Received: 23 August 2023 | Revised: 8 April 2024 | Accepted: 10 April 2024

DOI: 10.1111/aogs.14851

AOGS Acta Obstetricia et Gynecologica Scandinavica

ORIGINAL RESEARCH ARTICLE

Recurrent postmenopausal bleeding: Pathological findings and predictive factors. A multicenter, prospective, observational study

Laura D. P. R. van Maldegem[1] | Johanna A. van der Zande[1] | Lucy A. van Werkhoven[1] | Patricia C. Ewing-Graham[2] | Bernadette A. M. Heemskerk-Gerritsen[3] | Helena C. van Doorn[1]

[1]Department of Gynecologic Oncology, Erasmus MC Cancer Institute, University Medical Center Rotterdam, Rotterdam, the Netherlands

[2]Department of Pathology, Erasmus MC Cancer Institute, University Medical Center Rotterdam, Rotterdam, the Netherlands

[3]Department of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, the Netherlands

Correspondence
Laura D. P. R. van Maldegem, Erasmus MC Cancer Institute, University Medical Center Rotterdam, Dr. Molewaterplein 40, 3015 GD, Rotterdam, The Netherlands.
Email: lauravanmaldegem@live.nl

Abstract

Introduction: Recurrent postmenopausal bleeding (PMB) occurs in 6%–25% of postmenopausal women who have experienced a previous episode of PMB. The question of whether recurrent PMB leads to a higher risk of endometrial cancer (EC) in comparison to a single episode of PMB is, however, controversial. Furthermore, little is known about predictive factors for recurrent PMB.

Material and Methods: A multicenter prospective cohort study was conducted over a 5-year period in four hospitals in the Netherlands. Women with PMB undergoing endometrial sampling and aged 40 years and older were included. Occurrence of recurrent PMB was retrospectively determined. Primary outcomes included (1) the incidence of recurrent PMB and (2) differences in pathological findings between patients with a single episode vs recurrent PMB. Secondary outcomes included (1) the association between diagnosis of benign polyps at first PMB and pathological findings at recurrent PMB and (2) factors predictive for recurrent PMB.

Results: A total of 437 women with PMB were included, of whom 360 were at risk of recurrent PMB. With a median follow-up of 61 months (IQR (Interquartile range) 44–73), 26.4% experienced recurrent PMB. Patients with recurrent PMB were more often diagnosed with benign polyps (34.7% vs. 25.1%, *p*-value 0.015) and less frequently with a malignancy (5.3% vs. 17.8%, *p*-value 0.015), compared to patients with a single episode of PMB. Benign polyps at initial PMB were not associated with a (pre)malignancy at recurrence (OR 4.16, 95% CI 0.75–23.03). Predictive factors for recurrent PMB included use of hormone replacement therapy (HRT) (OR 3.32, 95% CI 1.64–6.72), and benign polyps at initial PMB (OR 1.80, 95% CI 1.07–3.04).

Conclusions: Recurrent PMB is common in women with a previous episode of PMB. Compared to patients with a single episode of PMB, patients with recurrent PMB and

Abbreviations: BMI, body mass index; CI, confidence interval; EC, endometrial cancer; EIN, endometrial intraepithelial neoplasia; HRT, hormone replacement therapy; OR, odds ratio; PMB, postmenopausal bleeding.

benign histological outcomes at accurate workup during their first episode were less often diagnosed with malignancies and more frequently with benign polyps. Benign polyps at first PMB are predictive for recurrent PMB, but not for a higher risk of (pre)malignancy.

KEYWORDS
endometrial cancer, endometrial neoplasms, endometrial polyp, postmenopausal bleeding, recurrence, recurrent postmenopausal bleeding

1 | INTRODUCTION

Postmenopausal bleeding (PMB) occurs in approximately 10% of postmenopausal women,[1] and is often attributable to either benign or malignant endometrial abnormalities.[2] The risk of endometrial cancer (EC) causing PMB varies between 1% for women aged ≤50 years, and up to 24% for those aged ≥80 years, while EC presents with PMB as a first sign in 90% of cases.[2,3] EC is the most common gynecological cancer in developed countries, and both incidence and mortality are rising worldwide.[4] PMB is therefore a symptom that should be taken seriously and requires an accurate diagnostic workup.

Recurrent PMB occurs in 6%–25% of women who have had one previous episode of PMB, with a median time since the first PMB of 1–2 years.[5–9] Despite the relatively common occurrence of PMB, a widely accepted definition and guideline are lacking. Controversy also exists as to whether a recurrent episode of PMB leads to a higher risk of EC in comparison with a single presentation of PMB. A recent prospective cohort study found that patients with recurrent PMB were at greater risk for endometrial intraepithelial neoplasia (EIN) and EC compared to those with a single episode.[10] However, larger prospective studies have reported that recurrent PMB is associated with a reduced risk of EC or hyperplasia with atypia, but a significantly higher risk of benign endometrial polyps in comparison to patients with a single episode of bleeding.[9,11] Furthermore, little is known about predictive factors for recurrent PMB. One study examined the association between predictive factors—including body mass index (BMI), age, hypertension, anticoagulant use, and time since menopause till the first PMB—but no predictive factors were identified.[5]

The aims of this prospective cohort study, which involved patients with PMB who underwent endometrial sampling, were to evaluate a possible association of recurrent PMB with a higher risk of EC and to identify factors associated with recurrent PMB.

