Management of Post Menopausal Bleeding

TARGET AUDIENCE	Primary and secondary care
PATIENT GROUP	Patients having undergone menopause who present with vaginal bleeding

Clinical Guidelines Summary

Guideline for patients presenting with post-menopausal (PMB) bleeding, being defined as bleeing occurring > 12 months after the last menstrual period

The importance of this being endometrial cancer affects 5–10% of women presenting with PMB.

Risk Factors should be screened and include

- Age: Highest risk in women over 70.
- Obesity: Strong dose-response relationship.
- Others: Tamoxifen use, nulliparity, early menarche/late menopause, Lynch syndrome, family history, persistent bleeding.

Clinicians take a thorough history and highlight the importance of investigations such as pelvic examination and transvaginal ultrasound scan (TVUS)

Advised management

- TVUS: ET >4mm offer biopsy/hysteroscopy.
- Endometrial Thickness (ET) ≤4mm: No biopsy unless recurrent PMB or risk factors.

Special Considerations

- Recurrent PMB: Investigate regardless of ET; hysteroscopy often needed.
- HRT (hormone replacement therapy) users: ET cutoff is 4mm (Continuous Combined Hormone Replacement Therapy [CCHRT]) or 7mm (Sequential).
- Asymptomatic thickened endometrium: Investigate if ET ≥11mm or risk factors present.
- Uterine fluid: Biopsy if ET >4mm or fluid is echogenic.
- Anticoagulants: Procedures are low risk; no need to stop medication.
- Tamoxifen: Poor correlation with ET; bleeding warrants full evaluation

Guideline Body

Definition

Post-menopausal bleeding is defined as vaginal bleeding occurring 12 months after the last menstrual period.

PMB clinic purpose

The main purpose of PMB/hysteroscopy clinic is to exclude endometrial cancer. Uterine cancer is the 4th most common cancer in females in the UK, accounting for 5% of all new cancer cases in females and incidence has increased by around 50% in the UK since the 1990's. (1) Increased incidence may be due to obesity (2), increased life expectancy and Tamoxifen use (3).

Women with endometrial cancer usually present with postmenopausal bleeding. The probability of endometrial cancer is women presenting with PMB is 5-10%. These risks vary and increases with age and other risk factors (4,5)

General risk factors for Endometrial cancer(EC)

- Age-specific incidence rates rise steadily from age 30-34, more steeply from age 45-59 before falling steeply from age 75-79. The highest rates are in the 75 to 79 age group. (6) The estimated cancer risk is 50% in women over the age of 70 years presenting with PMB. The risk of endometrial cancer (EC) in premenopausal women is lower with 6.5% of uterine cancers diagnosed in those under 50 years of age in the UK between 2015-17. (6)
- Obesity- There is a dose-response relationship that equates to a 60% greater EC risk for every 5 kg/m2 increase in BMI above healthy weight and a 10- 15% lifetime risk for BMI (body mass index) ≥40 kg/m2 (6)
- Tamoxifen <1 % per year
- Nulliparity
- Late menopause/early menarche
- Lynch syndrome
- Family history of gynaecology cancer
- Persistent PMB (bleeding for more than one month)

Causes of PMB

Uterine causes

- **Atrophic endometritis** (with atrophic vaginitis, most common cause) (6)
- **Endometrial adenocarcinoma** - reported aetiology in up to 10% of women with PMB((8). NHS Lanarkshire rate of endometrial cancer at PMB clinic ~ 5%. (6)
- **Endometrial hyperplasia –** without atypia 5% risk of progression to EC, with atypia 28% risk of progression to EC (7)
- **Endometrial polyp** (8)
    - **postmenopausal status and vaginal bleeding associated with increased risk of premalignant or malignant endometrial polyps**
    - 2.3% risk of malignancy in symptomatic postmenopausal women
    - 0.3% risk of malignancy in asymptomatic postmenopausal women
- **Submucosal leiomyoma**
- **Medication; anticoagulants**
- **Tamoxifen**
- **Hormone replacement therapy-** (9,10,11)

