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Health Service Executive



INSTITUTE OF OBSTETRICIANS
& GYNAECOLOGISTS

ROYAL COLLEGE OF PHYSICIANS OF IRELAND

CLINICAL PRACTICE GUIDELINE

Investigation of Postmenopausal Bleeding

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And

Directorate of Clinical Strategy and Programmes,
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Key Recommendations

1. Women presenting with postmenopausal bleeding (PMB) should have a detailed history and pelvic examination, including speculum examination.
2. Women presenting with PMB should be referred and seen promptly.
3. Women referred for investigation of PMB are not required to stop using hormone replacement therapy (HRT) prior to investigation.
4. In women not on HRT treatment an endometrial thickness of ≤ 3 mm on scan strongly reduces the probability of endometrial pathology.
5. In women on sequential combined HRT the probability of endometrial pathology is reduced in the presence of an endometrial thickness of ≤ 5 mm.
6. Women with PMB and increased endometrial thickness should undergo more invasive testing to exclude endometrial pathology.
7. A hysteroscopy and endometrial sampling is warranted in women with a thickened endometrium on ultrasound.
8. Women with recurrent or persistent PMB may need to be re-investigated in view of the false negative rate associated with all methods of diagnosis.
9. It is important that there is a clear flow of information between specialists, general practitioners and patients in order that the results of tests performed and their implications can be explained.

1. Purpose and Scope

The purpose of this guideline is to improve the investigation of women with postmenopausal bleeding (PMB). This guideline focuses on the detection of endometrial cancer, the most serious potential underlying cause of PMB. It must be remembered, however, that PMB may also be the presenting symptom of cervical or vulval cancer. Benign conditions represent the most frequent cause of PMB and can cause considerable distress, so most patients will expect a series of investigations that explain their symptoms and underscores the doctors' ability to reassure them that all reasonable assessments have been made. Specific recommendations on management of the different causes of PMB are not covered in this guideline.

The guideline is intended to be primarily used by health personnel working in the area of women's health which includes gynaecologists, nurse sonographers, radiographers, radiologists and general practitioners. This guideline aids clinical judgement and does not replace it. In individual cases a healthcare professional may, after careful consideration, decide not to follow the guideline if it is deemed to be in the best interest of the woman.

2. Background and Introduction

PMB represents one of the most common reasons for referral to gynaecological services, largely due to suspicion of an underlying endometrial pathology (Anderson et al, 2001). Endometrial cancer is present in approximately 10% of women referred with PMB (Astrup and Olivarius, 2004). Formerly, the principal means of hospital investigation was by dilatation and curettage (D&C), but newer methods of investigation such as outpatient endometrial biopsy, transvaginal ultrasonography and hysteroscopy have superseded D&C. However, there is professional uncertainty concerning the most accurate, acceptable and efficient diagnostic approach.

3. Methodology

This guideline was written after Medline, EMBASE and Cochrane Database of Systematic Reviews were searched using the terms 'menopause', 'bleeding', and 'postmenopausal bleeding'. Searches were limited to humans and restricted to the titles of English language articles published between August 1992 and August 2012. Relevant meta-analyses, systematic reviews, intervention and observational studies were reviewed.

Abbreviations

D&C:	Dilatation and Curettage
H&C:	Hysteroscopy and Curettage
HRT:	Hormone replacement therapy
HNPCC	Hereditary non-polyposis colorectal cancer

PMB:	Postmenopausal bleeding
TAS:	Transabdominal ultrasound scan
TVS:	Transvaginal ultrasound scan

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4. Service Provision

All gynaecology services should be able to assess women with postmenopausal bleeding. The service should be staffed by a midwife sonographer/ radiographer who have been trained in gynaecology ultrasound. Where the facilities are available, a one-stop ambulatory clinic will enable ultrasound, hysteroscopy and endometrial sampling to be carried out in a single visit. It is important that there is a clear flow of information between specialists, general practitioners and patients in order that the results of tests performed and their implications can be explained. Structured follow up and advice on what to do in the event of recurrence should also be available.

