

1 Point

Postmenopausal Bleeding

Joyce Chai, MBChB, FHKAM (O&G); Vincent YT Cheung, MBBS, FRCOG, FRCSC

INTRODUCTION

Postmenopausal bleeding (PMB) is defined as any vaginal bleeding occurring at least 12 months after the last menstrual period.¹ It represents one of the most common reasons for referral to the gynaecological services, and the incidence is estimated to be around 10%.² In 2004, it accounts for 2.5% of all gynaecological hospital admissions in Hong Kong,³ and it does not include many consultations that take place at the outpatient setting. In the United Kingdom, it accounts for about 5% of referrals to the gynaecology outpatient services.⁴

CAUSES OF PMB

Postmenopausal bleeding is alarming for both patients and clinicians because the classic teaching has labelled PMB as 'endometrial cancer until proven otherwise'. Depending on age and risk factors, 1–14% of women presenting with PMB will have underlying endometrial carcinoma.⁵ However, PMB in the majority of women is due to benign causes (Table 1), and the most common cause is atrophy of the vaginal mucosa or endometrium secondary to the lack of oestrogen production.⁶ It is therefore mandatory to evaluate any women with PMB promptly in order to exclude

underlying malignancy, as early stage endometrial cancer is amenable to curative treatment. The National Institute for Clinical Excellence guidelines advise that when women, who are not on hormone replacement therapy (HRT), present with PMB, they should be urgently referred for specialist assessment and be seen within 2 weeks of referral.⁷

MANAGEMENT OF PMB

History

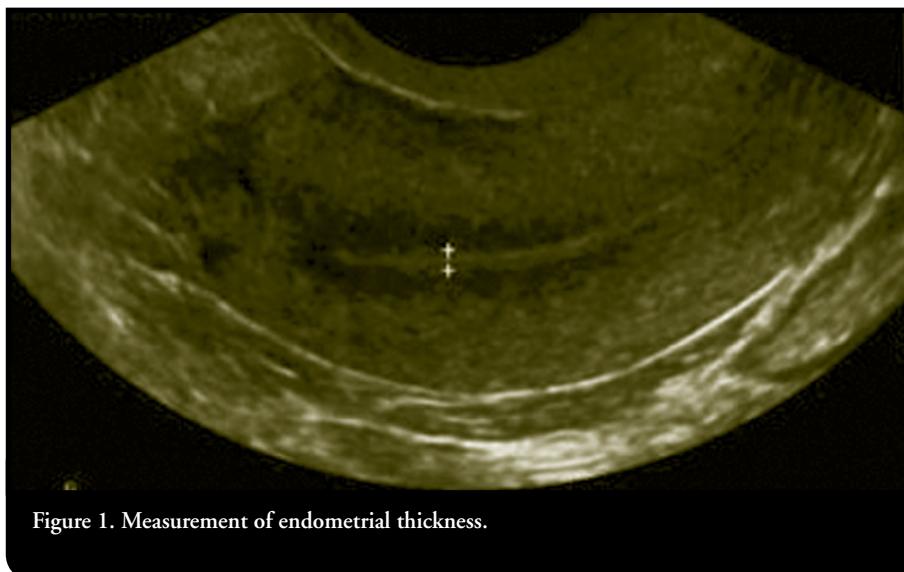
A detailed medical and drug history may help the clinician differentiate the different causes of abnormal bleeding, and it should aim to identify the risk factors for endometrial carcinoma. Women taking the selective oestrogen receptor modulator tamoxifen for breast cancer have two to three times higher risk of developing endometrial carcinoma than those of an age-matched population.⁸ Particular attention should also be paid to the use of HRT. Transient unscheduled bleeding is not uncommon during the first 6 months of continuous combined HRT and can be followed up, but PMB in unopposed oestrogen users with an intact uterus should prompt urgent investigation. Table 2 shows the risk factors for endometrial carcinoma and the respective relative risks when compared

