and endometrial thickness greater than 4 millimeters. *Obstet Gynecol* 2008;111:137-43.
27. Bossuyt PM, Lijmer JG, Mol BW. Randomised comparisons of medical tests: sometimes invalid, not always efficient. *Lancet* 2000;356:1844-7.