Postmenopausal bleeding : studies on the diagnostic work-up

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Follow-up of women after first episode of postmenopausal bleeding and endometrial thickness > 4 mm

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Abstract

Objective: To estimate the incidence of recurrent postmenopausal bleeding (PMB) among women who were diagnosed with an endometrial thickness > 4 mm.
Methods: We designed a prospective cohort study and included consecutive women not using hormone replacement therapy, presenting with a first episode of PMB. We evaluated patients who had an endometrial thickness > 4 mm at transvaginal ultrasound (TVU) and benign endometrial sampling; presence of carcinoma was ruled out by office endometrial sampling, hysteroscopy and/or dilatation and curettage (D&C). Time until recurrent bleeding was measured and diagnosis at recurrent bleeding was recorded.
Results: Among 318 patients who had an endometrial thickness > 4 mm, 222 patients had benign histology results and were available for follow-up. During follow-up 47 (21%) patients had recurrent bleeding with a median time to recurrent bleeding of 49 weeks (interquartile range 18 to 86 weeks). There was no difference with respect to recurrence rate between patients with polyp removal, patients with a normal hysteroscopy, and patients with office endometrial sampling alone at the initial work-up. Two patients were diagnosed with atypical endometrial hyperplasia upon recurrent bleeding.
Conclusion: The recurrence rate of PMB in women with endometrial thickness > 4 mm is 21%. This recurrence is not related to incorporation of hysteroscopy or polyp removal at the initial work-up.

Introduction

Postmenopausal bleeding (PMB) is often caused by abnormalities of the endometrium, being either benign or malignant. Dilatation and curettage (D&C) have been used for the diagnosis of endometrial carcinoma in women with PMB. At present, transvaginal ultrasound (TVU) is used as a first step in the evaluation of women with PMB.[1-5] The probability of malignant pathology is strongly reduced in cases wherein the endometrial thickness is less than 5 mm.[2,6,7] Above this cut-off level, endometrial sampling is warranted to rule out malignancy.[2,6] Office endometrial sampling is a minimally invasive alternative to D&C. It has been shown to be highly accurate in the detection of endometrial carcinoma in women with PMB with a sensitivity of 99.6%.[8]

After malignancy has been ruled out, expectant management can be recommended.[3,4] Alternatively, hysteroscopy or Saline Infusion Sonography (SIS) can be used to assess the uterine cavity for the presence of benign pathology, mostly endometrial polyps.[1,3,4,9,10] Hysteroscopy or SIS can be incorporated in the diagnostic work-up at first episode of bleeding or in case the bleeding persists or recurs.[1,3,4]

Little is known about the recurrence of bleeding in women with PMB and endometrial thickness > 4 mm after initial benign sampling. Feldman *et al.*[11] reported that 33% of the patients with PMB and initial benign sampling underwent another sampling during a follow-up of 2 years, but endometrial thickness was not measured in that study. Gull *et al.*[12] reported a recurrence of bleeding of 40% during ≥ 10 years follow-up in patients with endometrial thickness > 4 mm and initial benign sampling after a first episode of PMB. This issue raises several questions. First, what is the recurrence rate of bleeding after a first episode of PMB, in patients who have an endometrial thickness > 4 mm and benign histology? Second, does the recurrence rate depend on the performance and outcome of the initial diagnostic work-up; that is, do women with a hysteroscopy and/or D&C at the initial work-up of PMB experience less recurrent bleeding than patients with office endometrial sampling only? Third, is malignancy present in women with recurrent bleeding? If the recurrence rate would be low, then a policy with endometrial sampling would be sufficient. If, however, the recurrence rate would be high, or if malignancy would be diagnosed at follow-up, one could advocate that hysteroscopy and/or D&C should be applied immediately. To answer these questions, a prospective cohort study was performed among women not using hormone replacement therapy (HRT) with a first episode of PMB, endometrial thickness > 4 mm and benign histology. We hypothesized that the recurrence rate among women with normal findings at the initial work-up would be low.

Materials and Methods

The study was performed in one university hospital and seven university-affiliated teaching hospitals in the Netherlands. Between January 2002 and June 2003 consecutive patients who presented with a first episode of PMB at the outpatient department were registered prospectively. The study was limited to women not using HRT who had an endometrial thickness > 4 mm as measured with TVU. Data on body mass index (BMI), anticoagulant therapy, comorbidity, endometrial thickness and histology sampling, were recorded.