Table 1. Causes of postmenopausal bleeding

Condition	Women with the condition (%)
Atrophic vaginitis	59
Endometrial polyp	12
Endometrial hyperplasia	10
Endometrial carcinoma	10
Hormonal effect	7
Cervical carcinoma	2
Other	< 1

Table 2. Risk factors for endometrial cancer

Risk factor	Risk ratio
Overweight (age, 50–59 years)	
9–23 kg	3.0
> 23 kg	10.0
Nulliparity	2.0
Late menopause	2.4
Tamoxifen use	2.2
Diabetes mellitus	2.7
Unopposed oestrogen therapy	6.0



with those without the risk factor.⁹

Examination

General examination including body mass index is an essential part of examination, as obesity is an independent variable associated with a significantly increased risk of endometrial cancer.¹⁰ Speculum examination, which allows visual inspection of the genital tract, helps to assess the degree of atrophic changes and to rule out tumours of the cervix, vagina or vulva, or cervical polyps. However, the finding of atrophic vaginitis or a polyp should not be accepted as the explanation for the bleeding without further assessment of the endometrial cavity. Cervical smear should also be taken.

Investigation

The aim of investigating a woman presenting with PMB is to identify endometrial pathology, most notably to exclude endometrial carcinoma. The principle of management is to achieve an accurate diagnosis

with the least invasive investigation, if possible.

There is a range of diagnostic tests generally performed for women presenting with PMB. Specifically for the assessment of the endometrium, there are essentially four methods: sonographic measurement of endometrial thickness, endometrial sampling, hysteroscopy under various modes of anaesthesia, and saline sonohysterography. These four tests have been independently shown to be useful in identifying endometrial pathologies with different degree of accuracy. However, for the use of these tests in the exclusion of endometrial carcinoma, there are still unresolved concerns regarding the appropriate initial method of evaluation and the combination or sequence in which these methods should be employed.^{1,5,11–13}

Measurement of Endometrial Thickness

Transvaginal sonography (TVS) is a relatively non-invasive investigation that is

widely used in the evaluation of the endometrium. Although histological diagnosis is not available, sonographic imaging is an extremely helpful test in assessing women with PMB because endometrial cancer is nearly always associated with thickening and heterogeneity of the endometrial lining.^{6,14} The endometrial thickness should be measured from a longitudinal scan through the thickest area of the endometrium and from the outermost border of the antero-posterior endometrium (Figure 1).

There are different endometrial thickness thresholds that have been used for recommending further investigations; understandably, the lower the cut-off level used, the fewer the number of cases of endometrial carcinoma that will be missed but at the cost of needing further investigations in a greater number of women without cancer. The use of the traditional cut-off value of 5 mm, with the sensitivity for detecting endometrial carcinoma of 96% and the specificity of 61%, was based on the meta-analysis of 35 prospective studies performed in 1998.¹⁵ Using this cut-off value, the probability of endometrial cancer was reduced to 1% for a negative test. Subsequently, a meta-analysis and a consensus conference regarding the ability of TVS to detect endometrial pathology in women with PMB concluded that the negative predictive value of a thin endometrium of ≤ 4 mm was very high,^{12,16} and the chance of having endometrial cancer is 1 in 917 in this group of patients.¹⁷ The American College of Obstetricians and Gynecologists recommends that when TVS is performed for patients with PMB and an endometrial thickness of ≤ 4 mm is found,

endometrial sampling is not required.⁵ A more recent meta-analysis by Timmermans *et al* found a higher diagnostic accuracy for TVS with a cut-off value of ≤ 3 mm, in which the sensitivity was 98% and the specificity was 35%, giving a likelihood ratio for a negative test result of 0.06.¹⁸ The Scottish Intercollegiate Guidelines Network suggests that a cut-off threshold of 3 mm or less should be used.¹ On the other hand, cancer becomes increasingly more frequent as the endometrial thickness approaches 15 mm, which is highly suggestive of endometrial carcinoma (Figure 2).¹⁶

Conditions like previous pelvic surgery, coexisting leiomyoma, marked obesity, and adenomyosis may preclude an accurate assessment of the endometrial thickness. In such cases, alternative assessment like saline sonohysterography or endometrial sampling should be considered.

