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What is the recurrence rate of postmenopausal bleeding in women who have a thin endometrium during a first episode of postmenopausal bleeding?

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Abstract

Objective: To determine the incidence and significance of recurrent postmenopausal bleeding (PMB) among women who were diagnosed with an endometrial thickness ≤ 4 mm after a first episode of PMB.

Methods: Consecutive patients not using hormone replacement therapy (HRT) presenting with a first episode of PMB and an endometrial thickness ≤ 4 mm at transvaginal ultrasound (TVU) were managed expectantly. In case of recurrent bleeding the patient was evaluated according to hospital's local policy with TVU, office endometrial sampling, hysteroscopy or dilatation and curettage (D&C) or a combination of these tests. We evaluated the incidence of recurrent bleeding, potential risk factors for recurrent bleeding and the diagnosis that was made after recurrent bleeding.

Results: We registered 607 patients with a first episode of PMB, of whom 249 had an endometrial thickness ≤ 4 mm. Follow-up took place with a median of 174 weeks (range 4 to 250 weeks). During follow-up 25 of the 249 (10%; 95% CI 6.6 to 14%) patients had recurrent bleeding. Median time until recurrence of bleeding was 49 weeks (range 9 to 186 weeks). Two patients with recurrent bleeding turned out to have an endometrial carcinoma (8%; 95% CI 2.2% to 25%) and one patient had a malignant melanoma. Time since menopause, age, body mass index, hypertension, diabetes and anticoagulants were not predictive for recurrent bleeding.

Conclusion: The recurrence rate after a first episode of PMB managed expectantly is low and can not be predicted by patient's characteristics. Patients with recurrent bleeding should be re-evaluated, as they bear a considerable risk of carcinoma.

Introduction

Postmenopausal bleeding (PMB) is frequently caused by abnormalities of the endometrium, either benign or malignant. At present, transvaginal ultrasound (TVU) is used as a first step in the evaluation of women with PMB.¹⁻⁴ The probability of malignancy is reduced to < 1% in cases of an endometrial thickness ≤ 4 mm.^{2,5,6} Below this cut-off level most guidelines do not recommend endometrial sampling, whereas above this cut-off level endometrial sampling is warranted to rule out malignancy.^{1,3,4,7,8} Cost-effectiveness analyses show a diagnostic strategy starting with TVU followed by endometrial sampling in case of a thickened endometrium (> 4 mm) was the most cost-effective strategy.^{9,10} An important assumption in such a strategy is that the recurrence rate of PMB in women without malignancy is low, whereas women with a malignancy who are initially missed (false negatives) experience recurrent or persistent bleeding.

Few studies address the long-term outcome of conservative management of women with a first episode of PMB and endometrial thickness ≤ 4 mm. A randomized trial in which women with an endometrial thickness < 5 mm were either allocated to dilatation and curettage (D&C) or expectant management, showed that the recurrence rate of bleeding was 21% after D&C versus 33% after expectant management during a 12-month follow-up period ($p = 0.17$).¹¹ In another study, the recurrence rate of bleeding after a first episode endometrial thickness ≤ 4.4 mm was reported to be 13% after a median time of 13 months.¹² Gull *et al.*¹³ reported a recurrence rate of 6% after one year follow-up and 17% when these patients were followed ≥ 10 years.⁸ None of these studies diagnosed endometrial carcinoma during follow-up, although in the second study by Gull *et al.*⁸, two cases of atypical hyperplasia were diagnosed. None of these studies examined risk factors for recurrent bleeding.^{8,13}

With respect to the incidence and significance of PMB in women with an initial endometrial thickness ≤ 4 mm, several issues are at stake. If the recurrence rate was low, then a policy with TVU would be sufficient. If, however, the recurrence rate was high or if malignancy was diagnosed at follow-up, one could advocate that endometrial sampling should be applied immediately. Furthermore, if it was possible to know what patients would experience recurrent bleeding, one could apply a policy based on individual patient characteristics. We hypothesized that the recurrence rate among women with normal findings at the initial work-up would be low. To answer these questions, we performed a prospective cohort study among women with a first episode of PMB and endometrial thickness ≤ 4 mm.