<1% CCHRT

2.7-5% Sequential HRT after 3 years of usage

Vaginal/ Vulval causes

- **Atrophic vaginitis** (with atrophic endometritis most common cause)
- **Vulval,** vaginal malignancy (rare)

Cervical causes

- **Polyps**
- **Malignancy**

Haematuria

Rectal bleeding

PMB/ Hysteroscopy clinic workup

- History and evaluation
- Appropriate pelvic examination including inspection/palpation of cervix
- TVUS(transvaginal ultrasound scan) to evaluate ET +/- TAS (transabdominal ultrasound scan) or both
- Endometrial biopsy when indicated
- Hysteroscopy when indicated.
- Weight loss advice when required
- Appropriate referrals to be made

Role of Transvaginal ultrasound (TVUS)

Predictive performance of endometrial thickness to detect endometrial cancer.

- 3mm or over, sensitivity 97.9% and specificity 35.4%
- 4mm or over, sensitivity 94.8% and specificity 46.7%
- 5mm or over, sensitivity 90.3% and specificity 54% (12,13)

Optimal cut off for endometrial thickness to identify women with postmenopausal bleeding, including CCHRT users (PMB) at increased risk for malignancy is 4mm. (14) This reduces the probability of endometrial cancer to less than 1%.

Based on this guidance NHSL suggest endometrial biopsy +/- hysteroscopy as per the clinical situation. Care should be individualised if ET is >4 mm.

TVUS treatment pathways for postmenopausal bleeding (PMB) and endometrial biopsy indication

- endometrial thickening ≤ 4 mm, endometrial sampling or hysteroscopy not required – **unless recurrent PMB or risk factors or endometrium shows irregular outline** (6)
- endometrial thickening > 4 mm (or inability to visualize thickness), further evaluation should occur - hysteroscopy and endometrial biopsy if required, (especially if at high risk of endometrial ca or ultrasound irregularities) (6)

Given ~ 1% of endometrial cancers will remain undetected in TVUS findings of 4mm, there must be clear instructions for patients to return if any further bleeding.

Pipelle biopsy leads to overall diagnostic accuracy when an adequate specimen is obtained. Post-test probability of endometrial cancer = 81.7% for a positive test and 0.9% for a negative test (15,16)

Role of Hysteroscopy

Gold standard for investigating lesions within uterine cavity and visually assessing endometrium.

Hysteroscopy appears accurate for identifying intrauterine abnormalities in women with postmenopausal bleeding. It allows for direct visualisation of any focal lesions that can be missed with endometrial sampling

Systematic review of 26,346 women – (17)

- positive hysteroscopy result had pooled LR 60.9 (95% CI 51.2-72.5) increasing probability of cancer to 71.8% (95% CI 67%-76.6%)
- negative hysteroscopy result had pooled LR 0.15 (95% CI 0.13-0.18) decreasing probability of cancer to 0.6% (95% CI 0.5%-0.8%) (6)

Special situations

Recurrent PMB

Consider hysteroscopy and endometrial biopsy irrespective of endometrial thickness if patient presents with recurrent PMB (6)

If there is on-going concern, due to persistent symptoms, despite a negative Pipelle®, hysteroscopy should be considered. (Grade D)

Hysteroscopy is recommended, if outpatient endometrial biopsy by other means is not feasible, for women who have ultrasound irregularities, or for those at high risk of endometrial cancer. (Grade B

- All women need to be seen if recurrence happens after 6 months of negative evaluation – advise accordingly in GP letter.
- **In cases of unexplained recurrence, the management plan must be individualised. There must be a low threshold for investigations even with "normal" scan results or previously normal biopsies**
- Women with recurrent PMB often have a higher prevalence of endometrial polyps, rather than hyperplasia or cancer. Hysteroscopy may be warranted as first line investigation (18)
- A failsafe mechanism for reinvestigation of recurrent PMB is required in both primary and secondary care to ensure that women understand they should re-present to their primary care team, despite being discharged with reassuring investigations, if they experience continued bleeding (6)