Key message

Recurrent postmenopausal bleeding (PMB) occurs in about a quarter of women with a history of PMB with benign histological outcomes. Although the malignancy risk is lower in patients with recurrent compared to a single episode of PMB, it is not negligible.

2 | MATERIAL AND METHODS

The present study is a subgroup analysis of a larger observational multicenter prospective cohort study conducted in one academic and three non-academic hospitals in the Netherlands (the EIN study). The study included all women aged ≥40 years visiting these hospitals with any indication for endometrial sampling during the study period. For the purposes of the current analysis, we excluded non-postmenopausal patients, patients with any other indication for sampling than PMB, and patients presenting with a recurrent episode at inclusion.

Patients were enrolled from January 2016 until January 2021, and written consent was obtained. All patients were asked for permission to request missing data from their general practitioner. Patients were instructed to return to the clinic if they experienced a recurrent episode of bleeding. Patients who did not contact the hospital were considered non-recurrent. Patients were followed up at least 1 year after inclusion. Endometrial sampling was conducted by the attending gynecologist or resident, and data were retrospectively gathered on the occurrence of recurrent PMB, the diagnostic process, and outcome.

PMB was defined as an episode of bleeding occurring >12 months after the last menstrual period. Recurrent PMB was defined as any bleeding occurring 6 weeks or more after a previously investigated episode of PMB. Time till recurrent bleeding was measured from the day of first presentation with PMB to the day of presentation with recurrent PMB at the outpatient clinic.

Patients presenting with PMB were examined according to the Dutch guideline, which comprised gynecological examination, cervix cytology, and a transvaginal ultrasound. In patients with an endometrial thickness (ET) ≥4 mm or when the ET could not be measured properly, a Pipelle endometrial sample was suggested. When an intracavitary abnormality was suspected, saline infusion sonohysterography (SIS) or hysteroscopy was performed.[12] Pathological findings were based on endometrial sampling, hysteroscopy (with biopsy) or uterus extirpation. Cases and biopsies were assessed by the attending pathologist and classified as benign other than polyps, benign polyps, EIN, or malignant. Cases were diagnosed as benign if there was (1) an insufficient endometrial sample without additional examination and/or without recurrent bleeding during follow-up, (2) recurrent PMB and a regular and thin (<4 mm) endometrium without fluid and therefore no hysteroscopy or endometrial sampling was performed, or (3) a biopsy during hysteroscopy did not succeed due to atrophy. Cases were classified as benign polyps when pathologically proved, but also when polyps were seen during hysteroscopy without sampling.

Primary outcomes were (1) the incidence of recurrent PMB, and (2) pathological findings for single vs. recurrent episodes of PMB. Secondary outcomes included (1) the relationship between a diagnosis of benign polyps at first PMB and pathologic findings at recurrent PMB, (2) factors predictive for a recurrent episode of PMB, and (3) factors predictive for EC or EIN among women with one or more episodes of PMB.

2.1 | Statistical analyses

Categorical data are presented as frequencies and percentages, and continuous data are presented as medians with interquartile ranges. Differences between groups were tested using the Chi-square test or Fisher's exact test for dichotomous outcomes. Normally distributed continuous data were analyzed using an unpaired T-test, whereas a Mann–Whitney U test was applied in the case of skewed distribution. Multiple imputations were used for missing data, including time since menopause until first PMB, BMI, ET, and parity. Univariable and multivariable logistic regressions were performed to determine possible risk factors associated with recurrent PMB and EC, and the association between the pathological outcome at patients' first and recurrent episodes of PMB. Continuous variables, including time since menopause, were dichotomized for multivariable regressions in menopausal status of <3 years or >3 years and <1 year or >1 year. Regression analysis was also conducted for BMI categorized as <25, BMI 25–30 and BMI >30. Variables with a p-value of <0.1 in univariable analyses or risk factors based on previous studies were used in multivariable analyses. The Kaplan–Meier method was used to graphically present the time to recurrent bleeding. Censoring moments were end of follow-up, hysterectomy and death. Probability (p) values <0.05 were considered statistically significant. Statistical analyses were performed with IBM SPSS Statistics, version 28.