5. Clinical Guideline

5.1 Defining PMB

The menopause is defined by the World Health Organization as the permanent cessation of menstruation resulting from the loss of ovarian follicular activity. (Bergman et al, 2000). This definition of the menopause is unhelpful in determining when an episode of bleeding can be described as postmenopausal. From a symptomatic perspective, postmenopausal bleeding describes the occurrence of vaginal bleeding following a woman's last menstrual cycle. There is some debate regarding the minimum time period that must have passed after the end of menstruation before PMB can be considered to have taken place. For the purpose of this guideline, an episode of bleeding 12 months or more after the last period is accepted as postmenopausal.

Abnormal bleeding in women using hormone replacement therapy (HRT) can be difficult to assess (Bettocchi et al, 2003). For sequential (cyclical) regimens, abnormal bleeding may be considered if a woman experiences heavy or prolonged bleeding at the end of or after the progestogen phase or if bleeding occurs at an unscheduled time during the cycle. For women on tibolone or continuous combined HRT it can take up to six months for amenorrhoea to develop. Therefore in these women bleeding should be considered abnormal if it

occurs after six months of treatment or if it occurs after amenorrhoea has been established.

5.2 Risk of endometrial cancer

The absolute risk of endometrial cancer in non-users of HRT who present with PMB ranges from 5.7 to 11.5% (Astrup and Olivarius, 2004).

- *Age*
In a representative population of postmenopausal Swedish women it has been found that the incidence of bleeding decreases markedly with age (Astrup and Olivarius, 2004). However, the probability of endometrial cancer being present in women with PMB increased with age.
- *Hormone replacement therapy (HRT)*
Older HRT regimens that utilise unopposed oestrogen increase the relative risk of endometrial cancer by around six times after five years of use (Bornstein et al, 1999). Progestogens are added to HRT regimens to prevent endometrial hyperplasia and cancer. Their inclusion reduces the relative risk of endometrial cancer to around 1.5 (Bruchim et al, 2004).
- *Tamoxifen*
Women receiving tamoxifen in the treatment or prevention of breast cancer experience a three to six fold greater incidence of endometrial cancer. (Clark et al, 2006) The risk of endometrial cancer rises with both the use of higher doses and increasing duration of tamoxifen use. Treatment beyond five years increases risk by at least fourfold (Curtis et al, 1996). Furthermore, there is evidence to suggest that endometrial cancer occurring in long term users of tamoxifen has a poorer prognosis than cancers occurring in other women (Dijkhuizen et al, 1996).
- *Other risk factors*
Hereditary non-polyposis colorectal cancer (HNPCC) is one of the commonest inherited cancer syndromes. Its inheritance is autosomal dominant. It is characterised by a familial aggregation of colorectal cancer in addition to extra-colonic cancers of which endometrial cancer is the commonest. The estimated lifetime risk of developing endometrial cancer in women carrying these mutations is around 42 to 60% (Van Doorn et al, 2007). Importantly, in contrast to 'sporadic' endometrial cancer, women from such affected families usually develop endometrial cancer premenopausally (Dunlop et al, 1997).

The evidence on other risk factors is less robust but it suggests there are potential risk groups' i.e. obese women with diabetes; women with hypertension; a past history of hyper-oestrogenism (endogenous or exogenous). Examples of the latter include women with early menarche and late menopause (Gredmark et al, 1995).

5.3 Referral for assessment

Traditionally, PMB has represented an absolute indication for gynaecological investigation. This is because it is difficult, if not impossible to rule out endometrial cancer on clinical assessment alone. General Practitioners should take into account the pattern of bleeding, its relationship to the use of HRT and patient preference when considering referral. Concern from either general practitioner or patient about the possibility of PMB signalling endometrial cancer constitutes sufficient grounds for referral. Women referred with PMB should be seen promptly with the understanding that waiting times and the availability of rapid access and one-stop clinics will vary between units.