Patients were evaluated according to the guideline of the Dutch Society of Obstetrics and Gynaecology, which starts the work-up with measurement of endometrial thickness by TVU.[3] The thickness of the endometrium was measured from a longitudinal sonogram through the thickest area of the endometrium, measuring the outermost borders of the endometrium. All measurements were done with callipers on a frozen ultrasound image. Measuring the endometrium in postmenopausal women can be difficult due to an upright position of the uterus, vessel calcifications, and a diffuse endometrial-myometrial border. Cases where it was not possible to measure the endometrial thickness in a reliable way were recorded. When the endometrial layers were separated by intracavitary fluid, both layers were measured and the sum recorded.

In patients with an endometrial thickness > 4 mm and in patients in whom endometrial thickness was not measurable, endometrial sampling was performed either with an office endometrial sampling device, hysteroscopy with guided biopsies, D&C or a combination of these tests. Although the national Dutch guideline states that office endometrial sampling alone is sufficient, individual doctors could decide for subsequent testing by hysteroscopy alone or D&C or hysteroscopy combined with D&C.[3] Hysteroscopy and/or D&C were also performed in case office endometrial sampling showed insufficient material for diagnosis. Hysteroscopy and/or D&C were performed as is customary in the residential hospital, which could be in an inpatient setting under general anaesthesia or in an outpatient setting with local anaesthesia.

Patients whose histology results showed malignancy or atypical hyperplasia, were scheduled for further treatment and not included in the follow-up. In cases of benign histology results expectant management was recommended. The primary endpoint was recurrent bleeding. Each patient was instructed to contact her gynaecologist in case the bleeding recurred. In case of recurrent bleeding, the patient was evaluated according to the protocol of the local hospital. From November 2005 until February 2006 hospital records and patients charts were systematically reviewed to assess recurrence of bleeding. Since patients were instructed to contact the hospital in case of recurrent bleeding, it was assumed that if the patients had not contacted the hospital, they had not experienced recurrent bleeding. Time to recurrence of

bleeding was censored by this date of chart review if the patient had not contacted the hospital. If the patient had undergone a hysterectomy during the follow-up period for other indications (prolapse surgery) or if the patient had deceased, this date was taken for censoring.

Statistical analysis

Time to recurrent bleeding was assessed using Kaplan-Meier analysis. Subsequently, we evaluated whether the performance of a hysteroscopy and/or D&C, and the performance of polypectomy at the initial work-up were associated with recurrence of bleeding. The log-rank statistic was used to test for statistical significance. A p-value of < 0.05 was considered to indicate statistical significance. If differences were found to be proportional over time, Cox regression analysis was performed and a Hazard Rate Ratio (HRR) was calculated. Calculations were performed with SPSS 12.0 (SPSS Inc., Chicago, IL., USA).