3 | RESULTS

Between January 2016 and January 2021, 510 postmenopausal women were enrolled in the study. Patients already presenting with a recurrent episode of PMB ($n=30$), as well as patients with any indication for endometrial sampling other than PMB ($n=43$) were excluded, leaving 437 women who underwent endometrial sampling due to a first episode of PMB (Figure 1). Women who were

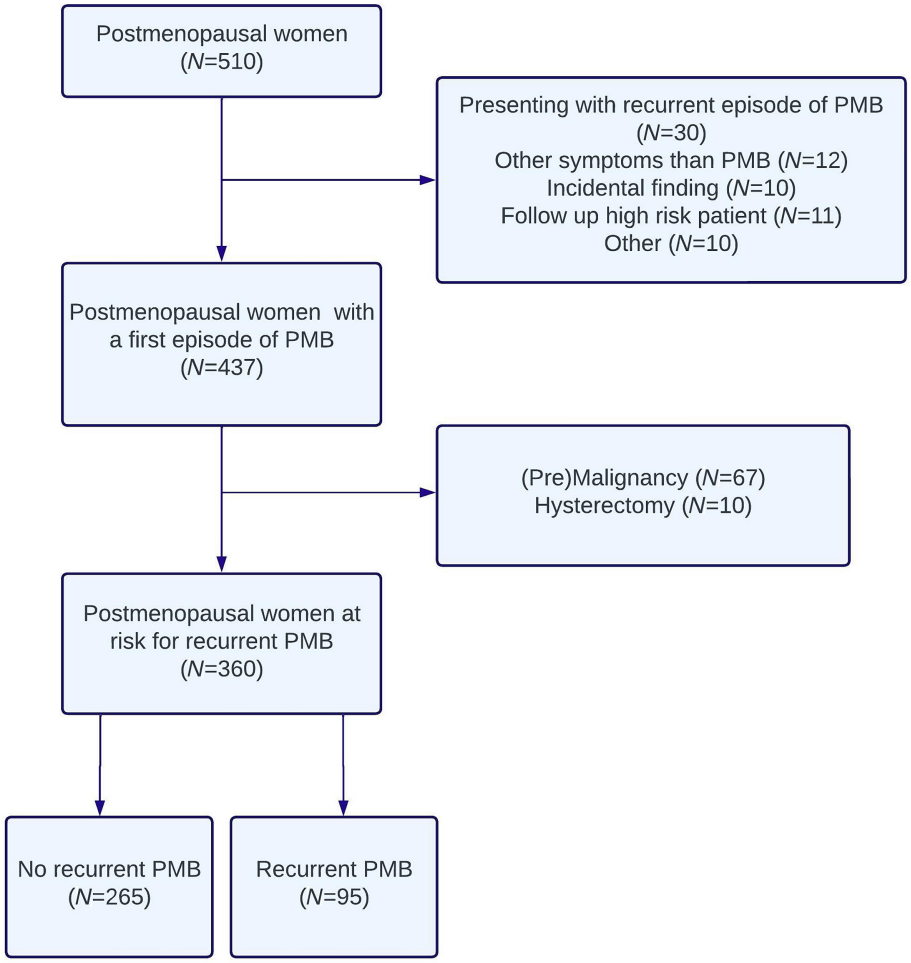

FIGURE 1 Flow diagram of patient recruitment.

TABLE 1 Baseline characteristics at moment of first PMB.

Variables	Total group with PMB (*N* = 437)[a]	Group at risk of recurrent PMB (*N* = 360)[b]		*p*-value*
		No recurrent PMB (*N* = 265)	Recurrent PMB (*N* = 95)[c]	
Age median (IQR) (years)	59 (53–69)	58 (53–67)	57 (53–65)	0.676
Time since menopause (median [IQR]) (months)	65 (24–207)	58 (24–182)	59 (25–135)	0.625
BMI median (IQR) (kg/m^2)	29 (26–34)	29 (25–32)	30 (25–35)	0.215
Diabetes *n* (%)	57 (13.0)	32 (12.1)	12 (12.6)	0.887
Hypertension *n* (%)	178 (40.7)	99 (37.4)	38 (40.0)	0.649
HRT[d] *n* (%)				0.003*
Estrogens	5 (1.1)	2 (0.7)	2 (2.1)	
Progestogens	6 (1.4)	4 (1.5)	1 (1.1)	
Estrogens and progestogens	5 (1.1)	3 (1.1)	2 (2.1)	
Mirena IUD	1 (0.2)	0 (0)	1 (1.1)	
Tamoxifen	18 (4.1)	8 (3.0)	10 (10.5)	
Aromatase inhibitor	12 (2.7)	7 (2.6)	3 (3.1)	
Anticoagulants *n* (%)	73 (16.7)	41 (15.5)	15 (15.8)	0.942
Parity *n* (%)				0.466
Nullipara	47 (10.8)	25 (11.0)	11 (14.1)	
Multipara	326 (74.6)	202 (89.0)	67 (85.9)	
Endometrial thickness *n* (%)				0.565
≤4 mm	32 (7.3)	22 (9.1)	6 (7.1)	
>4 mm	362 (82.2)	220 (90.1)	79 (92.9)	

Note: Values are numbers with percentages and median (IQR) for values with skewed distribution.
Abbreviations: BMI, body mass index; HRT, hormone replacement therapy; IQR, interquartile range; IUD, intra-uterine device; PMB, postmenopausal bleeding.

[a]All patients with PMB.