Materials and Methods

The study was performed in a university hospital and seven university-affiliated teaching hospitals in The Netherlands (listed at the end of this article). Between January 2002 and June 2003 consecutive patients who presented with PMB were registered prospectively. During this study period all women with PMB were registered prospectively. The study was limited to patients with a first episode of PMB, not using hormone replacement therapy (HRT) and who had an endometrial thickness ≤ 4 mm as measured with TVU. We recorded data regarding endometrial thickness, body mass index (BMI), relevant medical history, anticoagulant therapy and co-morbidity.

Patients were evaluated according to the guideline of the Dutch Society for Obstetrics and Gynaecology, which recommends starting the work-up with TVU measurement of endometrial thickness.³ The endometrial thickness was measured from a longitudinal sonogram through the thickest area of the endometrium, and from the outermost borders of the endometrium. All measurements were done with callipers on a frozen ultrasound image. In case it was not possible to measure the endometrial thickness in a reliable way, this was recorded. When the endometrial layers were separated by intracavitary fluid, each layer was measured and the sum recorded.

In case of endometrial thickness > 4 mm or endometrial thickness not measurable, endometrial sampling was performed; these groups were not included in this study. In case of an endometrial thickness ≤ 4 mm expectant management was recommended. Some gynaecologists performed endometrial sampling either with an office endometrial sampling device or with hysteroscopy and/or D&C, despite an endometrial thickness ≤ 4 mm.

Follow-up started on completion of the initial work-up. If endometrial sampling was performed, only patients with benign histology were included for follow-up. Patient were instructed to contact their gynaecologist again in case the bleeding recurred. The primary endpoints were incidence of recurrent bleeding and time to recurrent bleeding.

In case of recurrent bleeding, the patient was evaluated according to the protocol of the local hospital. This work-up contained different combinations of test (TVU alone, office endometrial sampling, hysteroscopy, D&C). We registered both the type of test(s) used at recurrent bleeding as well as the final diagnosis. From November 2005 until February 2006 hospital records and patients charts were systematically reviewed to assess if the patient had returned to the hospital with recurrent bleeding. Since patients were instructed to contact the hospital in case of recurrent bleeding, we 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

We used Kaplan-Meier analysis to assess time to recurrent bleeding. The prognostic value of potential indicators (age, BMI, anticoagulants, co-morbidity and time since menopause) was evaluated using log-rank statistics. A p-value of 0.05 was considered to indicate statistical significance. If log-rank statistics indicated statistical significance and the risk appeared to be proportionally constant over time, Cox regression analysis was performed and Hazard Rate Ratio's (HRR) were calculated. The diagnosis at recurrent bleeding was also evaluated.

Patients in whom an office endometrial sampling, hysteroscopy and/or D&C had been performed at initial work-up were compared with patients who had undergone only TVU at initial work-up. Calculations were performed with SPSS 12.0 (SPSS Inc., Chicago, IL., USA).

