



Investigation of Post-Menopausal Bleeding

A national clinical guideline

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KEY TO EVIDENCE STATEMENTS AND GRADES OF RECOMMENDATIONS

LEVELS OF EVIDENCE

1 ⁺⁺	High quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias
1 ⁺	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1 ⁻	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2 ⁺⁺	High quality systematic reviews of case control or cohort studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2 ⁺	Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2 ⁻	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

GRADES OF RECOMMENDATION

Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

A	At least one meta-analysis, systematic review of RCTs, or RCT rated as 1 ⁺⁺ and directly applicable to the target population; <i>or</i> A body of evidence consisting principally of studies rated as 1 ⁺ , directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2 ⁺⁺ , directly applicable to the target population, and demonstrating overall consistency of results; <i>or</i> Extrapolated evidence from studies rated as 1 ⁺⁺ or 1 ⁺
C	A body of evidence including studies rated as 2 ⁺ , directly applicable to the target population and demonstrating overall consistency of results; <i>or</i> Extrapolated evidence from studies rated as 2 ⁺⁺
D	Evidence level 3 or 4; <i>or</i> Extrapolated evidence from studies rated as 2 ⁺

GOOD PRACTICE POINTS

<input checked="" type="checkbox"/>	Recommended best practice based on the clinical experience of the guideline development group
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1 Introduction

1.1 THE NEED FOR THE GUIDELINE

Post-menopausal bleeding (PMB) represents one of the most common reasons for referral to gynaecological services, largely due to suspicion of an underlying endometrial malignancy. Endometrial cancer is present in approximately 10% of patients referred with PMB. 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.

The general practitioner (GP), as the usual first point of contact for a woman with this complaint, faces the unenviable task of assessing whether referral is required according to the clinical picture (which is not always clear-cut) and the woman's preferences. Furthermore, the growing use of hormone replacement therapy (HRT) has increased clinical uncertainty as to what constitutes unscheduled bleeding requiring referral for investigation.

The use of tamoxifen in the treatment of breast cancer has increased. Tamoxifen is associated with a higher risk of endometrial cancer. The presentation of PMB therefore requires urgent consideration in this group of women.

1.2 EVIDENCE AND CONTEXT

Despite numerous publications on the issue of PMB, there is a paucity of evidence on how best to address it. The literature often fails to differentiate the post-menopausal from the peri-menopausal or the patient with dysfunctional uterine bleeding. Investigative techniques in many reviews are applied to a variety of gynaecological problems. The number of cases is often small and these represent local interest, skills or referral patterns. Consequently, techniques that may well be useful and are certainly widely used have an inadequate evidence base to support their recommendation in guidelines.

Where good quality evidence has been identified, specific clinical recommendations have been made. Areas lacking good evidence or where recommendations have been extrapolated are highlighted throughout this guideline.

Whilst recognising the limitations of the current evidence base, the guideline development group is aware that the absence of evidence does not necessarily imply any lack of effectiveness or accuracy for a specific diagnostic approach.

The current availability and use of investigative approaches among gynaecological departments in Scotland have been assessed so that these guidelines can be placed into the relevant local context. It is necessary to take into account the resource implications of recommendations for NHS Scotland otherwise there is a danger of recommending practices for which there is no current infrastructure.

Although this guideline identifies the practices for which the most robust evidence exists, clinicians managing women presenting with PMB will have to assess their practice in the light of this evidence and their own facilities and experience.

1.3 DEFINING PMB

The menopause is defined by the World Health Organisation as the permanent cessation of menstruation resulting from the loss of ovarian follicular activity.² This definition of the menopause is unhelpful in determining when an episode of bleeding can be described as post-menopausal. From a symptomatic perspective, post-menopausal 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 purposes of this guideline, an episode of bleeding 12 months or more after the last period is accepted as post-menopausal bleeding.

Abnormal bleeding in women using HRT can be difficult to assess. Unscheduled bleeding is the term used for breakthrough bleeding occurring in women on cyclical HRT or any bleeding in women on tibolone (Livial) or continuous combined HRT, although it can take up to six months for amenorrhoea to develop in the latter treatments. Consequently, assessment depends upon the type of regimen.³

For sequential regimens, abnormal bleeding may:

- be heavy or prolonged at the end of or after the progestogen phase, or
- occur at any time (breakthrough bleeding).

Continuous combined regimens are designed largely to induce amenorrhoea and therefore avoid cyclical bleeding. However, nearly half of women on continuous combined regimens will experience bleeding at some time, usually within the first six months of treatment.⁴ Such bleeding and premenstrual symptoms represent the most common reasons for discontinuing continuous combined regimens. Amenorrhoea is more likely to be maintained in women starting continuous combined HRT 12 months or more after the menopause.

Pragmatically, bleeding on continuous combined regimens should be considered abnormal (requiring endometrial assessment) if:

- it occurs after the first six months of treatment, or
- it occurs after amenorrhoea has been established.

1.4 RISK ASSESSMENT AND PMB

Gynaecologists, general practitioners and most patients understand that the investigation of PMB primarily aims to identify any significant abnormality, particularly cancer. 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 cancer. Benign conditions represent the most frequent cause of PMB and can cause considerable distress, so most patients will expect a programme of investigations that explains their symptoms and underscores the doctor's ability to reassure them that all reasonable assessments have been made.

A significant minority of patients presenting with PMB will have endometrial cancer and PMB may also be the presenting symptom of cervical cancer. Endometrial cancer represents the most common gynaecological malignancy after ovarian cancer. This guideline will help to resolve the most accurate method of identifying these patients. However, diagnosis is only the first phase in planning the treatment of those women with endometrial cancer. Proper evaluation of each woman's cancer must be carried out before a definite treatment plan can proceed.

A negative test may be taken as a guarantee of normality by the patient, but the clinician should be aware of the possibility of a false negative result. Most patients expect their clinicians to determine or advise when investigations are complete. This decision is informed by knowledge of test performance, the test findings, and patient characteristics.

Sensitivity and specificity are often used to summarise the performance of a diagnostic test. Sensitivity is the probability of testing positive if the disease is truly present. Specificity is the probability of testing negative if the disease is truly absent. However, they are not particularly intuitive and are hence difficult to explain. More importantly, considered on their own they offer no help in the interpretation of test results in individual patients.

A more clinically-orientated method of interpreting diagnostic test results was used in drawing up some of the recommendations for this guideline. This focuses on the interpretation of the test result for a patient with a specified risk level for the disease. Several key recommendations are based upon evidence concerning the use of transvaginal ultrasound (TVUS). Two sources of information were combined to develop recommendations about the selection and interpretation of this investigation:

- test performance (i.e. sensitivity and specificity), by cut-off value used to determine whether a TVUS result is normal or abnormal;
- the probability that disease is present when the patient presents for investigation (i.e. pre-test probability).

For different subsets of patients presenting with PMB or unscheduled bleeding, these factors together allow estimation of the probability that disease is present following an investigation (i.e. post-test probability). Hence, if the (post-test) probability of endometrial cancer is sufficiently low following a negative test result, it is possible to reassure the patient and support taking no further action.

Therefore this guideline uses probabilities to inform recommendations on the selection and interpretation of TVUS. Further details of the methodology of this approach is available alongside the electronic version of this guideline at the SIGN website at www.sign.ac.uk.

1.5 STATEMENT OF INTENT

This guideline is not intended to be construed or to serve as a standard of medical care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. These parameters of practice should be considered guidelines only. Adherence to them will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement regarding a particular clinical procedure or treatment plan must be made in light of the clinical data presented by the patient and the diagnostic and treatment options available. However, it is advised that significant departures from the national guideline or any local guidelines derived from it should be fully documented in the patient's case notes at the time the relevant decision is taken.

1.6 REVIEW AND UPDATING

This guideline was issued in 2002 and will be considered for review as new evidence becomes available. Any updates to the guideline will be noted on the SIGN website: www.sign.ac.uk.