5.4 Clinical assessment of PMB

Women presenting with PMB require a pelvic examination, including speculum examination at some stage during their assessment. Examination by the general practitioner or practice nurse can alter the course of clinical management as it may expedite referral on grounds of raised suspicion of a malignancy (e.g. cervical cancer) or it may highlight an obvious cause of bleeding (e.g. cervical polyps). This examination may also represent an opportunity to take a routine cervical smear if this is due within the National Screening Program. Women who have not been examined by their General Practitioner should have a pelvic examination prior to or at the time of transvaginal ultrasound.

5.5 Continuation of HRT prior to investigation

Use of sequential HRT generally leads to thickening of the endometrial lining, whereas continuous combined HRT and tibolone cause endometrial atrophy. There is uncertainty as to whether HRT should be stopped or not prior to investigation for PMB. There is unlikely to be any problem in histological interpretation if the woman remains on HRT provided the pathologist is given details of the hormonal treatment. In addition the pathologist may be able to identify changes in the endometrium that are hormonally induced and could explain the abnormal or unscheduled bleeding. Alternatively, by stopping HRT and inducing an oestrogen withdrawal bleed, tissue may theoretically be lost that should be assessed.

5.6 Investigations

The principle aim of investigation of PMB is to identify or exclude endometrial pathology, most notably endometrial cancer.

- *Transvaginal ultrasonography (TVS)*
The mean endometrial thickness in postmenopausal women is much thinner than in premenopausal women. Thickening of the endometrium may indicate the presence of pathology. For the last two decades TVS has become widely used in the evaluation of women with PMB. High-resolution TVS can reliably assess thickness and morphology of the endometrium and can thus identify a group of women with PMB who have a thin endometrium and are therefore unlikely to have significant endometrial pathology.

- *Endometrial thickness measurement*
It is conventional to measure the double thickness measurement of both endometrial surfaces at the thickest point in the mid-sagittal view. If there is fluid in the cavity separating the two layers of endometrium then the layers are measured individually and summated. Use of the endometrial thickness cut-off assumes that the endometrial morphology is normal. Any abnormal features would require further investigation irrespective of endometrial thickness.
- *Endometrial thickness cut-off*
There are different endometrial thickness thresholds that may be used for recommending further investigation. However there is a trade off between sensitivity and specificity. The probability of endometrial pathology is strongly reduced in the presence of an endometrial thickness of ≤ 3 mm.¹³ This cut off should be considered in women who have never used HRT, in women who have not used any form of HRT for a year or more and in women using continuous combined HRT.

The mean endometrial thickness in women on sequential HRT with PMB is greater than in those with PMB who are not on sequential HRT. In women on sequential combined HRT the probability of endometrial pathology is reduced in the presence of an endometrial thickness of ≤ 5 mm.¹⁴

Women with PMB and increased endometrial thickness should undergo more invasive testing to exclude endometrial pathology. In addition, any other reported abnormalities such as endometrial polyps should prompt further investigation.

- *Dilatation and Curettage (D&C)*
D &C was traditionally the method of choice for investigating patients with PMB. However, in approximately 60% of D&C procedures less than half of the uterine cavity is curetted. A small case series where D&C was carried out before a hysterectomy showed that in up to 10% of instances endometrial lesions were overlooked by the D&C (Guner et al, 1996). Another drawback of D&C is that this procedure is performed under general anaesthesia in an inpatient setting (Bettocchi et al, 1993).
- *Endometrial sampling*
In postmenopausal women endometrial sampling with both the Pipelle device (Pipelle de Cornier, Paris, France) and the Vabra device (Berkeley Medevices, Inc, Richmond, California, USA) are very sensitive techniques for the detection of endometrial carcinoma, with detection rates of 99.6% and 97.1% respectively (Gull et al, 2001). However, sometimes the amount of tissue obtained by office sampling varies considerably and is insufficient for reliable histological diagnosis. A prospective study found that in four (6%) out of 66 women where there was insufficient tissue obtained from office sampling subsequent invasive testing detected endometrial pathology (Granberg et al, 1997). This finding implies that in women with an insufficient sample from office sampling and where a scan suggests thickened endometrium the clinician must not be reassured and more invasive testing may need to be performed.