Table 1. Patients' characteristics

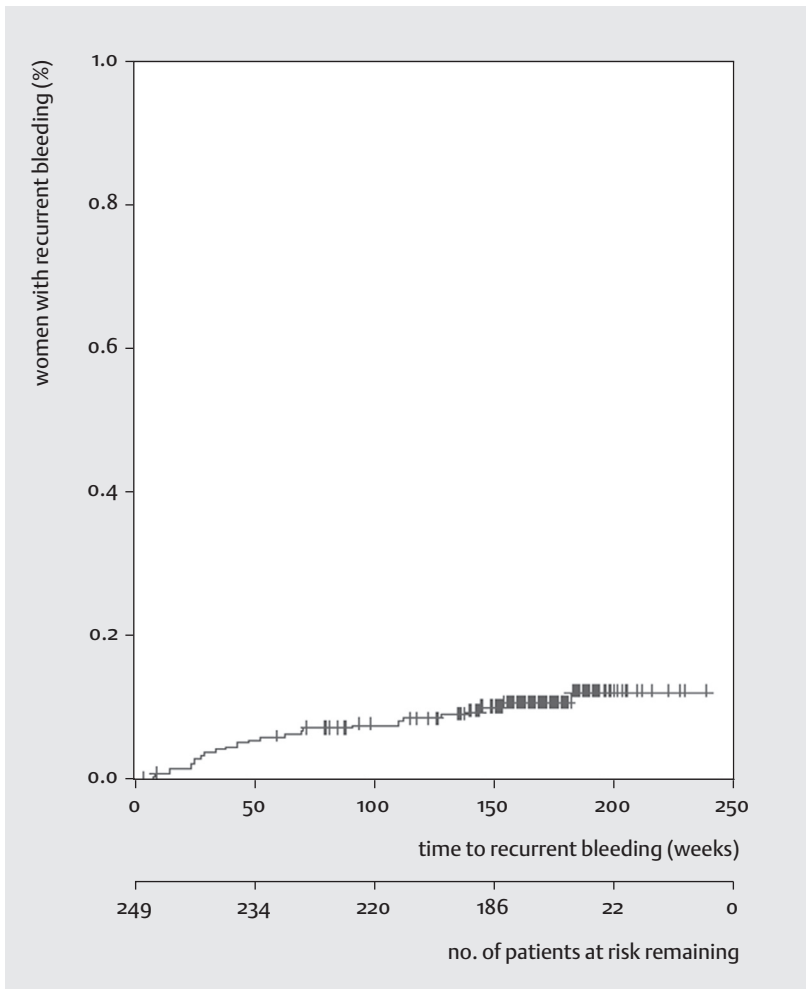
	All patients	TVU alone (N=181)	TVU and OES (N=47)	TVU and Hyst/ D&C (N=21)
Mean age (years) (SD)	61.8 (9.6)	61.7 (9.7)	61.4 (9.8)	62.2 (8.8)
Time since menopause (years) (SD)	11.4 (9.9)	11.6 (10.5)	10.7 (8.8)	11.7 (7.8)
Mean endometrial thickness (mm) (SD)	2.4 (0.96)	2.2 (0.9)	2.8 (1.0)	2.8 (1.1)
Mean BMI (kg/m ²) (SD)	26.5 (5.0)	26.3 (5.1)	27.5 (5.0)	27.6 (5.0)
Diabetes Mellitus (%)	8.0	7.7	8.5	9.5
Hypertension (%)	20.8	16.6	34.0	28.5
Anticoagulants users (%)	12.0	11.6	14.9	14.0

TVU, transvaginal ultrasound; OES, office endometrial sampling; Hyst/D&C, hysteroscopy and/or dilatation and curettage

Results

We registered 607 patients with a first episode of PMB, of whom 249 patients had an endometrial thickness ≤ 4 mm at TVU. The characteristics of the patients are presented in Table 1. In 181 (73%) patients only TVU was performed. At the initial work-up 52 (21%) patients had an office endometrial sampling. Five of these patients also underwent a hysteroscopy and/or D&C, whereas 16 other patients had a hysteroscopy and/or D&C but not an office endometrial sampling performed at their initial work-up. There were no malignancies diagnosed in the patients with endometrial sampling and/or hysteroscopy/D&C.

Figure 1. Kaplan-Meier curve showing time until recurrent bleeding



Median duration of follow-up was 174 weeks (range: 4 to 250 weeks, interquartile range: 157 to 188 weeks). During follow-up, 25 (10%; 95% CI 6.6 to 14%) patients contacted the clinic with recurrent bleeding. Median time until recurrence of bleeding was 49 weeks (interquartile range: 26 to 112 weeks) (Figure 1). None of the patient characteristics was associated with incidence of recurrent bleeding or with time to recurrent bleeding (Table 2). There was no statistically significant difference with respect to incidence of recurrent bleeding or time to recurrence between patients with TVU alone at initial work-up (15/181) and patients in whom an office endometrial sampling had been performed at the initial work-up (5/47) (log rank statistics 0.19, $p=0.66$). However, there was a statistically significant difference in recurrent bleeding between patients with hysteroscopy and/or D&C at initial work-up (5/21) and patients without hysteroscopy and/or D&C (20/208) ($p=0.04$). Therefore, Cox regression analysis was performed and a HRR was calculated as 2.8 (95% CI 1.05 to 7.5).