Saline Sonohysterography

Saline sonohysterography, an imaging technique in which normal saline is instilled into the uterine cavity, allows better detection of the endometrial polyp (Figure 3) and submucosal fibroid.¹⁹ In patients whose endometrial lining is not adequately visualized, it will allow an excellent depiction of the endometrial thickness. It will distinguish focal (Figure 4) from global lesions when TVS shows a thick endometrial echo. It can therefore act as an adjunct to TVS to clarify abnormal endometrial findings.²⁰

One systematic review described the evaluation of the diagnostic accu-

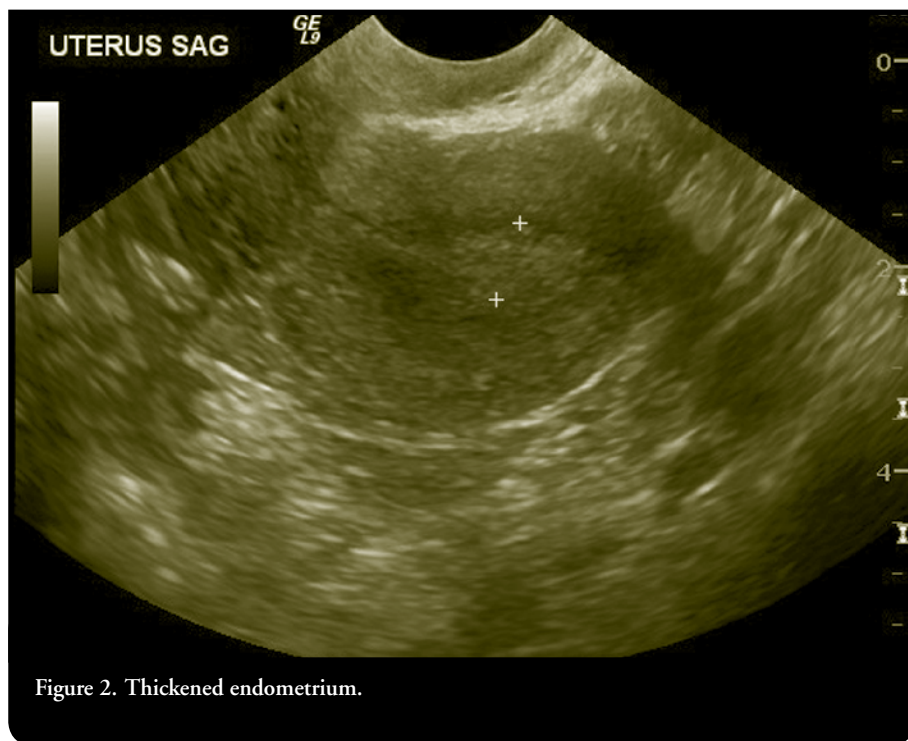


Figure 2. Thickened endometrium.