2 Risk of endometrial cancer

2.1 RISK FACTORS FOR ENDOMETRIAL CANCER

The absolute risk of endometrial cancer in non-users of HRT who present with post-menopausal bleeding ranges from 5.7% to 11.5%.⁵⁻⁷ 2+
3

No evidence was identified which determined whether different patterns of PMB, such as one-off or more frequent bleeds, are more or less likely to be associated with endometrial cancer.

2.1.1 AGE

Scottish cancer registration data indicate the background incidence of endometrial cancer by age group for women in Scotland (see Table 1). Note that these data represent the incidence for all women in the age group whereas the vast majority of women under 50, and a substantial proportion of those between 50 and 60 years, will not yet be post-menopausal. Therefore registration data cannot be used to estimate incidence of endometrial cancer in post-menopausal women under 60 years.

Furthermore, the data in Table 1 include all cases regardless of presentation, and so do not inform as to risk of endometrial cancer in women presenting with PMB. In a representative population of post-menopausal Swedish women it has been found that the incidence of bleeding decreases markedly with age.⁶ It was furthermore shown that the probability of endometrial cancer being present in the women with post-menopausal bleeding increased after 50 years of age, and increased further after 60, 65 and 80 years of age.

Table 1: Age specific rates of cancer of the body of the uterus in Scottish women (1986-95)⁸

Age Group (years)	Rates per 100,000 p.a.
< 50	0.4
50 - 59	6.36
60 - 69	8.68
70 - 79	8.22
80+	7.28

2.1.2 HORMONE REPLACEMENT THERAPY (HRT)

Older HRT regimens that utilise unopposed oestrogen increase the relative risk of endometrial carcinoma by around six times after five years of use.⁹ Progestogens are added to HRT regimens to prevent endometrial hyperplasia and cancer: their inclusion reduces the relative risk of endometrial cancer to around 1.5.¹⁰ Protection is provided by either 10-12 days of cyclical progestogens or continuous combined regimens. 1++

Sequential (or cyclical) combined regimens cause scheduled bleeding in most users. Continuous combined regimens are associated with a reduced relative risk of endometrial cancer⁹ but may cause unpredictable spotting or bleeding during initial use.^{11,12} 1+
4

The incidence of endometrial abnormalities in women receiving HRT may be higher in the general population than in clinical trial populations because the latter might be investigated before commencing HRT to exclude pre-existing problems. Data on incidence of endometrial cancer recorded from 1997 - 2000 at all CMR (continuous morbidity recording) practices in Scotland is available from the SIGN website (www.sign.ac.uk). Bleeding in HRT users is less likely to be associated with endometrial carcinoma than bleeding in non-HRT users although benign pathology, such as polyps, may be present.¹³ 2+

- C** Clinicians should be aware of the background incidence of endometrial cancer among users and non-users of HRT and in those who present with post-menopausal bleeding.
- A** HRT should include a progestogen regime which is protective against the endometrial effects of unopposed oestrogen.

2.1.3 TAMOXIFEN

Women receiving tamoxifen in the treatment or prevention of breast cancer experience a three to sixfold greater incidence of endometrial cancer.¹⁴⁻¹⁷ An increasing number of women are now receiving this therapy. 1+

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.^{18,19} 2+

Furthermore, there is evidence from one case control study that endometrial cancers occurring in long-term users of tamoxifen have a poorer prognosis (due to less favourable histology and higher stage) than cancers occurring in other women.²⁰ 2+

There has been some debate about how closely women on tamoxifen should be monitored for the development of endometrial cancer, including suggestions that this should take the form of periodic investigations in those with no history of PMB. However, evidence mainly from observational studies indicates that periodic investigations are unlikely to be cost-effective.^{21,22} Therefore, PMB should remain as the primary trigger for investigation of women on tamoxifen. 2+

- A** Clinicians should be aware that post-menopausal women receiving tamoxifen therapy, particularly for longer than five years, are at increased risk of endometrial cancer.

2.1.4 OTHER RISK FACTORS

Hereditary non-polyposis colorectal cancer (HNPCC) is one of the commonest cancer family 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%.^{23,24} Importantly, in contrast to "sporadic" endometrial cancer, women from such affected families usually develop endometrial cancer pre-menopausally.²⁵ 2+

See the SIGN guideline on Management of Colorectal Cancer which is under review in 2002.

The evidence on other risk factors is less robust but it suggests there are potential risk groups i.e. obese patients with diabetes; women with hypertension; a past history of hyper-oestrogenism (endogenous or exogenous).^{5,26} Examples of the latter include women with early menarche and late menopause. However, current evidence is insufficient to quantify this risk as a guide to referral practice. 2+
3

3 Referral for assessment

Post-menopausal bleeding represents a common clinical problem in primary care. Consultations for PMB with general practitioners are highest in women aged 50-59 years, at 14.3/1000 population over 1999-2000. (Further details of consultation rates and incidence by age group for all Continuous Morbidity Recording practices in Scotland between 1997 and 2000 are available on the SIGN website at www.sign.ac.uk.) This data also indicates that consultation rates are rising, possibly related to increasing use of HRT.

3.1 WHEN TO REFER

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. However, as discussed in section 2, the risk of cancer varies widely among different groups of women presenting with PMB.

Three considerations question the need for mandatory referral. First, the clinical assessment of PMB is complicated by irregular bleeding associated with the use of HRT. Second, there is little research evidence on the patterns of bleeding and whether, for example, light or 'one-off' bleeds should cause more alarm than heavier or recurrent bleeds – although intuitively either of the latter would be more likely to prompt referral. Third, there may be circumstances (e.g. patient preference) where any decision to refer may be deferred on mutual agreement.

General practitioners should take into account the pattern of bleeding, its relationship to the use of HRT and patient preferences when considering a referral. Concern from either general practitioner or patient about the possibility of PMB signalling endometrial cancer constitutes sufficient grounds for referral.²⁷

4

D The risk of endometrial cancer in non-HRT users complaining of PMB and in HRT users experiencing abnormal bleeding is sufficient to recommend referring all patients for investigation.

3.2 ASSESSING ABNORMAL BLEEDING IN WOMEN USING HRT

Abnormal bleeding in post-menopausal women receiving HRT can be caused by any of the following:

- poor compliance, especially related to omission of progestogens;
- poor gastrointestinal absorption (for oral preparations), e.g. due to gastroenteritis;
- drug interactions;
- coagulation defects;
- gynaecological disorders.

Clinical enquiry should aim to establish:

- whether the bleeding pattern is abnormal (as defined in section 1.3)
- any other related symptoms or contributory factors associated with endometrial cancer.

- The following questions should be asked in the assessment of patients with abnormal bleeding on HRT:
- When does bleeding occur with respect to the oestrogen and the progestogen phase? (Women on sequential regimens should ideally not experience withdrawal bleeding before completion of the progestogen component of the preparation).
 - How long does the bleeding last and how heavy is it?
 - Was there a period of amenorrhoea before HRT was started?
 - Is there a problem that suggests poor compliance?
 - Is there a reason to suspect poor gastrointestinal absorption?
 - Is the patient taking any other drugs?

3.3 CLINICAL EXAMINATION

Women presenting with PMB require a pelvic examination at some stage during their assessment. If referred to a gynaecologist, an examination by the general practitioner is not always necessary. However, examination by a general practitioner or practice nurse can alter the course of clinical management if it expedites referral on grounds of raised suspicion of a malignancy (including cervical carcinoma) or highlights 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 for women within the National Screening Programme.

- Women presenting with PMB should receive a pelvic examination at some stage during the course of their clinical assessment.

3.4 CONTINUATION OF HRT PRIOR TO INVESTIGATION

Use of 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 patient 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. In addition stopping HRT before investigation may transmit the wrong signals to patients regarding the risks of HRT.

For transvaginal ultrasonography the cut-off point of endometrial thickening beyond which further investigation is required can be adjusted for HRT use, although there is a greater risk of false positive results than if HRT were stopped.²⁸

- Whether or not to continue HRT use prior to investigation may depend on the patient's wishes and how long she has to wait for investigations, but there is no specific reason for discontinuing it.

3.5 EFFECTIVE COMMUNICATION BETWEEN PATIENTS AND PRACTITIONERS

It is important that there is a clear flow of information between specialists, GPs 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.