Results

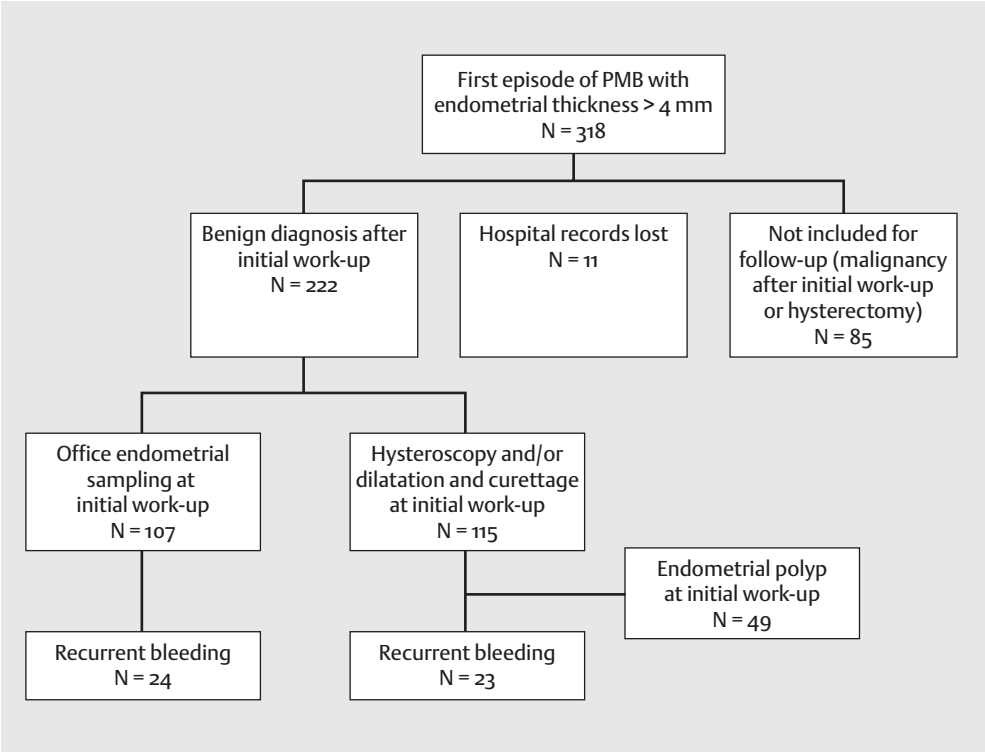
We registered 607 patients with a first episode of PMB, of whom 270 patients had an endometrial thickness > 4 mm and 48 patients had an endometrial thickness that could not be measured. Histology results showed endometrial carcinoma in 60 patients and atypical endometrial hyperplasia in eight patients. Five patients were diagnosed with other malignancies (three breast cancer metastases, one bladder carcinoma and one cervical cancer). Four patients were treated for squamous intraepithelial lesions of the cervix and one patient died shortly after initial work-up from a cause not related to her PMB. Seven patients underwent a hysterectomy for prolapse surgery shortly after their first visit. As a consequence, 233 patients were included in the present study. Of these 233 patients, 11 patients were lost to follow-up, as hospital records were not available or lost; these patients could not be included in the analysis. Patients' characteristics are summarized in Table 1. From the 222 patients in whom follow-up was known, 107 patients had had office sampling during the initial work-up and 115 patients had had a hysteroscopy with or without a D&C. In 49 of the patients undergoing hysteroscopy endometrial polyp(s) had been diagnosed and removed (Figure 1).

Table 1. Patients' characteristics of patients with first episode of postmenopausal bleeding, not on HRT, endometrial thickness > 4 mm or not measurable and benign histology

	All patients (N=222)	OES (N=107)	Hyst/D&C (N=115)	p-value
Mean age (years)	60.9 (±9.7)	59.4 (±8.6)	63.1 (±9.7)	ns
Mean time since menopause (years)	10.8 (±10.6)	9.2 (±9.0)	13.0 (±11.2)	0.01
Mean endometrial thickness (mm)	9.8 (±5.2)	9.6 (±4.6)	11.1 (±6.2)	0.001
Mean BMI (kg/m^2)	29.7 (±6.7)	29.5 (±6.3)	30.4 (±7.1)	ns
Diabetes Mellitus	12.9	11.0	16.9	0.06
Hypertension	26.6	26.2	27.1	ns
Anticoagulants users	15.9	12.4	22.0	0.009

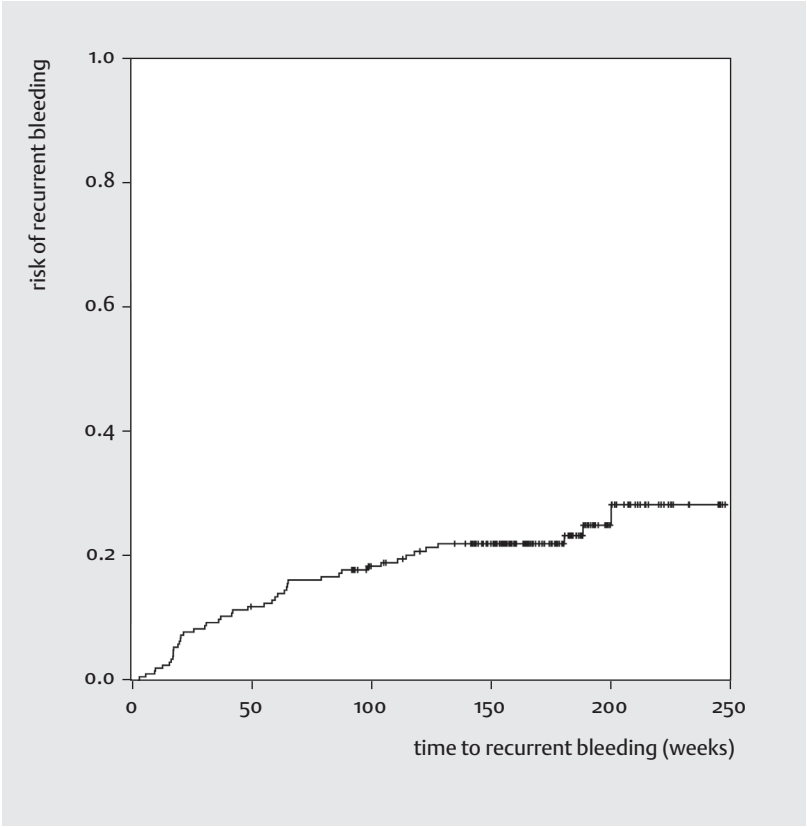
OES, office endometrial sampling; Hyst/D&C, hysteroscopy and/or dilatation and curettage; BMI, body mass index; ns: not significant
Data are mean (±standard deviation) or %