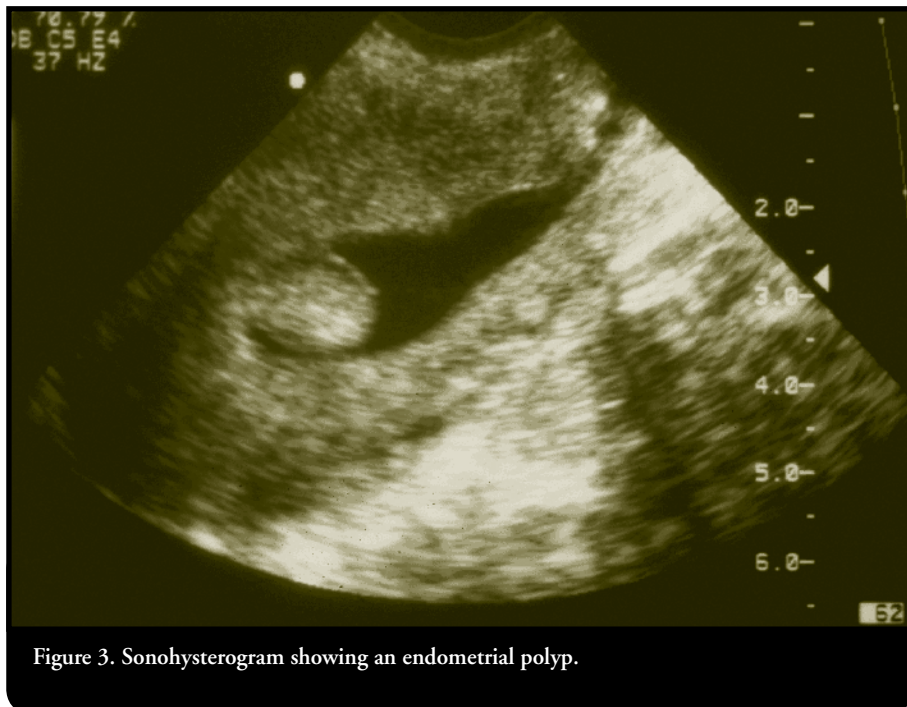


Figure 3. Sonohysterogram showing an endometrial polyp.

racy of sonohysterography in pre- and postmenopausal women with abnormal uterine bleeding.²¹ The review showed

that sonohysterography gave a sensitivity of 95% and a specificity of 88%, but the calculations for endometrial cancer were

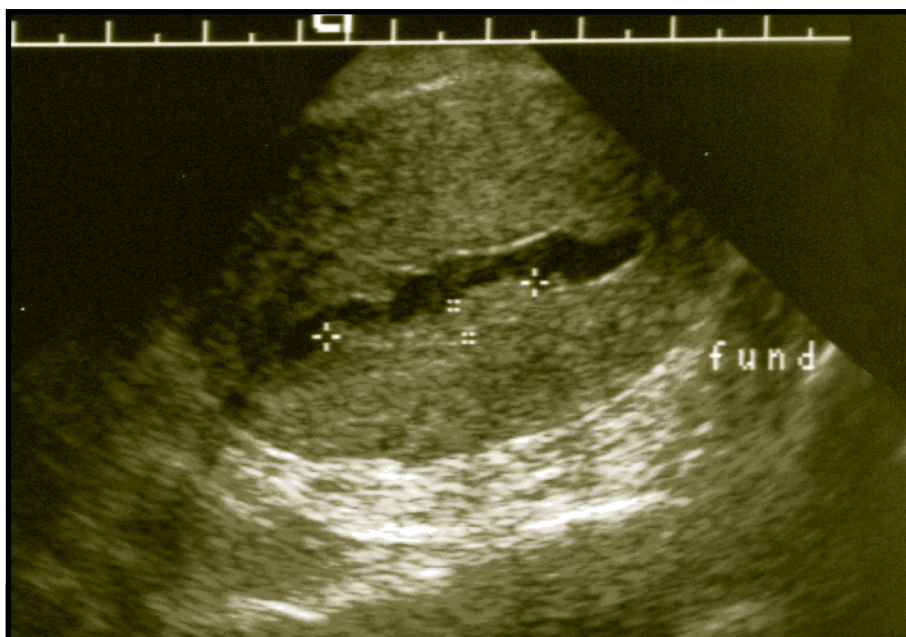


Figure 4. Sonohysterogram showing focal thickening of the endometrium.

not mentioned. In addition, Cheung *et al* suggested that the sonohysterographic appearance of endometrial carcinoma was variable and could even be normal. Therefore, sonohysterography should not be used as an initial investigation for women with PMB.²²