4 Investigative techniques

4.1 INTRODUCTION

This section presents an overview of evidence and recommendations relating to a range of investigations. Most evidence at present favours the use of transvaginal ultrasonography (TVUS) as the initial investigation in PMB. This is because there is both a much greater quantity and a higher quality of evidence supporting its use compared with other methods. No high quality studies were available directly comparing the performance of different investigations.

A range of investigations, including TVUS, are currently used in different gynaecology units across Scotland. Given the present limitations of the evidence base, the guideline development group has not specifically recommended the use of one investigation in preference to another. However, users of this guideline should note that the following section on the selection and interpretation of TVUS (section 5) is underpinned by a reliable evidence base.

4.2 THE ROLE OF INVESTIGATION IN PMB

The principal aim of the investigation of post-menopausal bleeding is to identify or exclude endometrial pathology, most notably endometrial carcinoma. It is also important to ensure that women are sufficiently reassured following normal tests, that symptomatic benign disease is identified, and that the process of investigation is both acceptable and efficient.

4.3 AVAILABLE TECHNIQUES

Two meta-analyses judged to be of sufficient rigour and involving one diagnostic technique – transvaginal ultrasonography – were identified.^{28,29} Most studies evaluating other techniques were small cohort studies.

4.3.1 TRANSVAGINAL ULTRASONOGRAPHY

The mean endometrial thickness in post-menopausal women is much thinner than in pre-menopausal women. Thickening of the endometrium may indicate the presence of pathology. In general, the thicker the endometrium, the higher the likelihood of important pathology (endometrial cancer) being present.³⁰

Transvaginal ultrasonography can reliably assess thickness and morphology of the endometrium and can thus identify a group of women with post-menopausal bleeding who have a thin endometrium and are therefore unlikely to have significant endometrial disease. This group may not require any further investigation unless there is a recurrence of bleeding.³¹⁻³⁴ The relatively non-invasive nature of TVUS may make it more acceptable than other investigations, especially to elderly women.

2+

The endometrial thickness cut-off

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, e.g. suspicion of a polyp, would require further investigation irrespective of the endometrial thickness.

There are different endometrial thickness thresholds that may be used for recommending further investigation. However there is a trade-off between sensitivity and specificity.^{28,31-33,38} In other words, the lower the threshold of endometrial thickness chosen as a cut-off point, the fewer cases of endometrial cancer will be missed but at the cost of referring for further investigation a much greater number of women without cancer. Setting the threshold of endometrial thickness at a higher level will result in more cases of cancer being missed whilst reducing the number of women without cancer referred for further investigation.

A recent meta-analysis reviewed evaluations of TVUS.²⁹ After lower quality studies had been excluded (those associated with a higher risk of bias that might affect estimates of test accuracy), only four high quality studies remained. These four studies all assessed the 5 mm threshold and, when pooled, showed that a negative TVUS result of 5 mm or less reduced the risk of disease by 84%. Whether this is sufficient to rule out disease depends on the pre-test risk of disease in the relevant patient group. Furthermore the authors caution against relying on the pooled findings of only four studies, for which there is a wide 95% confidence interval for the reduction in risk (54% to 94%) arising from a negative result. A range of factors need to be considered in determining the best use of TVUS and the optimal threshold.

2+

See section 5 for recommendations on the use of endometrial thickness cut-offs for estimating risk of cancer.

No endometrial thickness threshold completely excludes possible early endometrial carcinoma. This disease can, of course, be present in women without post-menopausal bleeding.³³ Inter-observer error in measuring endometrial thickness among experienced clinicians is minimal especially when the endometrium is thin. However, this may not hold if individual clinicians have less experience.³⁰

2+

Endometrial thickness and sequential HRT

The mean endometrial thickness in women on sequential hormone replacement therapy with post-menopausal bleeding is greater than in those women with post-menopausal bleeding who are not on sequential HRT. Thus an abnormal endometrial thickness in women with post-menopausal bleeding who are not using sequential HRT represents a greater probability of endometrial disease than in women taking hormone replacement therapy.^{28,35}

2++

In women using sequential HRT, the thickness of the endometrial wall can vary with each phase of the cycle. In order to standardise readings, TVUS measurements should probably take place during the first half of the cycle.

Training requirements

The interpretation of TVUS depends upon the skills of the operator as well as inter-operator variation. Therefore, gynaecological, radiological or radiography staff undertaking TVUS should be sufficiently trained in the technique and work to locally agreed standards.

B Where sufficient local skills and capacity exist, transvaginal ultrasound is an appropriate first-line procedure to identify which women with post-menopausal bleeding are at higher risk of endometrial cancer.

In patients on sequential HRT, TVUS measurements should take place during the first half of the cycle where possible.

Staff undertaking TVUS should be trained to ensure a consistent and acceptable level of performance.

4.3.2 TRANSABDOMINAL ULTRASOUND

Ultrasonic assessment of the uterus by a transabdominal approach has now been superseded by transvaginal ultrasound.^{36,37} The principle advantage of the latter is improved resolution, allowing more accurate endometrial thickness measurement and better assessment of endometrial morphology. Other advantages of TVUS include the lack of dependency upon a full bladder, improved access to the retroverted uterus and more successful assessment of more obese patients.

3

D Transabdominal ultrasound may be used as a complementary examination if the uterus is significantly enlarged or a wider view of the pelvis or abdomen is required. Transabdominal ultrasound may also be used in the small proportion of women in whom it proves technically impossible to perform a transvaginal ultrasound.

4.3.3 OTHER ULTRASONOGRAPHIC TECHNIQUES

Other methods of endometrial assessment such as transvaginal Doppler ultrasonography, three-dimensional ultrasonography, saline enhanced transvaginal ultrasonography and endometrial texture and margin analysis have been assessed in a limited manner with a view to improving specificity.³⁸⁻⁴² There is no evidence to support their introduction into routine clinical practice at present.

3

4.3.4 DILATATION AND CURETTAGE (D&C)

A definitive diagnosis in post-menopausal bleeding is made by histology. Historically, endometrial samples have been obtained by dilatation and curettage. This involves curetting the walls of the uterine cavity in a systematic fashion. However the technique is 'blind' and the operator cannot assess whether lesions have been missed. The sensitivity and specificity of D&C is difficult to assess because the true incidence of lesions *in uteri* subjected to D&C is unknown.

In several small case series, patients had a D&C immediately prior to hysterectomy. In these series, endometrial lesions were overlooked in up to 10% of the instances in which D&C was the only procedure used.⁴³ One study evaluating the completeness of endometrial sampling by D&C showed that in 60% of patients less than half the cavity was curetted.⁴⁴

3

D D&C should no longer be used as the first-line method of investigating PMB in most cases.

4.3.5 ENDOMETRIAL BIOPSY

Endometrial biopsy can be undertaken using endometrial samplers. These plastic tube-like devices are inserted into the uterine cavity. A plunger is withdrawn and the "negative" pressure permits aspiration of tissue into the device. There are a variety of different endometrial samplers available but there are no systematic comparisons between them.

All methods of sampling the endometrium will miss some cancers.^{33, 45-48} In a small proportion of patients, outpatient endometrial sampling is not technically possible.

Outpatient endometrial sampling has a procedure failure rate as well as a tissue-yield failure rate, each of approximately 10%.^{13,46,48,49} It should be noted that yield failures are not unexpected in women with atrophic endometrial linings, whereas failure to obtain tissue would be less likely if cancer was present. However, the success of Pipelle^(TM) endometrial sampling, in terms of obtaining a sample, is also related to operator experience, hence training is very important.⁴⁶

2+
4

When outpatient blind endometrial sampling was compared with inpatient hysteroscopy and curettage, it was found to be an effective screening procedure for atypical hyperplasia but did miss benign lesions, especially endometrial polyps.^{31, 48-50}

2+

C Hysteroscopy and biopsy (curettage) is the preferred diagnostic technique to detect polyps and other benign lesions.