Figure 1. Flow chart of women with postmenopausal bleeding and endometrial thickness > 4 mm



Median duration of follow-up was 176 weeks (interquartile range 156 to 194 weeks, range 50 to 260 weeks). During follow-up 47 of the 222 (21%; 95% CI: 16-27%) patients had recurrent bleeding (Figure 1). Median time until recurrent bleeding was 43 weeks (interquartile range 18 to 86 weeks) (Figure 2).

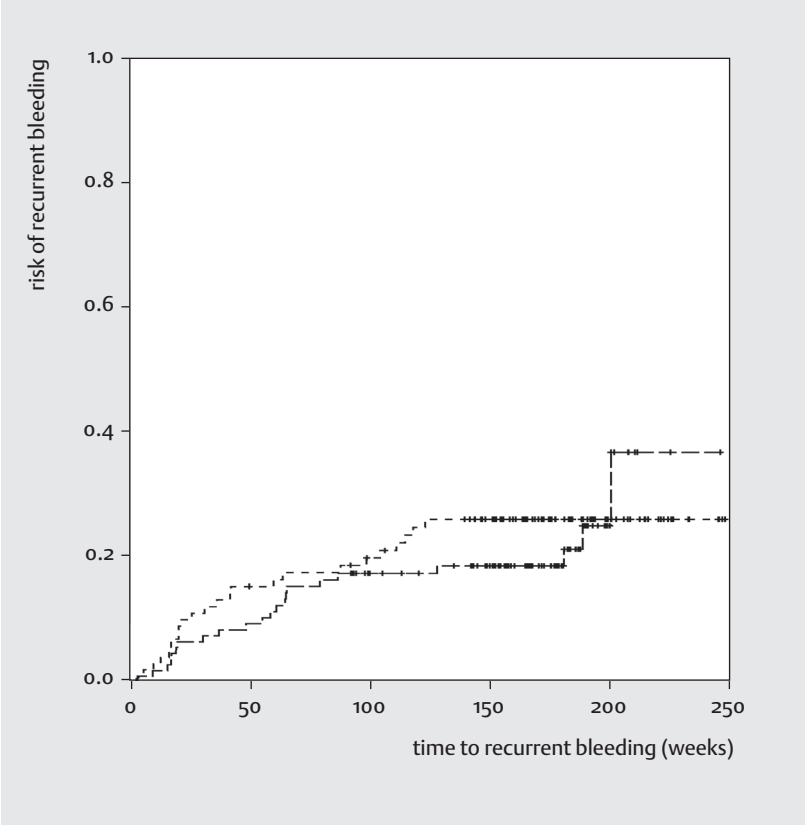
Figure 2. Kaplan-Meier analysis for recurrent postmenopausal bleeding



Solid line, survival function; cross, censored.

There were no statistically significant differences in patient characteristics in the recurrent bleeding group when compared with the group of patients without recurrent bleeding. In the group of patients with hysteroscopy and/or D&C 23 of 115 (20%; 95% CI: 14-28%) patients experienced recurrent bleeding and this was 24 of 107 (22%; 95% CI: 16-30%) in the group of patients undergoing office sampling. There was no statistically significant difference with respect to incidence of recurrent bleeding or time to recurrent bleeding between patients with hysteroscopy and/or D&C at initial work-up or patients without (Figure 3), nor was there a difference between patients in whom an endometrial polyp had been identified and removed at initial