[b]Patients with benign outcome at first episode of PMB and at risk for PMB recurrence.

[c]Recurrent PMB during follow-up. Median follow-up time was 61 months (IQR 44–73 months).

[d]One patient used tamoxifen and an aromatase inhibitor, no other combinations were used.

*p-value for patients with recurrent PMB vs. no recurrent PMB.

diagnosed with a (pre)malignancy (67/437) and women who underwent a hysterectomy due to any other reason (10/437) following the first episode of PMB were excluded from our analyses of the occurrence and prediction of recurrent PMB, as well as the analysis of pathological findings at recurrent PMB. A total of 360 women were eligible for the subsequent analyses.

The median follow-up time since the first PMB was 61 months (IQR 44–73 months). Recurrent PMB was seen in 95 (26.4%) patients, with a median time to recurrence of 18 months (IQR 9–34 months). Patients with recurrent PMB used HRT more often than patients without recurrence (20% vs. 8.7%, *p*-value 0.003) (Table 1). The diagnostic workup at first PMB among 437 patients included a transvaginal ultrasound in 436 patients (99.8%), endometrial sampling (Pipelle) in 434 patients (99.3%), cervix cytology in 321 patients (73.5%) and a diagnostic hysteroscopy in 148 patients (33.9%). After these results, a SIS was conducted in 52 patients (11.9%). Therapeutic hysteroscopy was performed in 64 patients (15.0%) and polyps were removed in 59 patients. MyoSure was conducted in 33 patients (7.6%) and polyps were removed in 29 patients.

Six (6.3%) patients with recurrent PMB were diagnosed with a malignancy or an EIN at 3, 8, 34, 40, 65, and 69 months, respectively, after their first episode of PMB (Figure 2). The details of these patients are presented in Table 2. The pathological findings in patients with PMB are presented in Table 3. Patients with recurrent PMB and benign histological outcomes at accurate workup during a first episode were less frequently diagnosed with a malignancy compared to patients with a single episode of PMB (5.3% vs. 17.8%, *p*-value 0.015). Benign polyps were diagnosed more often

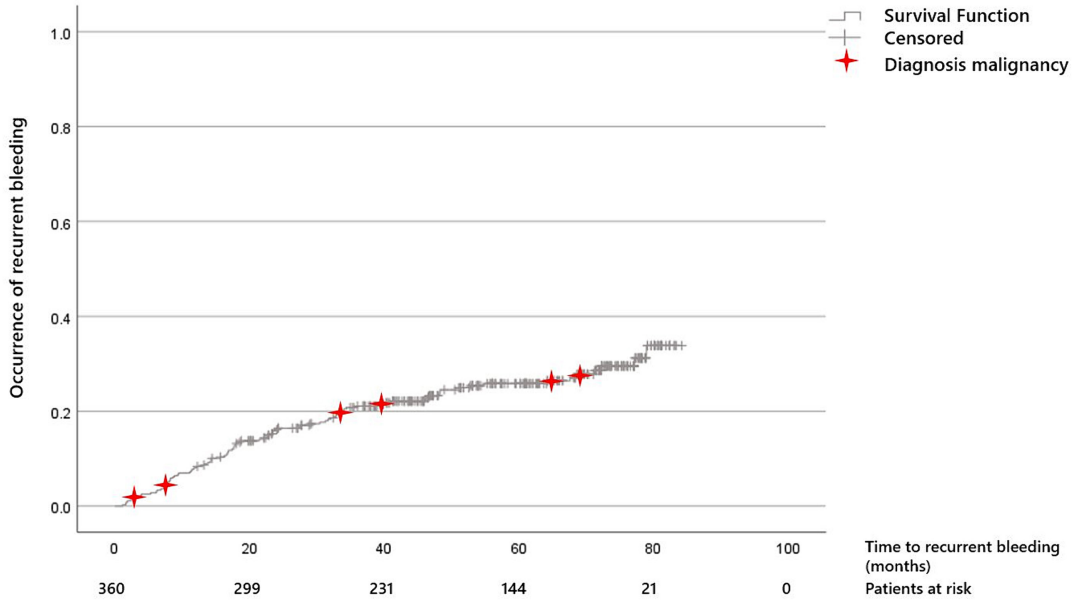

FIGURE 2 Kaplan–Meier curve showing time till recurrent postmenopausal bleeding.

in patients with a recurrent vs a single episode (34.7% vs. 25.1%, *p*-value 0.015). A diagnosis of benign polyps at a patient's first episode of PMB was associated with a higher chance of benign polyps at recurrent PMB (OR 4.74, 95% CI 2.21–10.16), but not with a higher risk of (pre)malignancy at recurrent PMB (OR 4.16, 95% CI 0.75–23.03). Pathological findings in patients presenting with recurrent PMB within vs beyond 12 months of the initial episode did not differ (Table 4).

Use of HRT (OR 3.32, 95% CI 1.64–6.72) together with a diagnosis of benign polyps at first PMB (OR 1.80, 95% CI 1.07–3.04) was associated with a higher risk of recurrent PMB. Time since menopause, BMI and use of anticoagulants were not associated with recurrent PMB (*p*-value >0.05) (Table 5).

