

Postmenopausal bleeding: correlation between pathology findings, endometrial thickness, and risk factors for endometrial cancer

Summary

Objectives: To analyze the correlation between pathological findings and risk factors for endometrial disease in patients with postmenopausal bleeding (PMB), assessing the presence of endometrial cancer and its relationship with specific clinical characteristics.

To determine the usefulness of transvaginal ultrasound in predicting malignancy and its agreement with histological findings.

Materials and methods: This is an observational, retrospective, descriptive study conducted between January 2017 and February 2025.

Postmenopausal patients with PMB who underwent hysteroscopy (HSC) were included. The variables analyzed were age, body mass index (BMI), hypertension (HTN), diabetes (DM), tamoxifen use, endometrial thickness (ET) assessed by transvaginal ultrasound, and the histopathology findings of the collected samples. A database was created for statistical analysis.

Results: A total of 548 postmenopausal patients with PMB were analyzed; all were evaluated with transvaginal ultrasound and hysteroscopy.

The median BMI was 29 kg/m² (n=506 with available data); 48.0% of patients were obese (n=243). Hypertension was the most prevalent risk factor (44.0%, n= 241), followed by diabetes mellitus (14.1%, n= 77) and tamoxifen use (8.8%, n= 48).

An endometrial thickness ≥ 10 mm was the most common ultrasound finding (49.8%, n=273). The most frequent diagnosis was endometrial polyp (43.6%, n=239), followed by endometrial atrophy (19.0%, n=104).

Endometrial cancer was diagnosed in 16.4% of patients (n=90). Among patients diagnosed with cancer, 74.4% had an endometrial thickness ≥ 10 mm, 20.0% between 5–10 mm, and 4.4% ≤ 5 mm; in one patient, endometrial thickness could not be assessed.

Older age and an endometrial thickness ≥ 10 mm were the only factors independently associated with endometrial cancer in multivariate analysis (OR 1.09 per year and OR 3.71, respectively; $p < 0.001$). Although hypertension was associated with cancer in the univariate analysis ($p = 0.006$), this association did not remain significant after adjusting for age and endometrial thickness.

Conclusion: Postmenopausal bleeding represents a key clinical sign for the suspicion and early detection of endometrial cancer. In our study, older age and an endometrial thickness ≥ 10 mm were the strongest independent predictors of endometrial cancer. While clinical risk factors such as hypertension and obesity were associated with malignancy in univariate analysis, these associations were attenuated after adjustment for age and endometrial thickness.

These findings underscore the importance of integrating clinical, ultrasonographic, and histopathological variables to optimize the diagnostic and therapeutic approach in postmenopausal women.

Keywords: postmenopausal bleeding, endometrial cancer, transvaginal ultrasound, hypertension, obesity, diabetes, hormone replacement therapy, endometrial thickness

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Abbreviations: PMB, postmenopausal bleeding; HSC, hysteroscopy; TVUS, transvaginal ultrasound; BMI, body mass index; HTN, hypertension; DM, diabetes mellitus; ET, endometrial thickness

Introduction

Postmenopausal bleeding (PMB) is a clinically significant symptom and a common reason for gynecological consultation, due

to its association with both benign and malignant pathologies of the genital tract.¹

The causes of PMB are diverse, with endometrial and/or genitourinary atrophy being the most frequent, accounting for approximately 60–80% of vaginal bleeding cases in this population.¹

Other etiologies include endometrial polyps, uterine fibroids, endometrial hyperplasia, urogenital infections, the use of certain

medications (such as estrogens, tamoxifen, and anticoagulants), foreign bodies, and various neoplasms of the genital tract.

However, among these conditions, endometrial cancer represents the most clinically significant cause, as postmenopausal bleeding is the presenting symptom in most affected women. This makes PMB the main warning sign for the early detection of this neoplasm.^{2,3}

Endometrial cancer is the third most common gynecologic malignancy worldwide. According to GLOBOCAN estimates, approximately 417,000 new cases of corpus uteri cancer were diagnosed globally in 2020, with an associated mortality of around 97,000 deaths.⁴

The incidence of endometrial cancer has been increasing, particularly among women with established risk factors such as advanced age, obesity, hypertension, type 2 diabetes, tamoxifen use, and increased endometrial thickness.⁵

The initial evaluation in these women generally includes transvaginal ultrasound, a key tool for measuring endometrial thickness, and hysteroscopy, which allows direct visualization of the uterine cavity and targeted biopsies.⁶

Given the close relationship between risk factors and endometrial carcinogenesis, it is essential to establish their correlation with ultrasonographic and histopathological findings in women with PMB. This approach may improve risk stratification and diagnostic accuracy for endometrial cancer and other endometrial conditions.^{5,6}

Objectives

The objective of this study is to analyze the correlation between pathological findings and risk factors for endometrial disease in patients with postmenopausal bleeding (PMB), assessing the presence of endometrial cancer and its relationship with specific clinical characteristics. Additionally, the study aims to determine the usefulness of transvaginal ultrasound in predicting malignant lesions and its degree of concordance with histopathological results.