Table 2. Log rank statistics for time to recurrent bleeding for potential indicators of recurrent bleeding

Patient's characteristic	Log rank	p-value
BMI > 25	0.10	0.75
Age > 55	0.00	0.98
Hypertension	0.31	0.58
Diabetes	0.00	0.99
Anticoagulants use	0.41	0.52
TMP < 3 years [‡]	0.60	0.81
TMP > 7 years [†]	0.04	0.85
TMP > 15 years [*]	0.00	0.99

TMP, time since menopause

[‡] Astrup¹⁴: higher risk of bleeding first 3 years after menopause

[†] Van Doorn¹⁵: higher risk of cancer more than 7 years after menopause

^{*} Bruchim¹⁶: higher risk of cancer more than 15 years after menopause

Table 3 shows the findings at the time of recurrent bleeding. In two patients (8%; 95% CI 2.2 to 25%) with recurrent bleeding an endometrial carcinoma was diagnosed, and in a third patient a malignant melanoma of the vagina was found. One patient with subsequent endometrial cancer had only undergone TVU at the initial work-up, whereas in the other patient a representative office endometrial sample was obtained as well, showing benign histology. Time to recurrent bleeding in these two patients with endometrial carcinoma was 44 weeks and 16 weeks respectively.

Table 3. Findings at recurrent bleeding in 25 women with initially an endometrial thickness ≤ 4 mm

Findings	No. (%)
Endometrial thickness ≤ 4 mm	7 (29)
Benign endometrium	10 (38)
Endometrial carcinoma	2 (8.3)
Malignant melanoma	1 (4.1)
Other	5 (21)
Total	25

Discussion

This study shows that recurrent bleeding in patients with PMB and endometrial thickness ≤ 4 mm occurs in only 10% of the patients. The median time to recurrent bleeding was approximately one year. We could not identify patient factors associated with recurrent bleeding, nor did we observe a difference in occurrence of recurrent bleeding for patients with TVU alone at initial work-up and patients with TVU and subsequent office endometrial sampling. However, patients with hysteroscopy and/or D&C at initial work-up were at higher risk for recurrent bleeding than patients without.

A potential limitation of this study is that patients were not systematically contacted for follow-up. Although patients were clearly instructed to contact the hospital in case of recurrent bleeding, it might be possible that patients experienced recurrent bleeding but did not contact the hospital or were evaluated in another hospital. Therefore the true incidence of recurrent bleeding might be underestimated. However, we feel that our follow-up was reliable, as patients were clearly instructed.

The incidence of recurrent bleeding in our study is in accordance with the incidence of 6% to 33% previously reported.^{8,11-13} Follow-up in these studies also took place by reviewing medical records, hospital registries and regional registries. Differences in study design, duration of follow-up, mean age, and frequency of HRT use might explain the variations in recurrent bleeding between these studies. In our study patients using HRT were excluded, whereas in the other studies HRT use was used by 35% to 68% of the patients.^{8,11,13} Furthermore, follow-up in the two largest studies took place for a minimum of 2.9 years to over 10 years, compared to minimum follow-up of 4 weeks in our study.^{8,12}

We found no difference in recurrence rates between patients who had undergone TVU alone and patients who had both TVU and office endometrial sampling at the initial work-up. Epstein *et al.*¹¹ reported a lower recurrent bleeding rate in a group initially managed with D&C when compared to a group managed with TVU alone. However, the difference observed was not statistically significant, possibly explained by a lack of power of that study. In contrast, in our study the group of patients with hysteroscopy and/or D&C at initial work-up had more frequent recurrent bleeding than the group of patients without such tests. This would argue for restrictive diagnostic management of women presenting with PMB and thin endometrium.

In summary, the recurrence rate of PMB after an initial reassuring TVU was low and not related to patients' characteristics. In our opinion, this is supportive for the use of TVU as a first test in the work-up for PMB. However, when recurrent bleeding occurred, a substantial number of patients was found to have malignancy. Therefore, patients managed expectantly should be instructed to contact their gynaecologist at recurrent bleeding and repeated gynaecological examination and subsequent endometrial sampling is warranted at that time.

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