Outpatient sampling may reduce inconvenience, anxiety and risk for the patient and costs for the hospital.^{47, 48, 51}

1+
2+
3

C Histological specimens may be obtained either at the same time as inpatient or outpatient hysteroscopy with curettage or using an endometrium sampling device, e.g. Pipelle^(TM).

4.3.6 HYSTEROSCOPY

Hysteroscopy allows the operator to visualise directly the endometrial cavity. The procedure can be performed either in the outpatient setting with the patient awake or under general anaesthesia. A biopsy of the endometrium is usually taken following hysteroscopy either with a sampler or by curettage.

Despite general consensus that it is the current gold standard, the evidence base for hysteroscopy is poor.

Hysteroscopy in the outpatient setting appears to have an accuracy and patient acceptability equivalent to inpatient hysteroscopy under general anaesthetic.^{47, 52}

1+

B Outpatient techniques for hysteroscopy and suction sampling of the endometrium should be available in all diagnostic units.

B Facilities to perform hysteroscopy and curettage under general anaesthetic should be available for when the outpatient procedure is not possible or the patient has a strong preference for a general anaesthetic.

4.4 SEQUENCING OF INVESTIGATIONS

There have been several innovations in the last two decades in the assessment of abnormal uterine bleeding. A significant development has been direct referral to 'one stop' specialist clinics. At such clinics several investigations are available to complement clinical evaluation, including ultrasound, endometrial sampling techniques and hysteroscopy. Following such assessment reassurance can be given or further investigations or treatment can be discussed and arranged.

It is reasonable to pursue a different approach to investigation if direct access to a 'one stop' service is not available or obtaining TVUS would be inconvenient (e.g. requiring a long distance return trip) or would appreciably delay assessment. Obtaining an initial endometrial sample may be in the patient's interest if it identifies a cancer prior to the ultrasound appointment. Even so, there is no robust evidence that demonstrates that endometrial sampling alone is sufficient to exclude endometrial cancer.

A possible flowchart of investigation is included in the Quick Reference Guide at the back of this guideline and available separately. The exact sequence of investigation will depend upon clinical judgement, local resources, local expertise and patient preference.

4.5 INVESTIGATION OF WOMEN USING TAMOXIFEN

Women with breast cancer who take tamoxifen on a long-term basis are at increased risk of endometrial cancer (see section 2.1.3). The main issues to consider are the optimal method of investigation and the case for regular screening investigations in women taking tamoxifen without post-menopausal bleeding.

In view of the increased risk of endometrial cancer associated with tamoxifen therapy, there is a case for heightened vigilance for post-menopausal bleeding by both the women and the clinician(s) responsible for their care. However, studies that have included women with vaginal bleeding in the assessment of diagnostic tests to detect abnormalities in women receiving tamoxifen have been of insufficient quality or size to enable any robust conclusions to be drawn.^{53,54}

Although strictly outside the scope of this guideline, the issue of whether to undertake screening investigations in women on tamoxifen is controversial and merits discussion. Current evidence does not justify the use of any investigation (ultrasonography, hysteroscopy, endometrial biopsy or D&C) in post-menopausal women receiving treatment with tamoxifen in the absence of vaginal bleeding.⁵⁵⁻⁶¹ Unnecessary investigation should be avoided as there are risks associated with further investigation.⁶⁰

C Endometrial investigation should only be carried out in post-menopausal women on tamoxifen who experience vaginal bleeding.

Ultrasonography is poor at differentiating potential cancers from other tamoxifen-induced thickening because of the distorted endometrial architecture associated with long term use of tamoxifen.

Endometrial thickening associated with tamoxifen therapy but not with pathology may decrease the specificity (i.e. increase the number of false positives) of ultrasonography.^{62,63} Ultrasonographic evaluation could employ a higher cut-off point of endometrial thickness (9 mm) to prompt further investigation but further, more rigorous studies are required to test this approach.⁵³ Furthermore, both women and clinicians may not accept any residual uncertainty about the risk of undetected pathology given this cut-off point. Therefore, the use of hysteroscopy and biopsy as first line investigations may be more appropriate and provide less ambiguous results in this high-risk group of women.

1+
2+

2+
4

D Hysteroscopy with biopsy is preferable as the first line of investigation in women taking tamoxifen who experience post-menopausal bleeding.

4.6 RECURRENT POST-MENOPAUSAL BLEEDING

There is no evidence to recommend when re-investigation should take place following recurrent or persisting post-menopausal bleeding. Clinical judgement is required but consideration of re-investigation must be given in view of the false negative rate associated with all methods of diagnosis.^{32, 37, 39, 43, 45}

2+
3
4

Re-investigation of recurrent post-menopausal bleeding should be considered after six months.

5 Interpretation of TVUS

5.1 INTRODUCTION

Transvaginal ultrasound is useful in the investigation of women with PMB because it helps to identify those at higher risk of endometrial cancer who require further investigation. TVUS is also an effective means of excluding endometrial cancer. But the interpretation of test results depends upon several factors, including the cut-off point used to define a positive result and how large or small the risk of cancer is for different groups of women.

This section outlines:

- Estimates of cancer risk for different groups of women presenting with PMB
- In which groups of women with PMB, TVUS is most likely to be useful
- How to interpret TVUS results for groups of women with varying risks of cancer

Traditional parameters essential to the evaluation of test performance, such as sensitivity and specificity, are neither necessarily intuitive nor readily transferable to clinical situations. However, the understanding and application of information about test performance to clinical practice is vital to the successful selection and implementation of the diagnostic test. This section sets out a complementary approach to judging how useful an investigation is, using parameters derived from available data on sensitivity and specificity.^{64,65} Further technical details on the derivation of recommendations in this section may be found on the SIGN website at www.sign.ac.uk.

For departments where TVUS is available, clinicians may wish to review their criteria for referral and further investigation in light of these recommendations. Where no TVUS is available, clinicians and managers interested in developing a service should consider the guideline development group's conclusions alongside resource and training implications.

5.2 TO WHICH PATIENTS DOES THIS SECTION APPLY?

The recommendations in this chapter apply to women referred to gynaecologists for investigation of PMB. It does not apply to women directly referred for TVUS by general practitioners, as most research is based upon secondary care populations.

5.3 ESTIMATING THE PROBABILITY OF ENDOMETRIAL CANCER IN WOMEN PRESENTING WITH PMB

An important issue in the initial clinical assessment concerns the probability that an individual woman with PMB will have endometrial cancer. This probability will influence the choice and interpretation of any investigation.

Approximately 10% of women up to 60 years of age presenting *and* referred with post-menopausal bleeding have endometrial cancer.^{6,28} Among women over 60 years presenting with post-menopausal bleeding, extrapolated from age-specific incidence rates, 13% are assumed to have endometrial cancer.⁶

2⁺⁺

Data on the proportion of women on combined HRT presenting with PMB or unscheduled bleeding who are found to have endometrial cancer are not available. The estimated proportions of such women developing endometrial cancer per annum range from 0.02% to 0.05%.^{66,67} A cautious baseline estimate of 1% for the risk of endometrial cancer in women on combined HRT presenting with PMB or unscheduled bleeding is assumed. The risk for women under 50 years is assumed to be 0.1%, and women over 60 years 1.5%. The risks for women on continuous combined HRT regimens is assumed to be similar to those not on HRT.

The guideline does not attempt to quantify the probability of a woman on tamoxifen with PMB having endometrial cancer. However, it is likely to be substantially higher than 10%.

5.4 INTERPRETATION OF TVUS

As stated earlier, it is in general true that the thicker the endometrium of a post-menopausal woman the higher the likelihood of endometrial cancer being present.³⁰ Therefore the measurement of a patient’s endometrial thickness by TVUS aims to distinguish between a low or significant probability of endometrial cancer in her case. The threshold value for deciding if there is a significant risk of cancer will depend, in part, on the ‘normal’ endometrial thickness for the relevant patient group. For example, women on sequential HRT tend to have thicker endometria, as a matter of course, and so a higher threshold needs to be used for identifying those with a significant probability of cancer.