Materials and methods

This was an observational, retrospective, analytical study conducted at the Gynecology Departments of Sanatorio Güemes and Hospital Alemán in Buenos Aires, Argentina, between January 2017 to February 2025.

Medical records of postmenopausal women presenting with PMB and undergoing hysteroscopy (HSC) were reviewed.

Inclusion and exclusion criteria

We included postmenopausal women who presented with postmenopausal bleeding. Menopause was defined as amenorrhea of at least 12 consecutive months. All included patients underwent transvaginal ultrasound and diagnostic hysteroscopy, with endometrial sampling for histopathological analysis; patients were included regardless of sample adequacy, reflecting routine clinical practice.

Patients receiving hormone replacement therapy were not excluded.

Patients with a previous diagnosis of endometrial cancer and those with a prior hysterectomy were excluded. No patients were excluded on the basis of missing data.

The variables analyzed included age, body mass index (BMI), diabetes mellitus (DM), hypertension (HTN), tamoxifen therapy for a personal history of breast cancer, endometrial thickness (ET)

as assessed by ultrasound, and pathological findings from samples obtained via hysteroscopy.

Regarding endometrial thickness (ET), three categories were established for analysis based on ultrasound measurements:

- a) $ET \leq 5$ mm
- b) ET between 5–10 mm
- c) $ET \geq 10$ mm

It should be noted that the indication for diagnostic hysteroscopy was not based exclusively on ultrasonographic endometrial thickness. All patients with persistent or recurrent postmenopausal bleeding were evaluated by hysteroscopy regardless of endometrial thickness, in accordance with international guidelines that recognize persistent bleeding as an independent indication for endometrial assessment.⁷

Finally, the histopathological results were categorized as follows:

- 1) Not analyzed/non-assessable
- 2) Polyp
- 3) Myoma
- 4) Proliferative/secretory endometrium
- 5) Malignancy
- 6) Others (IUD, synechiae, septa, endocervix, nonspecific findings)
- 7) Atrophy
- 8) Hyperplasia without atypia
- 9) Hyperplasia with atypia

Based on the information obtained, a database was created in which each of the previously described variables was recorded.

The data were recorded in Microsoft Excel® spreadsheets.

Categorical variables were expressed as absolute frequencies and percentages. Continuous variables were summarized as median and interquartile range or mean and standard deviation, according to their distribution, and compared between groups using Student's t-test or the Mann-Whitney U test as appropriate.

The diagnostic performance of endometrial thickness measured by ultrasonography for detecting malignancy was assessed by calculating sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) at cutoff points of >5 mm and >10 mm.

Associations between clinical and ultrasonographic factors and the presence of endometrial cancer were evaluated using the chi-square test or Fisher's exact test, as appropriate. A binary logistic regression model was then constructed to identify variables independently associated with endometrial cancer, including age, hypertension, and endometrial thickness as covariates; results were expressed as odds ratios (OR) with 95% confidence intervals (CI).

A p-value < 0.05 was considered statistically significant. Statistical analyses were performed using Jamovi® (version 2.7.30).

Results

General characteristics of the study population

A total of 548 patients with PMB were included, with a median age of 58 years (IQR 54–65). All patients were evaluated using transvaginal ultrasound and hysteroscopy.

The median BMI was 29 kg/m² (BMI available in 506 patients), with 48.0% classified as obese (n=243). Hypertension (HTN) was the most frequent risk factor, present in 44.0% of patients (n=241), followed by diabetes mellitus (DM) in 14.1% (n=77). Additionally, 8.8% (n=48) had a current or prior history of tamoxifen therapy (Table 1).