There is still controversy about the cut-off value for endometrial thickness

Endometrial Sampling

A definitive diagnosis of endometrial carcinoma is made by histology. The development of equipment and techniques for office-based endometrial biopsy has generally replaced the need for dilatation and curettage performed in the hospital. The current standard suction piston biopsy equipment known as the Pipelle is a plastic disposable catheter with its own internal piston to generate suction. Pipelle sampling has been shown to be more sensitive for the detection of endometrial cancer and atypical hyperplasia when compared with all other sampling devices.²³ However, it was found to miss 8–33% of cancer cases, especially for focal tumours.^{24–26} In a meta-analysis which assessed the accuracy of outpatient endometrial biopsy in the diagnosis of endometrial cancer found that the post-test probability of endome-

trial cancer after a positive test was 82% (95% confidence interval, 60–93%), and after a negative test it was 0.9% (95% confidence interval, 0.4–2.4%).²⁷ In this analysis, 15% of specimens were inadequate and one case of cancer was subsequently found among these patients; therefore, inadequate sampling is always one of the drawbacks of this technique. Farrell *et al* demonstrated that for women whose Pipelle result was insufficient, 20% had uterine pathology after further investigations, and 3% had malignancies.²⁸ In a small proportion of patients, outpatient endometrial sampling is not technically possible owing to stenotic cervical os.

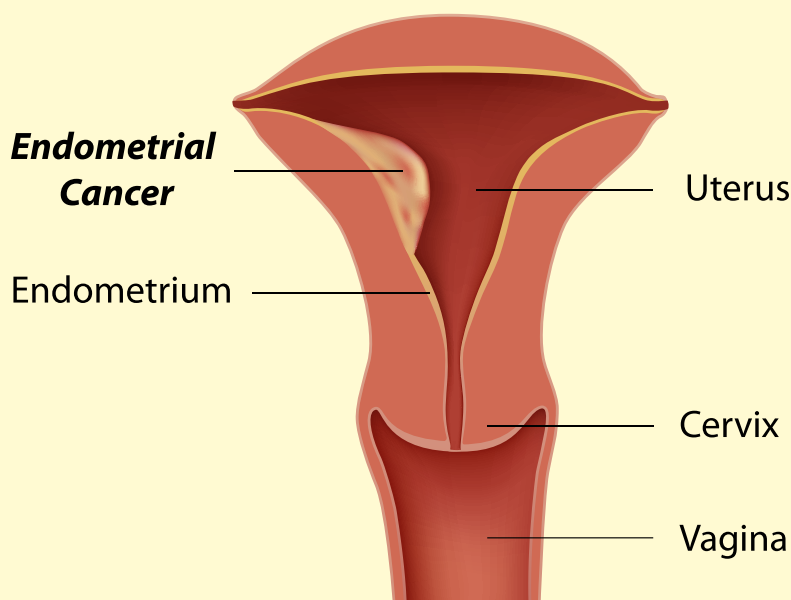
Hysteroscopy

Hysteroscopy provides direct visualization of the endometrial cavity, thereby allowing targeted biopsy during the procedure. However, it is more costly and invasive than most other modalities of endometrial assessment. A quantitative review showed a sensitivity and specificity of 86.4% and 99.2%, respectively, and its accuracy was related to diagnosing rather than excluding cancer.²⁹

Sequence of Investigations

The US guidelines recommend either TVS or outpatient endometrial sampling as the first step in evaluating women with PMB.^{5,12} The Canadian guideline recommends office endometrial biopsy as the initial choice of procedure owing to its convenience, accuracy, availability, safety, and low cost.¹³ In other guidelines, the first step is TVS, based on the high sensitivity and non-invasive character of

Endometrial Cancer



About 10% of women presenting with postmenopausal bleeding will have endometrial carcinoma.