The interpretation of a TVUS test result, for a patient presenting with PMB, depends both on what probability of cancer is considered acceptable (requiring no further investigation) and on the pre-test probability of that patient having cancer. The pre-test probability depends on her history of HRT (see Figure 1), and on her age (see section 5.3 and additional material on the SIGN website - www.sign.ac.uk). Consequently, differing cut-off points can be applied to specific groups of women with PMB or unscheduled bleeding. These cut-off points also need to be chosen in light of what is agreed as an acceptable remaining risk of cancer. In current practice the commonly accepted cut-off of endometrial thickness of 5 mm does not reduce the probability of endometrial cancer below 1% for women who have never taken HRT or have been on continuous combined HRT. For these groups of women with a pre-test probability of endometrial cancer of around 10%, given a TVUS measurement of 5 mm or less, the probability of cancer is 1.7%. Achieving agreement upon an acceptable level of probability of cancer after testing is problematic but for the purposes of this guideline, it is less than 1% (or less than 1 in 100).

According to the most recent meta-analysis, using an endometrial thickness of over 3 mm to define an abnormal result would represent a more sensitive approach.²⁹ Based upon a pre-test probability of cancer of 10%, the post-test probability following a negative test result is 0.4%. Unfortunately, the evidence base for a 3 mm threshold is less reliable and more prone to bias than that for the 5 mm threshold. Poorer quality studies tend to overestimate the accuracy of diagnostic tests.⁶⁸ The guideline development group faced the dilemma of whether to recommend a cut-off at a threshold (5 mm) which would probably be of insufficient use as a diagnostic test in most women, or one (3 mm) based on evidence overestimating its accuracy. It was decided to make approximate adjustments to the likelihood ratio to adjust for bias. Therefore, measured by TVUS, an endometrial thickness of 3 mm or less gives an approximate post-test probability of cancer of 0.6% to 0.8% in the following groups of women:

1+
2++

- Post-menopausal women who have never been on HRT
- Post-menopausal women who have not been on any form of HRT for a year or more
- Post-menopausal women on continuous combined HRT

For post-menopausal women who present with unscheduled bleeding on sequential HRT, an endometrial thickness of 5 mm or less gives an approximate post-test probability of 0.2%. Therefore use of the 5 mm threshold in this group provides equivalent (or greater) reassurance that cancer is not present, if the TVUS result is negative.

- B** A cut-off threshold of 3 mm or less should be used for TVUS in women with PMB or unscheduled bleeding who:
 - have never used HRT
 - have not used any form of HRT for a year or more
 - are using continuous combined HRT.
- B** If the clinician and the woman judge that the level of reassurance and reduced risk are acceptable following a TVUS measurement of 3 mm or less, no further action need be taken. Further investigations should be carried out if symptoms recur.
- B** If the clinician, the patient or both are not satisfied with this level of reassurance, further investigation is justified. This should include an endometrial biopsy to obtain a histological assessment.

B For women on sequential combined HRT presenting with unscheduled bleeding, TVUS using a cut-off point of 5 mm or less should be used to exclude endometrial cancer.

Women presenting with PMB and taking tamoxifen have a higher probability of malignancy (substantially greater than 10%). In these cases the ultrasound image is more difficult to interpret. Therefore it is advisable to sample the endometrium initially and examine the cavity hysteroscopically.

As indicated in the previous section, other considerations may influence the selection of TVUS as an initial investigation. TVUS may be appropriate as a non-invasive procedure in more elderly or frail women. Other investigations may be appropriate as a first line approach in certain circumstances, where there is a risk of substantial delay in waiting for TVUS, or as a second line if TVUS cannot be performed for technical reasons.

5.5 NEXT STEP AFTER IDENTIFYING A THICKENED ENDOMETRIUM

The finding of an endometrial thickness above the relevant cut-offs (3 mm or 5 mm) indicates that there is a risk of abnormality significant enough to warrant further investigation. The exact procedures to be followed will depend on clinical circumstances and local service provision, but should include a pathological assessment of the endometrium. As the false negative rate of endometrial sampling or biopsy is significant, current advice is that this should be combined with hysteroscopy. This should be carried out prior to endometrial sampling. If local facilities and organisation allow, hysteroscopy and endometrial sampling could be performed in a one stop service during the same session as the transvaginal ultrasound, although patient circumstances may not always be suitable for this.

If the local service is such that there would be a delay prior to performing hysteroscopy, there is merit in performing an endometrial sampling technique in the outpatient clinic. This may lead to earlier recognition of a significant lesion such as malignancy.

The hysteroscopic evaluation of the endometrial cavity reassures the clinician whether or not visible abnormality exists, indicates whether material for histological assessment is obtainable and may demonstrate the best method to achieve it. When endometrial sampling gives no yield, a negative hysteroscopy confirms that this outcome is acceptable.

Figure 1: Transvaginal ultrasonographic (TVUS) evaluation of women with post-menopausal bleeding

	All women with PMB (not using tamoxifen)			
HRT Status	Current or recent (within last year) use of sequential HRT		Never used HRT OR not used HRT for over 1 year OR using continuous combined HRT	
Estimated pre-test risk of cancer	1-1.5%		10%	
Endometrial thickness test result	≤ 5mm	> 5mm	≤ 3mm	> 3mm
Probability of cancer after test	0.1-0.2%	2-5%	0.6-0.8%	> 20-22%
Action required	No further investigation	Investigation for tissues sampling	No further investigation	Investigation for tissues sampling

6 Resource implications

6.1 INTRODUCTION

The development process for this guideline has included explicit consideration of economic issues at each stage, as part of a pilot study being run by SIGN and the Scottish Health Economists' Network. This pilot study recognises that by taking account of the resource implications of guidelines the NHS can ensure that the quality of services is improved, while contributing to the goal of efficient use of scarce resources.

6.2 METHODOLOGY

The first stage of the process of incorporating economic considerations is to review the economics literature in addition to the clinical literature. Where high quality information is obtained from this review it is incorporated into the clinical recommendations. The second stage involves consideration of the economic implications of the guideline where no economic evaluations are available. This involves considering the following questions:

- Are the resource implications of implementation of the guideline likely to be significant nationally or locally, such that they cannot be absorbed within existing resource allocation?
- Will the guideline affect outcomes or resource use in other areas of the NHS (such as primary care, other clinical specialties, support departments)?
- Will the guideline affect outcomes or resource use in partner organisations (e.g. social work departments; the voluntary sector, etc.)?
- Will the guideline affect costs to patients, for example will they face additional visits to hospital/GP or have to spend longer in hospital?
- Will the guideline affect outcomes or resource use in future time periods?
- Will other groups benefit or be potentially disadvantaged by the recommendation / guideline?
- Are there disproportionate costs or outcomes for a particular group?

6.3 RESULTS

The literature review found no high quality economic evaluations of the investigation of post-menopausal bleeding which could be used to inform the clinical recommendations. As a result, an economic analysis of the guideline was undertaken.

6.3.1 SIGNIFICANCE OF RESOURCE IMPLICATIONS?

- *What are the existing facilities for investigating PMB?*

A telephone survey was undertaken of all 31 gynaecology and community gynaecology units in Scotland. Fourteen units have specialist clinics to which women with PMB can be referred. All but one unit have access to TVUS, although this did not necessarily mean that all women with PMB were referred for TVUS, nor that the service provision was adequate. In the unit where TVUS was not available on site, women could be referred to another hospital for TVUS. Outpatient hysteroscopy facilities are available in only 16 units in Scotland. Anonymised data for existing facilities for the investigation of PMB in gynaecology units within Scotland is available from the SIGN website at www.sign.ac.uk.

There are, at present, no reliable data on the patterns of initial investigation for women with PMB referred to the above units. Data from a national audit of the care of endometrial cancer suggests that endometrial biopsy (Pipelle™), TVUS, hysteroscopy and D&C accounted for respectively 36%, 13%, 30% and 16% of initial investigations in 1996-7. Five percent of women received no investigation. These findings may not be representative of investigation of the current population of women presenting with PMB (most of whom will not have endometrial cancer).