- *Hysteroscopy*
Hysteroscopy offers the possibility of visualising macroscopic or focal abnormalities and taking directed biopsies. With the development of smaller diameter hysteroscopic systems and the introduction of the vaginoscopic approach to hysteroscopy, outpatient hysteroscopy has received considerable acceptance by women (Gupta et al, 2002).

5.7 Diagnostic strategies

Depending on the endometrial cancer prevalence, a strategy with TVS as an initial investigation is cost effective (Van Leeuwen et al, 1994). However, it is reasonable to pursue a different approach to investigation if direct access to TVS is not available. Obtaining an initial endometrial sample may be in the patient's interest if it identifies a cancer prior to the ultrasound appointment.

The finding of a thickened endometrium on ultrasound indicates that the risk of abnormality is significant enough to warrant further investigation. As the false negative rate of endometrial sampling is significant, it is recommended that endometrial sampling is combined with a hysteroscopic examination of the endometrial cavity. The hysteroscopic evaluation of the endometrial cavity reassures the clinician whether or not a visible abnormality exists, indicates whether material for histological assessment is obtainable and may demonstrate the best method to achieve it.

When sampling gives no yield, a negative hysteroscopy confirms the outcome is acceptable. It is not unreasonable to pursue a different approach to investigation if there is a delay in performing a hysteroscopy. Obtaining an initial endometrial sample may be in the patient's interest if it identifies a cancer prior to the hysteroscopic examination.

Women with breast cancer who take tamoxifen on a long term basis are at increased risk of endometrial cancer (Clark et al, 2006). However, ultrasonography is poor at differentiating potential endometrial pathology from tamoxifen induced thickening because of the distorted endometrial architecture associated with long term use of tamoxifen (Lethaby et al, 2002). The use of hysteroscopy and biopsy as first line investigations may be more appropriate and provide less ambiguous results in this high risk group (Moirits et al, 1999).

Women with a normal vaginal and speculum examination and normal transvaginal ultrasound can be reassured that no further investigation is needed unless bleeding recurs.

Women with recurrent or persistent PMB may need to be re-investigated in view of the false negative rate associated with all methods of diagnosis (Gull et al, 2001; Opmeer et al, 2007). There is no evidence when re-investigation should take place and in such circumstances clinical judgement is required.

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7. Implementation Strategy

- Distribution of guideline to all members of the Institute and to all gynaecology units.
- Implementation through HSE Obstetrics and Gynaecology programme local implementation boards.
- Distribution to other interested parties and professional bodies.

8. Key Performance Indicators

- Referral to review waiting time.
- Percentage of women having a one-stop approach, including the availability of hysteroscopy and biopsy in the outpatient setting.
- Percentage of women where re-investigation was carried out.

9. Qualifying Statement

These guidelines have been prepared to promote and facilitate standardisation and consistency of practice, using a multidisciplinary approach. Clinical material offered in this guideline does not replace or remove clinical judgment or the professional care and duty necessary for each pregnant woman. Clinical care carried out in accordance with this guideline should be provided within the context of locally available resources and expertise.

This Guideline does not address all elements of standard practice and assumes that individual clinicians are responsible for:

- Discussing care with women in an environment that is appropriate and which enables respectful confidential discussion.
- Advising women of their choices and ensure informed consent is obtained.
- Meeting all legislative requirements and maintaining standards of professional conduct.
- Applying standard precautions and additional precautions, as necessary, when delivering care.
- Documenting all care in accordance with local and mandatory requirements.