Figure 3. Kaplan-Meier analysis for recurrent postmenopausal bleeding

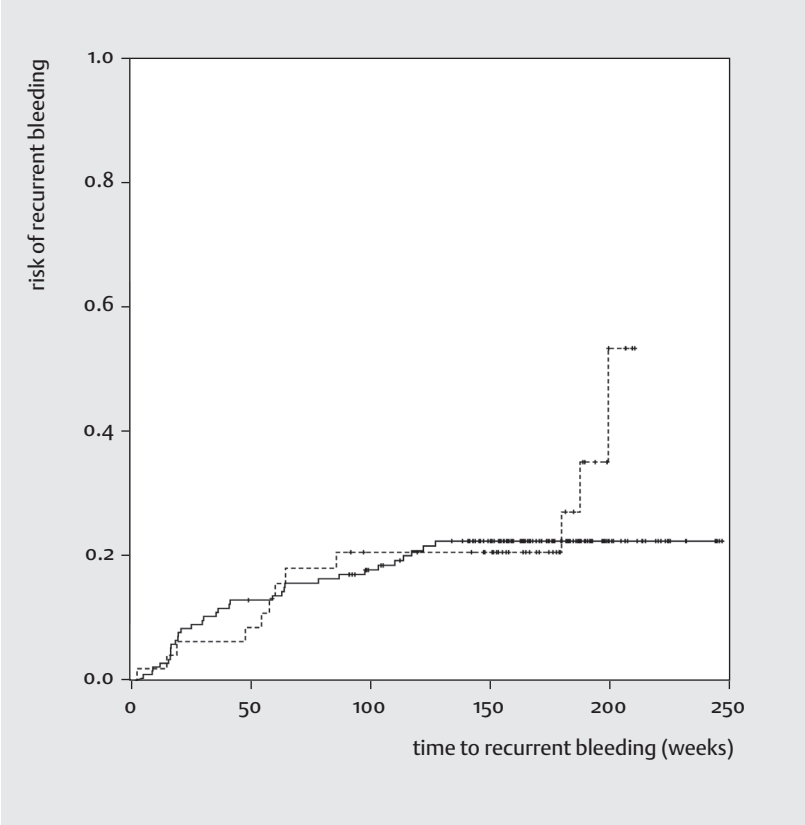


Hysteroscopy or dilatation and curettage at work-up: Solid line, no; dashed line, yes; cross, censored.

work-up (Figure 4) and patients in whom such an endometrial polyp was not diagnosed. There were no statistically significant differences in patient characteristics between patients with hysteroscopy and/or D&C at initial work-up and recurrent bleeding and patients with office endometrial sampling and recurrent bleeding, nor was there such a difference for patients with polyp diagnosis and removal.

The subsequent diagnostic process and findings were evaluated for patients with recurrent bleeding. Patients with a hysteroscopy performed at recurrent bleeding had a shorter time to recurrent bleeding (median 32 weeks interquartile range 18 to 66 weeks) than patients in whom hysteroscopy at recurrence was not performed (median 64 weeks, interquartile range 49 to 180 weeks) (Log rank statistics 8.13; p=0.004). Cox regression analysis showed a Hazard Rate Ratio of 2.8 (95% CI 1.3-5.8).

Figure 4. Kaplan-Meier analysis for recurrent postmenopausal bleeding



Endometrial polyp at initial work-up: Solid line, no; dashed line, yes; cross, censored.

At recurrent bleeding two of 47 (4.3%; 95% CI: 1.2-14%) patients were diagnosed with atypical endometrial hyperplasia. The first patient was a 53-year old multipara with diet-regulated diabetes, BMI of 43, and 1.6 years postmenopausal. Office endometrial sampling at initial bleeding episode had shown benign histology; hysteroscopy was also performed at initial work-up, during which an endometrial polyp had been removed, also with benign histology. Time to recurrent bleeding was 49 weeks, and atypical hyperplasia was diagnosed with office endometrial sampling. The second patient was a 69-year-old multipara with no history of diabetes or hypertension and BMI of 32, and she was 16 years postmenopausal. Hysteroscopy was performed at initial work-up, during which an endometrial polyp was removed, with benign histology. Time to recurrent bleeding was 3.5 years in this patient, and atypical hyperplasia was diagnosed with office endometrial sampling.

In 13 patients an endometrial polyp was diagnosed at recurrent bleeding. Seven of these patients had not had a hysteroscopy at initial work-up, in two patients the hysteroscopy at the initial work-up revealed a normal uterine cavity, and the other four patients had had an endometrial polyp removed at the primary work-up. The 32 other patients with recurrent bleeding had benign office endometrial sampling or no intracavitary pathology at hysteroscopy.