- *Will the number of women referred for investigation of post-menopausal bleeding change if the guideline is used?*

At present there is no reliable estimate of the number of women referred each year for the investigation of post-menopausal bleeding. However, it is likely that the need for TVUS will increase overall if gynaecology units shift practice towards greater use of TVUS as recommended in this guideline. It is also likely that the number of women referred to secondary care will increase over the next few years as a result of demographic change and increased use of hormone replacement therapy.

- *Are additional facilities required?*

If all women referred for post-menopausal bleeding were to receive TVUS with subsequent outpatient hysteroscopy for further investigation of those with positive findings, then there may be significant resource implications for the NHS, depending on the level and capacity of current provision. There may, however, be some saving in resource use (although this is unlikely to be reflected in financial savings because of the existence of fixed costs) associated with moving from current practice, as described above, to a policy of TVS and outpatient hysteroscopy. For example:

- In units which currently undertake TVUS on a routine basis and have access to outpatient hysteroscopy, there are unlikely to be significant resource implications, unless there is a significant increase in the number of women referred. This may require the purchasing of additional TVUS equipment and additional clinic slots
- In units currently offering TVUS, the threshold (cut-off point) for a 'positive' result influences the proportion of patients subsequently referred for further investigation. Therefore, any change in local policy towards the use of lower cut-off points will result in a greater number of patients being referred for further investigation. However, this cost may be offset by a potential reduction in cancers missed on initial investigation and reduced use of other first-line investigations
- The resource implications may be more significant for the one unit where TVUS is either not currently used or used for only a small number of patients. Additional resources required will include the purchase of ultrasound equipment and the provision of accommodation in which to undertake scanning and staff training.

Overall, it is likely that the recommendation of TVUS and outpatient hysteroscopy will have resource implications for each gynaecology unit in Scotland, but these will vary according to current provision of services, existing capacity and the existence of trained staff. This may be matched by a reduction in the use of other forms of investigation.

6.3.2 IMPACT ON OTHER AREAS OF THE NHS

It is unlikely that there will be a significant effect on other areas of the NHS in Scotland of implementing the guideline. Where the TVUS service is provided in the radiology department there may be an effect on waiting times for other radiological procedures.

6.3.3 IMPACT ON PARTNER ORGANISATIONS

It is unlikely that there will be significant impact of the guideline on partner organisations.

6.3.4 IMPACT ON PATIENT COSTS

There is unlikely to be a significant increase in the private costs faced by women under investigation for PMB and there may be a decrease if investigation is undertaken on an outpatient basis.

6.3.5 IMPACT OVER TIME

The guideline and increasing HRT use may result in more women being referred for investigation over time.

6.3.6 IMPACT ON OTHER GROUPS

If all women with PMB are referred then waiting list for other women to be seen may increase.

7 Information for patients

7.1 NOTES FOR DISCUSSION WITH PATIENTS AND CARERS

It is recognised that good communication is central to the clinician-patient relationship and to good clinical care. Patients require information about the reasons for investigating their condition, the methods of testing, an explanation of the procedures themselves, as well as options available for management of established conditions.

What is PMB?

Post-menopausal bleeding involves vaginal bleeding following a woman's last menstrual period. For the purposes of this guideline, an episode of bleeding 12 months or more after the last period is accepted as post-menopausal bleeding.

Why does it need investigation?

Post-menopausal vaginal bleeding must always be investigated. In the majority of cases no serious problem will be found but there are times when the bleeding is the first symptom of serious disease including cancer. Even when the bleeding is related to cancer, if it is diagnosed early there is a very good chance that the disease can be cured.

What causes PMB?

In 90% of cases examination and investigation will find either no obvious cause or an innocent one. The commonest innocent cause is atrophic vaginitis (inflammation of the lining of the vagina due to the lower levels of the circulating hormone oestrogen at this time). Cervical and endometrial polyps are further common findings and they are usually benign. In around 10% of cases, PMB will be associated with endometrial (uterine) or cervical cancer.

How is PMB investigated?

There are a range of different techniques which health care professionals might use to investigate PMB. Transvaginal ultrasonography (TVUS) is described in detail below. Hysteroscopy uses a thin telescope that is inserted through the cervix into the uterus. Modern hysteroscopes are so thin that they can fit through the cervix with minimal discomfort. They are fitted with small video cameras to allow the operator to visualise the inside of the uterus. Biopsy involves removing a small sample of the womb lining for pathological analysis. This is painless and can usually be carried out at the same time as hysteroscopy.

How accurate are the test results?

All women have an underlying chance of developing endometrial cancer which is dependent on their use of HRT and a range of other factors. TVUS measures the thickness of the lining of the womb and the test results can be interpreted to show how the underlying likelihood of cancer is either increased or decreased in the light of the measured endometrial thickness. The risks of cancer are given in ranges which reflect the accuracy of the TVUS technique. Your doctor will discuss the test results with you and will come to a decision with you as to whether any further investigation or treatment is required.

7.2 THE TRANSVAGINAL ULTRASOUND INVESTIGATION

What is ultrasound?

Ultrasound is a harmless way to show the structures inside your pelvis using high-frequency sound waves and a type of sonar detection system to generate a black and white picture. Depending on the view of your pelvic organs, the radiographer may position the ultrasound machine's transducer wand to look through your abdominal wall (transabdominal ultrasound) or to look through your vagina (transvaginal ultrasound). With the transvaginal technique, the ultrasound transducer (a hand-held probe) is inserted directly into the vagina. It is therefore closer to pelvic structures than with the conventional transabdominal technique (probe on skin of the abdomen), providing superior image quality. Ultrasound of the pelvic organs is used to scan for pregnancy and is also useful for

finding cysts on your ovaries, examining the lining of your uterus, looking for causes of infertility, and looking for cancers or benign tumours in the pelvic region.

How to prepare for the test?

No preparation is necessary in most cases. If you are having a transvaginal ultrasound, you will need to remove a tampon if you have one in place. If you are to have a transabdominal scan you will be asked to fill your bladder by drinking a few glasses of water before the test. You may continue taking all of your medications as prescribed by your health care provider. The test can be performed without concern at any stage of a woman's menstrual cycle, however if you are using a sequential HRT regimen, you may be asked to attend during the first half of your menstrual cycle.

How is the test performed?

You will lie on your back on a couch for the test. For transvaginal ultrasound, the probe used for internal scans is small and shaped to fit easily and painlessly into your vagina. The probe will be covered with a clean condom and some lubricating jelly. When the sensor is in place, a picture will appear on a TV screen, and the radiographer will move the sensor in your vagina to see the uterus and ovaries from many different views. The test takes around 15 minutes to perform and will feel similar to an internal examination.

What are the risks involved with the test?

Studies have shown ultrasound is not hazardous and there are no harmful side effects. In addition, ultrasound does not use ionising radiation, as X-ray tests do.

How long is it before the result of the test is known?

You might be able to get an indication of the results of your test immediately. However, the test will be recorded on paper or film and the recording can be formally reviewed by a radiologist, a process that might take a day or two before your doctor has the report.

7.3 SOURCES OF FURTHER INFORMATION / SUPPORT

THE BRITISH MENOPAUSE SOCIETY

36 West Street, Marlow, Bucks, England SL7 2NB

Tel: 01628 890199 Fax: 01628 474 042

Email: britishmenopausesociety@compuserve.com

<http://www.the-bms.org/>

WOMEN'S HEALTH CONCERN - WHC

P.O.Box 2126, Marlow, England SL7 2RY

Tel: Helpline: 01628 483612 Fax: 01628 474042

<http://www.womens-health-concern.org/>

Based at the British Menopause Society. Aims to help women obtain the information and advice they need concerning their health, with particular reference to gynaecological problems; also information on problems connected with the menopause and the proper use of HRT.

WOMEN'S HEALTH (PREVIOUSLY WHRRIC)

52 Featherstone Street, London EC1Y 8RT

Tel: Helpline: 0845 125 5254 Fax: 020 7250 4152 Textphone: 020 7490 5489

Email: womenshealth@pop3.poptel.org.uk

<http://www.womenshealthlondon.org.uk>

Women's Health provides accessible information in a supportive manner to help women make their own informed decisions about their health; services include a national helpline and postal and email enquiry service, reference library and database to help put women in touch with individuals or groups for self-help and support. Produces a wide range of leaflets and a newsletter.