Age at first PMB was associated with a higher risk of EC (OR 1.07, 95% CI 1.01–1.13, Table 6), whereas having polyps at initial presentation was associated with a lower EC risk (OR 0.03, 95% CI 0.00–0.20). Other investigated variables were not associated with differences in risk of EC at first or recurrent PMB (*p*-value >0.05) (Table 6). Using regression analysis, no other significant outcomes were found after dichotomizing time since menopause and BMI (not shown).

4 | DISCUSSION

Recurrent PMB occurred in over a quarter of women with a previous episode of non-malignant PMB. Although women with recurrent PMB and benign histological outcomes at an accurate first workup were diagnosed more frequently with benign polyps and less often with malignancies compared to women with a single episode of PMB, 6.3% of these women with recurrent PMB were nevertheless diagnosed with an endometrial (pre)malignancy. We also found that use of HRT and a diagnosis of polyps at the first episode are both risk factors for recurrent PMB, but the presence of polyps at first PMB does not confer a higher risk for malignancy at recurrent PMB.

We observed a rate of recurrent PMB in patients with one previous episode of PMB at the higher end of the spectrum compared with previous studies, where rates ranged from 6 to 25%.[5–7,9] This finding might be due to our longer follow-up time of up to 6 years, as a previous study with a 1- to 5-year follow-up reported a 15.3% recurrence rate,[6] while studies with follow-up of 5,[9] or 10 years reported similarly high rates (20.2% and 25.7%, respectively).[7] Another explanation could be the use of different definitions of recurrent PMB. We used the Dutch College of Obstetrics and Gynecology definition -"Any bleeding at least six weeks after the initial episode of PMB, unless this can be explained by cyclic hormone use or histological or hysteroscopic examination of the uterus",[12] but most studies either did not report a specific definition, or in the case of Ghoubara et al., defined it as: "Bleeding episodes that recurred, after negative investigations at first referral, necessitating a new referral to the PMB clinic by the family doctor".[9] However, this definition does not specify a timeframe and specifying a longer time period since initial PMB episode will likely result in lower incidence rates.

We found that patients at recurrence were more often diagnosed with benign polyps and less frequently diagnosed with malignancies compared to patients with only a single episode. This finding is in line with an earlier prospective cohort study by Smith et al. of 106 patients with recurrent PMB, and with a large observational study including 385 patients with recurrent PMB.[9,11] To the best of our knowledge, our study is the first to examine a possible association between the pathological outcome at first diagnostic workup and at recurrent PMB. We found that patients diagnosed with benign polyps at initial workup were at higher risk for benign polyps at recurrence, but not at higher risk for a (pre)malignant outcome.

TABLE 2 Characteristics of patients with a malignancy at recurrent postmenopausal bleeding (PMB)[a]

Patient	Time until recurrence[b]	Age	BMI	Anticoagulants	ET[c]	Use of HRT	Examinations at first PMB[d]	Examination results at first PMB	Treatment[e]	Diagnosis at recurrence
1	3	61	23	No	12.0	No	SIS	Endometrial sample: Benign SIS: No polyps, but thickened endometrium	No	Malignancy
2	8	67	37	No	7.7	No	Hysteroscopy	Endometrial sample: Benign Hysteroscopy: Not enough tissue for pathological review	No	Malignancy
3	34	52	29	No	12.0	No	Hysteroscopy	Endometrial sample: Benign Hysteroscopy: Benign polyp[f]	No	EIN
4	40	66	36	No	9.1	No	Hysteroscopy	Endometrial sample: Benign Hysteroscopy: Polyp was seen, no histopathology	No	Malignancy
5	65	59	33	Yes	8.0	No	Hysteroscopy	Endometrial sample: Simple hyperplasia, no atypia Hysteroscopy: Benign polyp[f]	Therapeutic hysteroscopy with polyp removal	Malignancy
6	69	65	37	Yes	23.0	Yes, Tamoxifen	Hysteroscopy	Endometrial sample: Benign Hysteroscopy: Benign polyp[f]	Therapeutic hysteroscopy with polyp removal	Malignancy

Abbreviations: BMI, body mass index; ET, endometrial thickness; HRT, hormone replacement therapy; PMB, postmenopausal bleeding; SIS, saline infusion sonohysterography.

[a]First presentation with a recurrence after the first episode of PMB.

[b]Time till recurrence in months.

[c]Thickness in millimeters.

[d]Additional to transvaginal ultrasound, cervix cytology, and endometrial sampling.

[e]Treatment including polyp removal after diagnostic workup at first PMB.

[f]Histopathologically proven.

TABLE 3 Pathological findings at initial workup in patients with only one episode of postmenopausal bleeding (PMB) vs. patients with recurrent PMB.