Table 1 General characteristics of the study population

Characteristic	Patients with PMB (n = 548)	%
Age, years – median (IQR)	58 (54-65)	-
BMI≥30	243	48.0%*
DM	77	14.10%
HTN	241	44.00%
Tamoxifen	48	8.80%

*The percentage of obesity (BMI ≥30) was calculated over the 506 patients with available BMI data (42 patients had missing BMI). All other percentages were calculated over the total population (n=548).

IQR, interquartile range; BMI, body mass index; DM, diabetes mellitus; HTN, hypertension.

Smoking status was excluded from the analysis because data were missing from most medical records.

Ultrasound findings

An endometrial thickness ≥10 mm was the most frequent ultrasonographic finding, present in 49.8% (n = 273) of cases (Table 2).

Table 2 Ultrasound findings

Characteristic	Patients with PMB (n=548)	%
ET≤ 5mm	85	15.50%
ET5-10mm	161	29.40%
ET>10mm	273	49.80%
ET non-assessable	29	5.30%

ET, endometrial thickness

Histopathological findings

The most common diagnosis was endometrial polyp, accounting for 43.6% (n=239), followed by endometrial atrophy at 19.0% (n=104). The third most frequent finding was malignancy, present in 16.4% (n=90) of cases (Table 3).

Table 3 Histopathological findings

Pathology diagnosis	Patients with PMB (n=548)	%
Polyp	239	43.60%
Endometrial atrophy	104	19.00%
Malignancy	90	16.40%
Proliferative endometrium	35	6.40%
Others	30	5.50%
Not analyzed/non assessable	19	3.50%
Submucosal myoma	15	2.70%
Hyperplasia with atypia	10	1.80%
Hyperplasia without atypia	6	1.10%

Transvaginal ultrasound and endometrial thickness (ET)

Among patients diagnosed with endometrial cancer, 74.4% (n=67) had an ET ≥10 mm, 20.0% (n=18) had an ET between 5–10 mm, 4.4% (n=4) had an ET ≤5 mm, and endometrial thickness could not be assessed in one patient.

The diagnostic utility of endometrial thickness (ET) for predicting malignancy in patients with PMB was analyzed using cutoff points of >5 mm and >10 mm. The results are summarized in Table 4.

Table 4 The diagnostic utility of endometrial thickness

Cutoff point	Sensitivity	Specificity	PPV	NPV
ET>5 mm	94.40%	23.80%	19.60%	95.60%
ET>10 mm	74.40%	55.00%	24.50%	91.60%

ET, endometrial thickness; PPV, positive predictive value; NPV, negative predictive value.

The >5 mm cutoff considers as positive any endometrium measuring more than 5 mm (i.e., the 5–10 mm and ≥10 mm categories), and as negative an endometrium ≤5 mm. The >10 mm cutoff considers as positive an endometrium ≥10 mm, and as negative any endometrium ≤10 mm. Non-assessable cases were classified as negative for the calculation

The distribution of endometrial thickness differed significantly between patients with and without cancer ($\chi^2 = 28.4$; $df = 3$; $p < 0.0001$). An endometrial thickness ≤5 mm was associated with a lower likelihood of malignancy ($p = 0.003$), and the proportion of patients in the 5–10 mm range was also lower among those with cancer ($p = 0.044$), whereas an endometrial thickness ≥10 mm was strongly associated with cancer ($p < 0.0001$). Overall, 74.4% of patients with cancer had an endometrial thickness ≥10 mm, compared with 45.0% of those without cancer (Table 5).

Table 5 The distribution of endometrial thickness differed significantly between patients with and without cancer

ET	Cancer (n=90)	No cancer (n=458)	P value
≤ 5 mm	4 (4.4%)	81 (17.7%)	0.003
5-10 mm	18 (20.0%)	143 (31.2%)	0.044
≥ 10 mm	67 (74.4%)	206 (45.0%)	<0.0001
Non-assessable	1 (1.1%)	28 (6.1%)	-

ET, endometrial thickness. Percentages are calculated within each group (column). Each p-value corresponds to the comparison of that thickness category versus the rest, between cancer and non-cancer groups.

Risk factors associated with endometrial cancer

The association between clinical factors and the presence of cancer in patients with PMB was analyzed. In the univariate analysis, hypertension was significantly associated with endometrial cancer ($p = 0.006$), and a similar association was observed for the combination of obesity and hypertension ($p = 0.007$). No statistically significant associations were found for obesity, diabetes, or tamoxifen use when considered individually. As shown in the multivariate analysis below, however, the association between hypertension and endometrial cancer did not remain statistically significant after adjusting for age and endometrial thickness (Table 6).