- Hysterectomy may be considered in cases of unexplained recurrent PMB. (Grade D)

Patients on HRT

The upper limit of the endometrial thickness which warrant further investigations is 4 mm for patients on CCHRT and 7 mm for patients who use Sequential HRT. Ideally patients should be seen within a week after the progesterone phase if using sequential.(11) In NHSL >80 percent use CCHRT and our local audits showed two cases of hyperplasia or endometrial cancer. (< than 1 %)

Asymptomatic women with incidental finding of thickend endometrium

- In asymptomatic women with a thickened endometrium, a cut off of <11mm can be used prior to investigating/appointing to PMB/hysteroscopy clinic. (19)
- The risk of endometrial cancer in asymptomatic women with an endometrial thickness of 11 mm or more is around 5.9%. (20,21)
- Hysteroscopy should be performed if any concerning features (inhomogeneity, increased vascularity or particulate fluid) or significant risk factors (obesity, hypertension, diabetes, history of breast cancer, on tamoxifen etc) (19,22)
- Shared decision making is recommended in this group of patients after explaining the current policies.

Fluid in uterus

- Although fluid in the cavity is generally considered to be “normal”, there is no convincing evidence to support this.(23) Most intrauterine fluid collections are caused by transudate from an atrophic endometrium which accumulates in the endometrial cavity due to cervical Stenosis (24)
- The fluid may represent pyometra with potential for serious infection if hysteroscopy carried out.
- Cervical carcinoma must always be excluded in presence of uterine fluid (25,26)
- Endometrial thickness should be measured from either side of the fluid, giving 2 measurements which can be added together.
- Obtain endometrial biopsy if total ET is greater than 4mm or if echogenic fluid (27)
- If ET less than 4mm in the presence of clear intrauterine fluid of depth (3mm or less) can be discharged (26)

  Pragmatically, NHS Lanarkshire, recommend that in the presence of fluid and an ET greater than 4m, endometrial biopsy should be taken and each case to be individualised. Antibiotic cover to be considered if hysteroscopy is planned. If the fluid is <3mm and clear and ET <4 mm, no further investigations are required.

Investigations for women on anticoagulants

- Diagnostic hysteroscopy and pipelle biopsy procedures are considered to be low risk procedures for bleeding for women on anticoagulants (28)

- **Anticoagulants do not require to be stopped before diagnostic hysteroscopy and/or pipelle biopsy as this procedure is deemed to be low risk for bleeding.**
- **Risks and benefits need to be balanced and each case to be individualised as this may delay investigations**

Investigations for women on Tamoxifen use

- Ultrasound measurements of endometrial thickness are poorly correlated with endometrial pathology due to Tamoxifen-induced sub-epithelial stromal hypertrophy in asymptomatic women.(29)

- Abnormal vaginal bleeding, and other red flag symptoms as per NICE guidelines (NG12), (30)) should prompt urgent investigation by TVS, hysteroscopy and endometrial sampling (Grade D)

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Appendices

1. Governance information for Guidance document

Lead Author(s):	Sheila Hughes, Anna Pandravada
Endorsing Body:	Gynaecology Clinial Effectivness Group (GCEG)
Version Number:	2
Approval date	**03/05/2025**
Review Date:	May 2028
Responsible Person (if different from lead author)	Sheila Hughes (Nursing Team Lead UHH) , Anna Pandravada (Consutlant Gynecologist)

CONSULTATION AND DISTRIBUTION RECORD	
Contributing Author / Authors	Sheila Hughes, Anna Pandravada
Consultation Process / Stakeholders:	Gynaecology Clinical Effectivness Group (GCEG)
Distribution	NHSL Gynaecology department

CHANGE RECORD			
Date	**Lead Author**	**Change**	**Version No.**

2020	Anna Pandravada	Production of initial departmental guideline	1
2025	Sheila Hughes	Review and update in line with current guidance	2
			3
		.	4
			5