Pathological outcome at end of evaluation	Patients with only one episode of PMB ($N = 342$)[a]	Recurrent PMB ($N = 95$)[b]	*p*-value*
Benign	191 (55.8)	56 (58.9)	0.015*
Benign polyp	86 (25.1)	33 (34.7)	
EIN	4 (1.2)	1 (1.1)	
Malignancy	61 (17.8)	5 (5.3)	

[a]All patients at risk for recurrent PMB but in whom recurrent PMB did not occur.

[b]Patients with recurrent PMB during follow-up.

*p-value for patients with one episode of PMB vs recurrent PMB.

TABLE 4 Comparison of endometrial pathology in women with recurrent postmenopausal bleeding stratified by time till recurrent postmenopausal bleeding ($N = 95$)[a].

	<12 months	>12 months	*p*-value
Benign	16 (53.3)	40 (61.5)	0.744
Benign polyp	12 (40.0)	21 (32.3)	
(Pre)malignancy[b]	2 (6.7)	4 (6.2)	
Total	30	65	

[a]Values are given as *n* (%).

[b](Pre)malignancy includes endometrial intraepithelial neoplasia (EIN) and malignancies.

We identified two predictive factors for recurrent PMB: the use of HRT, which can be explained by higher estrogen exposure,[13] and benign polyps diagnosed at initial PMB. The association between predictive factors and recurrent PMB has been evaluated in only one other study,[5] which found no predictive factors for recurrent PMB. That study had a smaller patient population ($n = 249$) and excluded HRT use and the presence of polyps as potential risk factors for recurrent PMB, in contrast to our study.

Astrup et al. reported that patients are especially at risk for PMB in the first 3 years after final menstruation.[1] In our study, time since

TABLE 5 Univariable and multivariable logistic regression analyses for associations of variables with risk of recurrent postmenopausal bleeding among women with benign findings at first episode of postmenopausal bleeding ($N = 360$).

	Univariable		Multivariable[a]	
Variable	**OR (95% CI)**	***p*-value***	**OR (95% CI)**	***p*-value***
Age	0.99 (0.97–1.02)	0.657		
Time since menopause	1.00 (1.00–1.00)	0.651	1.00 (1.00–1.00)	0.309
BMI	1.03 (0.99–1.07)	0.210	1.03 (0.99–1.08)	0.139
Diabetes	1.05 (0.52–2.14)	0.887		
Hypertension	1.12 (0.69–1.81)	0.649		
Anticoagulants	1.02 (0.54–1.95)	0.942	1.22 (0.60–2.46)	0.587
HRT	2.63 (1.36–5.09)	0.004*	3.32 (1.64–6.72)	<0.001*
Multiparity	0.75 (0.35–1.61)	0.467		
ET ≥4 mm	1.32 (0.52–3.37)	0.566		
Benign polyps[b]	1.67 (1.03–2.72)	0.040*	1.80 (1.07–3.04)	0.028*

Note: After multiple imputations for BMI (17.8%), time since menopause (33.3%), ET (9.2%), and parity (15.3%). Values are odds ratios including corresponding confidence intervals, based on logistic regression analysis.

Abbreviations: BMI, body mass index; ET, endometrial thickness; HRT, hormone replacement therapy; OR, Odds ratio.

[a]Outcomes with a $p < 0.1$ in univariable analyses and expected risk factors were entered in multivariable analysis.

[b]Diagnosis of benign polyps at first presentation of postmenopausal bleeding.

*p-values <0.05 were considered as significant risk factors for recurrent bleeding.

TABLE 6 Univariable and multivariable logistic regression analysis for associations of variables with the risk of endometrial malignancy among women with one or more episodes of postmenopausal bleeding ($N = 437$).

	Univariate		Multivariate[a]	
Variable	**OR (95% CI)**	***p*-value***	**OR (95% CI)**	***p*-value***
Age	1.09 (1.06–1.12)	<0.001*	1.07 (1.01–1.13)	0.022*
BMI	1.02 (0.98–1.06)	0.414	1.00 (0.95–1.06)	0.957
Time since menopause	1.01 (1.00–1.01)	<0.001*	1.00 (1.00–1.01)	0.445
Diabetes	1.94 (0.95–3.93)	0.067	1.20 (0.85–1.69)	0.306
Hypertension	1.96 (1.13–3.43)	0.018*	1.10 (0.55–2.22)	0.782
Anticoagulants	0.94 (0.51–1.72)	0.830		
HRT	0.27 (0.06–1.15)	0.077	0.32 (0.07–1.66)	0.184
ET ≥4 mm	1.54 (0.35–6.84)	0.561		
Benign polyps[b]	0.04 (0.01–0.25)	<0.001*	0.03 (0.00–0.20)	<0.001*
Multiparity	0.64 (0.28–1.47)	0.293		

Note: After multiple imputations for BMI (14.9%), time since menopause (36.6%), endometrial thickness (9.8%) and multiparity (14.6%). Values are odds ratios including corresponding confidence intervals, based on logistic regression analysis.

Abbreviations: BMI, body mass index; ET, endometrial thickness; HRT, hormone replacement therapy; OR, Odds ratio.