Table 6 Multivariate analysis

Factor	Patients with cancer	Patients without cancer	P- value
BMI≥30	44/86 (51.2%)	199/420 (47.4%)	0.6
DM	14/90 (15.6%)	63/458 (13.8%)	0.78
HTN	52/90 (57.8%)	189/458 (41.3%)	0.006
Tamoxifen	5/87 (5.7%)	43/457 (9.4%)	0.37
HTN+DM	12/90 (13.3%)	49/458 (10.7%)	0.59
Obesity+Tamoxifen	3/83 (3.6%)	13/419 (3.1%)	0.74
Obesity+HTN	33/86 (38.4%)	99/420 (23.6%)	0.007
HTN+Tamoxifen	4/87 (4.6%)	11/457 (2.4%)	0.28

Percentages are calculated over patients with available data for each variable. Hypertension and diabetes were recorded in all patients (denominators: 90 cancer / 458 no cancer). BMI was available in 506 patients (86 cancer / 420 no cancer); therefore, obesity and all combinations including obesity were calculated over these denominators. Tamoxifen status was available in 544 patients (87 cancer / 457 no cancer). BMI: body mass index; DM: diabetes mellitus; HTN: hypertension

Age and multivariate analysis

Patients diagnosed with endometrial cancer were significantly older than those without cancer (mean age 67.0 vs 59.0 years; median 65.5 vs 57.0; $p < 0.001$).

To identify factors independently associated with endometrial cancer, a binary logistic regression model was constructed including age, hypertension, and endometrial thickness as covariates. In this

model, age (OR 1.085 per year; 95% CI 1.057–1.113; $p < 0.001$) and an endometrial thickness ≥ 10 mm (OR 3.71; 95% CI 2.17–6.34; $p < 0.001$) were independently associated with endometrial cancer. Hypertension, which had shown a significant association in the univariate analysis, did not remain significant after adjustment (OR 0.98; 95% CI 0.57–1.67; $p = 0.94$). These results are summarized in Table 7.

Table 7 Age and multivariate analysis

Predictor	Model 1 — OR (95% CI)	P value	Model 2 — OR (95% CI)	P value
Age (per year)	1.085 (1.057–1.113)	<0.001	1.088 (1.060–1.117)	<0.001
Hypertension	0.98 (0.57–1.67)	0.94	0.95 (0.56–1.62)	0.85
ET ≥ 10 mm	3.71 (2.17–6.34)	<0.001	—	—
ET >5 mm	—	—	6.03 (2.30–15.80)	<0.001

OR, odds ratio; CI, confidence interval; ET, endometrial thickness.

Model 1 uses an endometrial thickness cutoff of ≥ 10 mm; Model 2 uses a cutoff of > 5 mm. Both models were adjusted for age and hypertension.

A second model using an endometrial thickness cutoff of > 5 mm yielded similar results: both age (OR 1.088; 95% CI 1.060–1.117; $p < 0.001$) and ET > 5 mm (OR 6.03; 95% CI 2.30–15.80; $p < 0.001$) remained independent predictors, while hypertension again lost statistical significance ($p = 0.85$).

Discussion

This study provides evidence of associations among clinical factors, ultrasonographic findings, and histopathological results in postmenopausal women, highlighting the role of bleeding as a warning sign and the utility of transvaginal ultrasound in assessing the risk of malignancy. In our cohort, older age and an endometrial thickness ≥ 10 mm emerged as the factors most strongly and independently associated with endometrial cancer. Although several clinical risk factors, particularly hypertension, were associated with malignancy in the univariate analysis, these associations did not remain significant after multivariate adjustment, suggesting that their effect is largely mediated by age and endometrial thickness.

A central finding of our study was the strong and independent association between advancing age and endometrial cancer. Patients with cancer were, on average, eight years older than those without (67 vs 59 years), and age remained a significant independent predictor in the multivariate model (OR 1.085 per year). This is consistent with large studies showing that age is one of the most important risk-stratifying variables in women with postmenopausal bleeding. In a risk-assessment study of women with abnormal bleeding, the

maximum risk of endometrial cancer was observed in those aged 60 years or older (17.7%), exceeding the risk associated with recurrent bleeding.⁸ Similarly, the Norwich DEFAB prospective cohort of over 3,000 women with postmenopausal bleeding found that patients with endometrial cancer were more likely to be older and to have a higher BMI, recurrent bleeding, diabetes, hypertension, or a history of breast cancer, and incorporated age as a core component of its validated predictive algorithm.⁹ Our results reinforce the value of integrating age into clinical risk stratification, rather than relying on endometrial thickness alone.