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tamoxifen**

the procedure.^{1,11} The ideal setting will be 'one-stop' specialist clinics where investigations including TVS, endometrial sampling and hysteroscopy are available to complement clinical evaluation at the same time. Depending on the resources

available, initial endometrial sampling may be appropriate if obtaining TVS would delay assessment. If TVS is readily available, endometrial sampling is only needed if the endometrial thickness is above the cut-off value as suggested by the European guidelines.^{1,11} However, the exception applies to women taking tamoxifen, as hysteroscopy with biopsy is preferably the first line of investigation in view of the high false-positives with ultrasonography.^{1,8} Saline sonohysterography can be added to distinguish between diffuse and focal pathology, and hysteroscopy will be advised if focal lesion is found. The exact sequence of investigation will depend upon clinical judgment, local resources, local expertise, and patient preference. The available evidence evaluated the dif-

ferent investigations independently, without any consideration of combinations of tests or previous test results. Clark *et al* constructed a decision model and evaluated 12 different strategies for the initial investigation of PMB.³⁰ It was concluded that a strategy with TVS as the initial test with a cut-off of 4 mm followed by endometrial sampling was most cost-effective while strategies involving initial evaluation with test combinations or hysteroscopy alone were not.

RECOMMENDATIONS/ SUMMARY

- PMB should always be investigated, as 10% of patients will have endometrial carcinoma.

- The most common cause of PMB is atrophic vaginitis or endometritis.
- Speculum examination should always be performed to rule out local lesions.
- Either endometrial biopsy or TVS can be used as initial investigation depending on the availability of resources.
- There is still controversy about the cut-off value for endometrial thickness. The

traditional ≤ 4 mm cut-off has a high negative predictive value for malignancy, and endometrial biopsy is not necessary unless in cases of recurrent bleeding.

- Insufficient sample from endometrial biopsy should always lead to further investigations.
- Hysteroscopy should not be the first-

line investigation for PMB except for women taking tamoxifen.

About the Authors

Dr Chai is Clinical Assistant Professor in the Department of Obstetrics and Gynaecology, The University of Hong Kong. Dr Cheung is Consultant Obstetrician and Gynaecologist and Honorary Associate Professor in the Department of Obstetrics and Gynaecology, The University of Hong Kong.

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CME Article

1 Point

Postmenopausal Bleeding

Answer True or False to the questions below.

	True	False
1. The incidence of postmenopausal bleeding is estimated to be around 20%.	<input type="radio"/>	<input type="radio"/>
2. The most common cause of postmenopausal bleeding is endometrial carcinoma.	<input type="radio"/>	<input type="radio"/>
3. Women with postmenopausal bleeding should be urgently referred for specialist assessment and be seen within 4 weeks of referral.	<input type="radio"/>	<input type="radio"/>
4. Using an endometrial thickness cut-off value of 5 mm, the probability of endometrial carcinoma is 1% for a negative test.	<input type="radio"/>	<input type="radio"/>
5. An ultrasound finding of thickened endometrium in women with postmenopausal bleeding should prompt further investigation with endometrial sampling for histology.	<input type="radio"/>	<input type="radio"/>
6. Saline sonohysterography should be used as an initial investigation for women with postmenopausal bleeding because it can distinguish focal from global lesions.	<input type="radio"/>	<input type="radio"/>
7. With an inadequate endometrial sampling, we can comfortably exclude underlying endometrial carcinoma.	<input type="radio"/>	<input type="radio"/>
8. Tamoxifen use is a risk factor for endometrial carcinoma, and hysteroscopy should be the first-line investigation for this group of women.	<input type="radio"/>	<input type="radio"/>
9. Either transvaginal ultrasound or endometrial biopsy can be used as initial investigation for postmenopausal bleeding.	<input type="radio"/>	<input type="radio"/>
10. Women with endometrial thickness of 3 mm but with recurrent bleeding do not require further investigation.	<input type="radio"/>	<input type="radio"/>

Name in BLOCK CAPITALS: _____

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ANSWERS

1	2	3	4	5	6	7	8	9	10
F	T	F	T	F	T	T	T	F	F