[a]Outcomes with a $p < 0.1$ in univariate analyses and known risk factors were entered in multivariate analysis.

[b]Diagnosis of polyps at first presentation.

*p-values <0.05 were considered as significant risk factors for endometrial malignancy.

menopause was therefore evaluated as a potential risk factor for recurrent PMB. However, no association with recurrent PMB was found, even after dichotomizing time since menopause as >3 years and <3 years. This outcome might be due to the relatively low percentage of patients in our cohort with a time since menopause of <3 years (24%).

Assessing pathological findings in patients presenting either within or beyond 12 months of initial presentation with recurrent PMB, we found no differences between the two groups. Most guidelines view a presentation beyond 12 months not as a recurrence of an initial problem but as a new occurrence and therefore, needs another diagnostic workup. A previous study with a median

follow-up of 12 months also reported no time-related differences in pathological findings.[11] With a median follow-up of 61 months, our study represents a valuable extension of the known timeframe in which pathological characteristics appear stable.

While the risk of a (pre)malignant outcome was only 6.3% in women with recurrent PMB, this is not a negligible risk and a good diagnostic workup remains essential, even for women with benign findings at first PMB. This is also applicable for women presenting within a year of their first episode of PMB, since two patients in our study were diagnosed with a malignancy within 1 year.

Regarding strengths and limitations of the present study, strengths include the multicenter aspect and the long median follow-up time of 61 months. To minimize selection bias, patients were enrolled prospectively and every postmenopausal patient over 40 years undergoing endometrial sampling was invited to participate in the study, regardless of the indication for sampling. Furthermore, patients were enrolled before the final diagnosis of a sample was known.

Nevertheless, our findings also have certain limitations. As some patient files did not include all data, multiple imputations were required in a number of cases, although this is a recognized and validated method for handling missing data.[14] Furthermore, the categorization of the final diagnosis after the first episode was based in principle on pathological findings, but where a histopathological diagnosis was missing, we used hysteroscopy findings and follow-up to categorize patients. This meant that patients with a benign or insufficient endometrial sample, without further examination or recurrent PMB during follow-up, were classified as benign. This might have led to observer bias. However, a substantial majority of the patients (371/437, 85%) had a sufficient sample.

Moreover, it is uncertain if all polyps were removed at a patients' first episode of PMB. While some patients underwent polyp removal via therapeutic hysteroscopy (59 patients) or Myosure (29 patients), the records of the remaining 31 patients with polyps, did not clarify if polyps were removed. Gynecologists may have removed the polyps during diagnostic hysteroscopy or decided to not remove the polyp based on daily practice, despite the guideline suggests polyp removal. This could also be the reason for not sampling every polyp, although it is known that polyps are not in all cases benign. However, this reflects daily practice.

Also, patients with an ET <4 mm did not undergo additional diagnostic workup, despite the fact that an ET <4 mm does not reliably rule out EC, since particularly type II EC may present with a normal ET. However, we adhered to the Dutch guideline relying on previous studies concluding that an ET of <4 mm implies a similar risk of EC as the general population.[12,15]

Despite the lack of a central pathology review, all pathologists involved in the study were very experienced in the field. This expertise was further reinforced by adherence to a central pathology protocol, with back-up from pathologists experienced in gynecological pathology. Another possible limitation was that despite clear instructions to contact the hospital in case of recurrent PMB, not all women may have done so. In which case, this might have led to both an underestimation of the rate of PMB recurrence and an overestimation of the (pre)malignancy rate at recurrent PMB. A final potential limitation was our post-hoc analysis approach which, as mentioned earlier, involved some missing data.

5 | CONCLUSION

Recurrent PMB is a common phenomenon in postmenopausal women with a previous episode of PMB, especially among women using HRT or those with benign polyps at first PMB. While the risk of a (pre)malignancy at recurrent PMB is relatively low for patients with benign findings, including benign polyps, at first episode of PMB, it cannot be ignored. Therefore, accurate diagnostic workup at presentation with recurrent PMB remains recommended.

AUTHOR CONTRIBUTIONS

Johanna A van der Zande, Lucy A van Werkhoven, and Laura DPR van Maldegem: data curation. Patricia C Ewing-Graham: obtaining pathology results. Laura DPR van Maldegem: initial analysis, interpretation, and writing original draft of this manuscript. Bernadette A.M. Heemskerk- Gerritsen assisted in further analysis. Helena C van Doorn: Supervision and conceptualization. All authors have reviewed and approved the final version.

ACKNOWLEDGMENTS

We thank all gynecologists who contributed to the inclusion of patients. We also thank the EIN study group South West Holland as stated below:

Maria C. Breijer,[1] Manja Z. Dorman[2], Peggy M.L.H. Vencken[2], Judith de Waard[3], Ward Hofhuis[3], Gatske M. van Nieuwenhuyzen-de Boer[4], Heleen J. van Beekhuizen[4], Klaas Hoogduin[5], A. (Lex) C. F. Makkus[6], Katrien Schelfout[7].