Regarding transvaginal ultrasound (TVUS), there is consensus on its role as an initial tool in the evaluation of the endometrium in patients with PMB. The guidelines from the American College of Obstetricians and Gynecologists (ACOG) recommend performing endometrial sampling in women with PMB when the endometrial thickness (ET) is ≥ 4 mm, as the probability of malignancy is low below this threshold.⁷ Consistently, systematic studies such as that by Van Hanegem et al.¹⁰ and the meta-analysis by Timmermans et al.¹¹ demonstrated that an ET ≤ 4 mm provides a negative predictive value of up to 99% for ruling out cancer.

Although an endometrial thickness ≤ 4 –5 mm on transvaginal ultrasound is associated with a low risk of endometrial cancer and a high negative predictive value, it does not fully exclude clinically significant endometrial pathology. In our cohort, 4.4% of patients with endometrial cancer (4/90) had an endometrial thickness of ≤ 5 mm. These findings support a diagnostic approach that does not rely solely

on ultrasonographic endometrial thickness and emphasize persistent bleeding as an indication for further evaluation, even in the presence of a thin endometrium, in line with international guidelines.

Previous studies suggest that the presence of additional risk factors should modify the diagnostic approach. Clinical guidelines recommend that, in women with endometrial thickening and risk factors for endometrial cancer such as obesity, hypertension, diabetes, or late menopause, the decision to pursue further investigation should be individualized rather than based on endometrial thickness alone.¹² In our study, approximately 20% of patients with endometrial cancer had an endometrial thickness of 5–10 mm, supporting the value of a more individualized diagnostic approach that integrates clinical risk factors alongside ultrasonographic findings.

Tamoxifen use has been associated with a higher incidence of endometrial abnormalities, including hyperplasia, polyps, and cancer. In the NSABP B-14 trial, tamoxifen-treated patients had an approximately 7.5-fold increased relative risk of endometrial cancer compared with placebo, corresponding to an absolute incidence of about 1–2 cases per 1,000 patient-years.¹³ The risk increases with longer treatment duration, with a more than fourfold increase reported after five years of use.¹⁴ In our cohort, 5 of the 48 patients on tamoxifen (10.4%) were diagnosed with endometrial cancer; however, tamoxifen use was not significantly associated with cancer in our comparative analysis ($p = 0.37$), possibly reflecting the limited number of exposed patients. These findings nonetheless support the need for evaluation with transvaginal ultrasound and, when indicated, hysteroscopy in patients on tamoxifen presenting with bleeding.

This study has several limitations inherent to its retrospective, observational design, including potential selection bias and limited standardization of ultrasound reports across operators and institutions. Body mass index data were missing in some patients, which reduced the sample available for analyses involving obesity. In addition, the number of patients exposed to tamoxifen was limited, restricting the statistical power to detect associations for this variable. Finally, the multivariate model included a limited set of covariates; other recognized risk factors, such as parity, age at menopause, or hormone replacement therapy, were not available for analysis. Despite these limitations, the study offers a valuable interinstitutional assessment of the diagnostic management of postmenopausal bleeding, with histopathological confirmation in all cases.

Conclusion

Postmenopausal bleeding represents a warning symptom that justifies careful and targeted diagnostic evaluation, given its strong association with endometrial cancer. This study confirms that transvaginal ultrasound is an effective and accessible tool for initial assessment, with endometrial thickness being a key parameter for risk stratification. Specifically, an endometrial thickness ≥ 10 mm was independently associated with higher odds of endometrial cancer.

In addition, our analysis identified advancing age as an independent predictor of malignancy, whereas the associations observed for clinical risk factors such as hypertension and obesity did not persist after multivariate adjustment. This suggests that age and endometrial thickness, rather than individual comorbidities, are the most relevant variables for risk stratification in this population.

Overall, our findings highlight the importance of a comprehensive evaluation in patients with PMB. The combination of clinical assessment, measurement of endometrial thickness by transvaginal ultrasound, and consideration of age constitutes a key tool in the modern approach to postmenopausal bleeding, allowing for appropriate

risk stratification and more accurate and efficient decision-making. Importantly, persistent or recurrent bleeding warrants histological evaluation even when the endometrium appears thin.

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Conflicts of interest

The authors declare no potential conflicts of interest.

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