Discussion

This study shows that recurrent bleeding in patients with PMB and endometrial thickness > 4 mm occurred in 21% of the patients. The median time to recurrent bleeding was approximately one year. There was no difference in recurrent bleeding for patients with hysteroscopy and/or D&C at initial work-up and patients with office endometrial sampling, nor was there a difference between patients with an endometrial polyp diagnosed and treated at initial work-up and patients without a polyp. During follow-up, two (4.3%) endometrial pre-malignancies were found among patients with recurrent bleeding.

A potential limitation of this study is the fact that patients were not systematically contacted for follow-up. Although patients were instructed to contact the hospital in case of recurrent bleeding, it might be possible that patients experienced recurrent bleeding and did not contact the hospital or were evaluated in another hospital. Therefore, the true incidence of recurrent bleeding might be underestimated. However, it seems unlikely that patients would not contact the hospital in case of recurrent bleeding, especially since it is known that patients with PMB, would like as much certainty as possible in the diagnostic process.[13] Furthermore, the Dutch guideline for general practitioners advises to refer patients with PMB to a gynaecologist.[14] Therefore, even if the patient would contact her general practitioner instead of her gynaecologist with recurrent bleeding, it would have been highly unlikely if the patient had not been referred to the gynaecologist.

Another potential limitation of this study is the fact that initial endometrial sampling procedure was based on clinical choice of the physician. Patients with higher risk profile or more suspicious ultrasound findings (Table 1) may have tended to be treated initially with hysteroscopy rather than office endometrial sampling. However, at recurrent bleeding, patient characteristics were not statistically significantly different between the hysteroscopy group and the office endometrial sampling group; therefore, we think that this did not influence our results. The found absence of significant differences in the recurrent bleeding could be explained by the limited power of the current study. Post-hoc power analyses indicated, however, that we would have needed a sample sizes of approximately 1,400 women to detect a reduction in the 5-year recurrence rate from 90% to 85% with an α error of 5% and a β error of 20%.

The incidence of recurrent bleeding in our study (21%) is lower than the incidence found in the study of Gull *et al.*[12] (40%).This difference might be explained by the fact that women on HRT were not included in our study whereas they were included in the study by Gull *et al.*[12] where 35% of the women used HRT. An additional explanation for this difference might be the fact that the follow-up in our study was shorter than in the study by Gull *et al.*[12] as in that study patients were followed for more than 10 years. In both our study as well as in the study by Gull *et al.*[12] follow-up took place by reviewing patients' medical records and hospital registries.

In cases where malignant pathology has been excluded by office endometrial sampling without performing hysteroscopy, significant benign pathology, that is endometrial polyps, may have been overlooked. In patients with PMB and an endometrial thickness > 4 mm the prevalence of endometrial polyps has been reported to be 40%.[15,16] Both D&C and office endometrial sampling are known to miss such focal disease.[16,17] Imaging of the distended uterine cavity is required to most accurately diagnose focal lesions such as endometrial polyps and the techniques most often employed are hysteroscopy or SIS.[9] Hysteroscopy has the advantage over SIS of allowing simultaneous removal of polyps at the time of diagnosis, although data regarding the efficacy of polypectomy in treating PMB are scarce.[18]

In our study, there was no difference in recurrent bleeding between patients with a hysteroscopy incorporated in the initial work-up and patients without a hysteroscopy, nor was there a difference between patients with polypectomy at initial work-up and patients without a polypectomy. Therefore, with respect to recurrent bleeding symptoms, it is not beneficial for the patient to include a hysteroscopy in the initial work-up. Patients' preference analysis showed that if the risk of recurrent bleeding due to benign pathology exceeded 25%, the majority of the patients would prefer a hysteroscopy to diagnose and treat such benign pathology.[13] As the risk of recurrent bleeding in this study was approximately 21%, it therefore seems justified to refrain from uterine cavity evaluation at the initial work-up of PMB. However, a randomized controlled trial comparing polypectomy with expectant management in case of PMB and cost-effectiveness analysis would be needed to fully answer this question.[18]

The recurrence rate after a first episode of PMB and endometrial thickness > 4 mm was estimated to be 21% and not related to incorporation of hysteroscopy or endometrial polyp removal at initial work-up. Therefore, the performance of hysteroscopy at the initial work-up can be questioned. Endometrial sampling has to be undertaken if patients experience recurrent bleeding, because two patients were diagnosed with atypical endometrial hyperplasia at time of recurrent bleeding. Further research should focus on the diagnostic work-up of women with recurrent PMB.

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