FAMILY PLANNING ASSOCIATION SCOTLAND

FPA Scotland, Unit 10, Firhill Business Centre, 76 Firhill Road, Glasgow G20 7BA
Tel: 0141 576 5015 Fax: 0141 576 5006
Email: fpascotland@dial.pipex.com
<http://www.fpa.org.uk>

FPA's highly trained helpline staff provide a confidential advice service for the public answering over 100,000 enquiries a year; its Library and Information service provides access to a unique and comprehensive collection of materials on sexual health. Patients can phone FPA to get contact information on their local menopause clinic.

FAMILY PLANNING AND WELL WOMAN SERVICES

18 Dean Terrace, Edinburgh EH4 1NL
Tel: 0131 332 7941 Fax: 0131 332 2931 Textphone: 0131 315 3424

Menopause clinic; NHS provision of all forms of contraception; advice and referral for unplanned pregnancy; psychosexual counselling; well-woman clinics; vasectomy performed; young people's clinics.

GLASGOW CENTRE FOR FAMILY PLANNING AND SEXUAL HEALTH

2-6 Sandyford Place, Glasgow G3 7NB
Tel: 0141 211 8130 Fax: 0141 211 8139

Confidential self-referral menopause clinic. Offers free abortion counselling, colposcopy / cervical screening, family planning, free condoms, HIV counselling / testing, pregnancy testing, psychosexual therapy, vasectomy counselling / operations, well woman screening. Refers for female sterilisation and abortion. Services are also provided from 28 other sites within Glasgow.

HEALTH EDUCATION BOARD FOR SCOTLAND

Woodburn House, Canaan Lane, Edinburgh EH10 4SG
Tel: 0131 536 5500
<http://www.hebs.scot.nhs.uk/>

NHS24:

<http://www.nhs24.com/> - Scheduled to be available throughout Scotland in 2004.

NHS Helpline:

0800 22 44 88

FOR CANCER PATIENTS:

Cancer Research UK

(<http://www.cancerresearchuk.org/>)

Produce a good patient information leaflet entitled Womb Cancer.

CancerBACUP

(<http://www.cancerbacup.org.uk/>)

Produce a good patient information leaflet entitled Understanding cancer of the womb (endometrium).

8 Development of the guideline

8.1 INTRODUCTION

SIGN is a collaborative network of clinicians, other health care professionals and patient organisations, funded by the Clinical Resource and Audit Group (CRAG) of the Scottish Executive Health Department. SIGN guidelines are developed using a standard methodology, based on a systematic review of the evidence. Further details about SIGN guideline development methodology are contained in *SIGN 50: A guideline developer's handbook* available at www.sign.ac.uk.

8.2 THE GUIDELINE DEVELOPMENT GROUP

Dr Jo Davis (chairman)	<i>Consultant in Oncology and Gynaecology, Stobhill Hospital, Glasgow</i>
Dr Robbie Foy (methodologist)	<i>MRC / CSO Training Fellow, Scottish Programme for Clinical Effectiveness in Reproductive Health (SPCERH)</i>
Dr Simon Crawford (secretary)	<i>Specialist Registrar in Obstetrics and Gynaecology, Stobhill Hospital, Glasgow</i>
Dr Alison Biggig	<i>Director, Glasgow Centre of Family Planning and Sexual Health</i>
Dr Lucy Caird	<i>Consultant Gynaecologist, Raigmore Hospital, Inverness</i>
Professor Hilary Critchley	<i>Consultant Gynaecologist and Professor of Reproductive Medicine, Royal Infirmary, Edinburgh</i>
Dr Heather Deans	<i>Consultant Radiologist, Aberdeen Royal Infirmary</i>
Dr Eleanor Guthrie	<i>General Practitioner, Scotstoun</i>
Mr Robin Harbour	<i>Quality and Information Director, SIGN</i>
Sister Jacqueline McConville	<i>Practice Nurse, Hamilton</i>
Dr Rod Muir	<i>Consultant in Public Health Medicine, Information and Statistics Division, Edinburgh</i>
Dr Moray Nairn	<i>Programme Manager, SIGN</i>
Dr Shelagh Neil	<i>General Practitioner, New Galloway, Castle Douglas</i>
Mrs Winnie Sherry	<i>Patient Representative, Motherwell</i>
Dr Sara Twaddle	<i>Health Economist, North Glasgow University Hospitals NHS Trust</i>
Mrs Pamela Warner	<i>Medical Statistician, Medical Statistics Unit, University of Edinburgh</i>

The membership of the guideline development group was confirmed following consultation with the member organisations of SIGN. Declarations of interests were made by all members of the guideline development group. Further details are available from the SIGN Executive.

8.3 SYSTEMATIC LITERATURE REVIEW

The evidence base for this guideline was synthesised in accordance with SIGN methodology. A systematic review of the literature was carried out using an explicit search strategy devised by the SIGN Information Officer in collaboration with members of the guideline development group.

Searches were restricted to systematic reviews, meta-analyses, randomised controlled trials, and longitudinal studies. Internet searches were carried out on the Web sites of the Canadian Practice Guidelines Infobase, the UK Health Technology Assessment Programme, the US National Guidelines Clearinghouse, and the US National Institutes of Health. Searches were also carried out on the search engines Northern Light and OMNI, and all suitable links followed up. Database searches were carried out on Cochrane Library, Embase 1985 - May 1999, Healthstar 1975 - May 1999, and Medline 1966 - May 1999. Search strategies were reviewed by an independent information specialist. The Medline version of the search strategy can be viewed on the SIGN web site.

The main searches were supplemented by material identified by individual members of the development group and were updated in the course of development. All selected papers were evaluated using standard methodological checklists before conclusions were considered as evidence.

8.4 CONSULTATION AND PEER REVIEW

A national open meeting is the main consultative phase of SIGN guideline development at which the guideline development group present their draft recommendations for the first time. The national open meeting for this guideline was held on 12 May 2000 attended by representatives of all key specialties. The draft guideline was also available on the SIGN web site for a limited period at this stage to allow those unable to attend the meeting to contribute to the development of the guideline.

8.4.1 SPECIALIST REVIEWERS INVITED TO COMMENT ON THIS DRAFT

The guideline was also reviewed in draft form by the following independent expert referees, who were asked to comment primarily on the comprehensiveness and accuracy of interpretation of the evidence base supporting the recommendations in the guideline. SIGN is very grateful to all of these experts for their contribution to the guideline.

Dr Jim Beattie	<i>General Practitioner, Inverurie</i>
Dr Sarah Chambers	<i>Consultant Radiologist, New Royal Infirmary of Edinburgh</i>
Mr Patrick Chien	<i>Senior Lecturer, Dept of Obstetrics & Gynaecology, Ninewells Hospital, Dundee</i>
Mr Bernard Croal	<i>Senior Clinical Research Fellow, Dept of Pathology, Aberdeen Royal Infirmary</i>
Dr Heather Currie	<i>Associate Specialist Gynaecologist, Dumfries & Galloway Royal Infirmary</i>
Dr Graham Ellis	<i>Principal Biochemist, Dept of Clinical Biochemistry, St. John's Hospital, Livingstone</i>
Dr Anna Glasier	<i>Director, Family Planning & Well Woman Services, Edinburgh</i>
Dr Martha Hickey	<i>Division of Paediatrics, Obstetrics & Gynaecology, Faculty of Medicine, Imperial College, London</i>
Dr Jennifer Higham	<i>Division of Paediatrics, Obstetrics & Gynaecology, Faculty of Medicine, Imperial College, London</i>
Dr Ruth Holman	<i>Consultant in Sexual & Reproductive Health Care, Ayrshire Central Hospital</i>
Dr Jo McHugo	<i>Consultant Radiologist, Birmingham Women's Hospital</i>
Dr Allan Merry	<i>General Practitioner, Ardrrossan</i>
Dr Dorothy Moir	<i>Director of Public Health, Lanarkshire Health Board</i>
Ms Nicola Ring	<i>Nurse Co-ordinator, Stirling University</i>
Dr Allan Stevenson	<i>Consultant Radiologist, Western General Hospital, Edinburgh</i>
Dr Mike Weston	<i>Consultant Radiologist, St James Hospital, Leeds</i>