1) Department of Gynecology, Admiraal de Ruyter Hospital, Goes, The Netherlands; 2) Department of Gynecology, Bravis Hospital, Bergen op Zoom, The Netherlands; 3) Department of Gynecology, Franciscus Hospital, Rotterdam, The Netherlands; 4) Department of Gynecologic Oncology, Erasmus MC Cancer Institute, University Medical Center Rotterdam; 5) Department of Pathology, Franciscus Hospital, Rotterdam, The Netherlands; 6) Laboratory of Pathology, Dordrecht, The Netherlands; 7) Department of Pathology, Bravis Hospital, Bergen op Zoom, The Netherlands.

ETHICS STATEMENT

Approval of this study was obtained from the Medical Ethical Committee of Erasmus Medical Center, Rotterdam on March 18, 2019 (MEC 2015-740). The study was registered on the Dutch trial register (www.onderzoekmetmensen.nl, NL7608).

ORCID

Laura D. P. R. van Maldegem https://orcid.org/0009-0004-5274-4121

Johanna A. van der Zande https://orcid.org/0000-0002-9569-6551

Patricia C. Ewing-Graham https://orcid.org/0000-0002-1779-1115
Bernadette A. M. Heemskerk-Gerritsen https://orcid.org/0000-0002-9724-6693
Helena C. van Doorn https://orcid.org/0000-0003-1062-4485

REFERENCES

1. Astrup K, Olivarius NDF. Frequency of spontaneously occurring postmenopausal bleeding in the general population. *Acta Obstet Gynecol Scand*. 2004;83:203-207.
2. Gredmark T, Kvint S, Havel G, Mattsson LA. Histopathological findings in women with postmenopausal bleeding. *Br J Obstet Gynaecol*. 1995;102:133-136.
3. Malkasian GD Jr, Annegers JF, Fountain KS. Carcinoma of the endometrium: stage I. *Am J Obstet Gynecol*. 1980;136:872-888.
4. Gu B, Shang X, Yan M, et al. Variations in incidence and mortality rates of endometrial cancer at the global, regional, and national levels, 1990-2019. *Gynecol Oncol*. 2021;161:573-580.
5. Van Doorn HC, Timmermans A, Opmeer BC, et al. What is the recurrence rate of postmenopausal bleeding in women who have a thin endometrium during a first episode of postmenopausal bleeding? *Acta Obstet Gynecol Scand*. 2008;87:89-93.
6. van Hanegem N, Breijer MC, Slockers SA, et al. Diagnostic workup for postmenopausal bleeding: a randomised controlled trial. *BJOG*. 2017;124:231-240.
7. Gull B, Karlsson B, Milsom I, Granberg S. Can ultrasound replace dilation and curettage? A longitudinal evaluation of postmenopausal bleeding and transvaginal sonographic measurement of the endometrium as predictors of endometrial cancer. *Am J Obstet Gynecol*. 2003;188:401-408.
8. 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;111:137-143.
9. Ghoubara A, Sundar S, Ewies AAA. Endometrial pathology in recurrent postmenopausal bleeding: observational study of 385 women. *Climacteric*. 2018;21:391-396.
10. Clarke MA, Long BJ, Sherman ME, et al. Risk assessment of endometrial cancer and endometrial intraepithelial neoplasia in women with abnormal bleeding and implications for clinical management algorithms. *Am J Obstet Gynecol*. 2020;223:549.e1-549.e13.
11. Smith PP, O'Connor S, Gupta J, Clark TJ. Recurrent postmenopausal bleeding: a prospective cohort study. *J Minim Invasive Gynecol*. 2014;21:799-803.
12. (NVOG) DSoOaG. NVOG richtlijn Postmenopauzaal bloedverlies [NVOG Guideline: Postmenopausal bleeding]. NVOG. 2023. Accessed 01-02-2023 https://www.nvog.nl/wp-content/uploads/2018/02/Postmenopauzaal-bloedverlies-1.0-12-11-2015.pdf
13. Mair KM, Gaw R, MacLean MR. Obesity, estrogens and adipose tissue dysfunction – implications for pulmonary arterial hypertension. *Pulm Circ*. 2020;10:2045894020952019.
14. Jakobsen JC, Gluud C, Wetterslev J, Winkel P. When and how should multiple imputation be used for handling missing data in randomised clinical trials – a practical guide with flowcharts. *BMC Med Res Methodol*. 2017;17:162.
15. Gynecologists TACoOa. ACOG Committee opinion No. 734: the role of transvaginal ultrasonography in evaluating the endometrium of women with postmenopausal bleeding. *Obstet Gynecol*. 2018;131:e124-e129.

How to cite this article: van Maldegem LDPR, van der Zande JA, van Werkhoven LA, Ewing-Graham PC, Heemskerk-Gerritsen BAM, van Doorn HC. Recurrent postmenopausal bleeding: Pathological findings and predictive factors. A multicenter, prospective, observational study. *Acta Obstet Gynecol Scand*. 2024;103:1283-1291. doi:10.1111/aogs.14851