8.4.2 SIGN EDITORIAL GROUP

As a final quality control check, the guideline was reviewed by an Editorial Group comprising the relevant specialty representatives on SIGN Council to ensure that the peer reviewers' comments had been addressed adequately and that any risk of bias in the guideline development process as a whole had been minimised. The Editorial Group for this guideline was as follows:

Dr Doreen Campbell	<i>CRAG Secretariat, Scottish Executive Department of Health</i>
Dr Grahame Howard	<i>Royal College of Radiologists - Faculty of Clinical Oncology</i>
Ms Juliet Miller	<i>Editor</i>
Dr Lesley MacDonald	<i>Faculty of Public Health Medicine</i>
Dr Gillian Penney	<i>Royal College of Obstetricians and Gynaecologists</i>
Professor Joanna Wardlaw	<i>Royal College of Radiologists - Faculty of Radiology</i>
Dr Bernice West	<i>National Nursing, Midwifery and Health Visiting Advisory Committee, Scotland</i>

9 Implementation and audit

9.1 LOCAL IMPLEMENTATION

Implementation of national clinical guidelines is the responsibility of each NHS Trust and is an essential part of clinical governance. It is acknowledged that every Trust cannot implement every guideline immediately on publication, but mechanisms should be in place to ensure that the care provided is reviewed against the guideline recommendations and the reasons for any differences assessed and, where appropriate, addressed. These discussions should involve both clinical staff and management. Local arrangements may then be made to implement the national guideline in individual hospitals, units and practices, and to monitor compliance. This may be done by a variety of means including patient-specific reminders, continuing education and training, and clinical audit.

9.2 KEY POINTS FOR AUDIT

- Comparison of diagnosis predicted by hysteroscopy or ultrasound with definitive pathology
- Long term outcomes of false negative investigations
- Acceptability of outpatient procedures and requirements for analgesia
- Occurrence of false reassurance (i.e. cancers found after failure to investigate).

9.3 RECOMMENDATIONS FOR FUTURE RESEARCH

The following have been identified as important areas requiring further research:

- The epidemiology of different risk categories of women presenting with PMB in primary care and the prognostic significance, if any, of different patterns of bleeding
- Epidemiological and economic modelling of the costs and benefits of adopting different cut-off values for TVUS
- The significance of the recurrence of post-menopausal bleeding following negative investigations and the time interval at which investigations should be repeated if post-menopausal bleeding continues
- The cost-effectiveness of different sequences of investigation
- The extent of inter-observer variation for all diagnostic techniques
- The optimal setting and method for outpatient procedures such as hysteroscopy and endometrial sampling
- The extent and characteristics of incidental findings with transvaginal ultrasonography for post-menopausal bleeding and subsequent costs and benefits to both patients and the NHS.

It is worth emphasising that there is currently a large quantity of poorly conducted research, and that future studies should aim to employ a more rigorous methodology.

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ALL WOMEN WITH PMB	WOMEN USING HRT	WOMEN USING TAMOXIFEN								
REFERRAL										
<p>GPs should take into account patterns of bleeding, their relationship to the use of HRT and patient preferences when considering a referral. Concern from either general practitioner or patient about the possibility of PMB signalling endometrial cancer constitutes sufficient grounds for referral.</p> <p>D The risk of endometrial cancer in non-HRT users complaining of PMB and in HRT users experiencing abnormal bleeding is sufficient to recommend referring patients for investigation.</p> <p>Women presenting with PMB require a pelvic examination at some stage during their assessment. If referred to a gynaecologist, an examination by the GP is not always necessary. However, examination by a GP or practice nurse can alter the course of clinical management if it expedites referral on grounds of raised suspicion of a malignancy.</p>	<p><input checked="" type="checkbox"/> Questions to ask in the assessment of patients with abnormal bleeding on HRT:</p> <ul style="list-style-type: none"> When does bleeding occur with respect to the oestrogen and the progestogen phase? How long does the bleeding last and how heavy is it? Was there a period of amenorrhoea before HRT was started? Is there a problem suggesting poor compliance? Is there a reason to suspect poor gastrointestinal absorption? Is the patient taking any other drugs? <p><input checked="" type="checkbox"/> Whether or not to continue HRT prior to investigation may depend on the patient's wishes and how long she has to wait. There is no specific reason for discontinuing HRT.</p>	<p><i>In view of the increased risk of endometrial cancer associated with tamoxifen therapy, there is a case for heightened vigilance for PMB by both the woman and the clinician(s) responsible for her care.</i></p> <p><i>However, current evidence does not justify the use of any investigation (ultrasonography, hysteroscopy, endometrial biopsy or dilatation and curettage) in post-menopausal women receiving treatment with tamoxifen in the absence of vaginal bleeding.</i></p> <p><i>Unnecessary investigation should be avoided as there are risks associated with further investigation.</i></p> <p>C Endometrial investigation in post-menopausal women on tamoxifen should only be carried out in those experiencing vaginal bleeding.</p>								
INVESTIGATION										
<p>B Where sufficient local skills and capacity exist, transvaginal ultrasound is the first-line procedure* to identify which women with post-menopausal bleeding are at higher risk of endometrial cancer.</p> <p>B An endometrial thickness of ≤ 3 mm can be used to exclude endometrial cancer in women who:</p> <ul style="list-style-type: none"> have never used HRT, OR; have not used any form of HRT for ≥ 1 years, OR; are using continuous combined HRT. <p>Estimated pre-test risk of cancer: 10%</p> <table border="1" data-bbox="89 1085 741 1198"> <tr> <td>≤ 3 mm</td> <td>> 3 mm</td> </tr> <tr> <td>post-test risk: 0.6-0.8%</td> <td>20-22%</td> </tr> </table>	≤ 3 mm	> 3 mm	post-test risk: 0.6-0.8%	20-22%	<p>B An endometrial thickness of ≤ 5 mm can be used to exclude endometrial cancer in women using sequential combined HRT (or having used it within the past year) with unscheduled bleeding.</p> <p>Estimated pre-test risk: 1-1.5%</p> <table border="1" data-bbox="815 1085 1464 1198"> <tr> <td>> 5 mm</td> <td>≤ 5 mm</td> </tr> <tr> <td>post-test risk: 2-5%</td> <td>0.1-0.2%</td> </tr> </table>	> 5 mm	≤ 5 mm	post-test risk: 2-5%	0.1-0.2%	<p><i>Ultrasonography is poor at differentiating potential cancer from other tamoxifen-induced thickening because of the distorted endometrial architecture associated with long term use of tamoxifen.</i></p> <p>D Hysteroscopy with biopsy is preferable as the first line of investigation in women taking tamoxifen who experience PMB.</p>
≤ 3 mm	> 3 mm									
post-test risk: 0.6-0.8%	20-22%									
> 5 mm	≤ 5 mm									
post-test risk: 2-5%	0.1-0.2%									
<p>C Histological specimens may be obtained either at the same time as inpatient or outpatient hysteroscopy with curettage or using an endometrium sampling device e.g. Pipelle™.</p> <p>C Hysteroscopy and biopsy (curettage) is the preferred diagnostic technique to detect polyps and other benign lesions.</p>										
<p>B If the clinician and the woman judge that the level of reassurance and reduced risk are acceptable following TVUS, no further action need be taken. Further investigations should be carried out if symptoms recur. If the clinician or patient are <i>not</i> satisfied with this level of reassurance, further investigation is justified. This should include an endometrial biopsy to obtain a histological assessment.</p>										

* The sequence of investigation will depend on clinical judgement, local resources and expertise, and patient preference. Obtaining an initial endometrial sample may be in the patient's interest if it identifies a cancer prior to the ultrasound appointment.

Transabdominal ultrasound may be used as a complementary examination if the uterus is significantly enlarged or a wider view of the pelvis or abdomen is required. Transabdominal ultrasound may also be used in the small proportion of women in whom it proves technically impossible to perform a transvaginal ultrasound.