

REVIEW ARTICLE

Investigation of Women with Postmenopausal Uterine Bleeding: Clinical Practice Recommendations

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Perm J 2014 Winter;18(1):55-70

<http://dx.doi.org/10.7812/TPP13-072>**Abstract**

Postmenopausal uterine bleeding is defined as uterine bleeding after permanent cessation of menstruation resulting from loss of ovarian follicular activity. Bleeding can be spontaneous or related to ovarian hormone replacement therapy or to use of selective estrogen receptor modulators (eg, tamoxifen adjuvant therapy for breast carcinoma). Because anovulatory “cycles” with episodes of multimonth amenorrhea frequently precede menopause, no consensus exists regarding the appropriate interval of amenorrhea before an episode of bleeding that allows for the definition of postmenopausal bleeding. The clinician faces the possibility that an underlying malignancy exists, knowing that most often the bleeding comes from a benign source. Formerly, the gold-standard clinical investigation of postmenopausal uterine bleeding was institution-based dilation and curettage, but there now exist office-based methods for the evaluation of women with this complaint. Strategies designed to implement these diagnostic methods must be applied in a balanced way considering the resource utilization issues of overinvestigation and the risk of missing a malignancy with underinvestigation. Consequently, guidelines and recommendations were developed to consider these issues and the diverse spectrum of practitioners who evaluate women with postmenopausal bleeding. The guideline development group determined that, for initial management of spontaneous postmenopausal bleeding, primary assessment may be with either endometrial sampling or transvaginal ultrasonography, allowing patients with an endometrial echo complex thickness of 4 mm or less to be managed expectantly. Guidelines are also provided for patients receiving selective estrogen receptor modulators or hormone replacement therapy, and for an endometrial echo complex with findings consistent with fluid in the endometrial cavity.

Guideline History and Scope

The Abnormal Uterine Bleeding Working Group (AUBWG) was originally created in 2004 to develop evidence-based, consensus guidelines for the management of abnormal uterine bleeding for women in Kaiser Permanente's Southern California (KPSC) Region (see Sidebar: Members of the Abnormal Uterine Bleeding Working Group). The Southern California Permanente Medical Group (SCPMG) is the only Medical Group contracted to provide care for the more than three million members of the Kaiser Foundation Health Plan in the Southern California Region. The AUBWG determined that the scope of these guidelines included the investigation and initial management of women with postmenopausal bleeding thought or

known to emanate from the vagina.⁴¹ The first version of these guidelines, based on evidence published to December 2004, was completed in 2005 and published in an abbreviated format on the Guideline Clearinghouse Web site of the Agency for Healthcare Research and Quality, with the full text made available on request. This version of the guidelines includes the result of a major systematic review of the evidence published since January 2005.

Postmenopausal uterine bleeding, either spontaneous or that related to ovarian hormone replacement therapy (HRT) or selective estrogen receptor modulator (SERM) use (eg, tamoxifen adjuvant therapy for breast carcinoma) collectively results in a substantial number of patient encounters. These encounters directly

involve physicians and other clinicians in the Departments of Family Medicine, Internal Medicine, Obstetrics and Gynecology, and Oncology and include physicians, nurse practitioners, and other midlevel clinicians. The clinical problem also indirectly affects medical clinicians and resources in the Departments of Radiology and Pathology, particularly because of the use of endometrial sampling and imaging of the uterus. Consequently, recommendations have been developed considering this diverse spectrum of practitioners and departments.

Methods

The Chair of the AUBWG was selected by the Regional Chief of Obstetrics and Gynecology for SCPMG. The remaining members of the AUBWG were selected by the chairs of each of the 12 KPSC Medical Centers on the basis of their interest in abnormal uterine bleeding and ability to contribute to guideline development.

After an introductory discussion on the general and SCPMG-specific issues involved in the investigation of postmeno-

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Table 1. Definitions of terms

Term	Definition
Postmenopausal bleeding	Spontaneous uterine bleeding that occurs more than one year after the date of the last menstrual period
Breakthrough bleeding	Unscheduled uterine bleeding encountered in any postmenopausal woman using hormone replacement therapy
Satisfactory endometrial biopsy	Comprises perceptible passage of the sampling device through the cervical canal into the endometrial cavity and appropriate functioning of the aspiration mechanism. Adequacy of the specimen for histologic interpretation is determined by the pathologist.

Table 2. Hierarchy of evidence^a

Class	Type of evidence
1a ^b	Meta-analysis of randomized clinical trials
1b	Randomized clinical trial
2	Meta-analysis of studies that are not randomized
3	Nonrandomized, but internally controlled trials. Controls are considered to be "internal" if they are included in the original design of the study. Post hoc or historical comparisons are not considered internal controls. Comparisons of otherwise uncontrolled clinical series are not considered internal controls.
4	Case-control studies
5	Cohort studies
6	Clinical series, without internal comparison
7 ^b	Expert opinion without available clinical studies

^a Source: Kaiser Foundation Guideline Development Group, Edition 3, September 1, 2004, using a modification of the system adopted by the US Preventive Services Task Force of the Agency for Health Research and Quality.
^b Level of evidence added by the Abnormal Uterine Bleeding Working Group.

pausal bleeding, the committee met as a whole to review methods of guideline development, agree on terms for evidence classification, define basic terms (Table 1) and to come to consensus on the scope of the guidelines to be developed. (See prior section, Guideline History and Scope;

Tables 2 and 3; the Sidebars: Problem Formation and Suggested Contents for Report of Endometrial Echo Complex Evaluation.) The Working Group Chair prepared a template to aid the guideline development process. For the revision process, the existing document underwent

a draft revision following a systematic review of the literature.

For the original review, a subgroup of three individuals was charged with leading the investigation and developing draft documents for meetings of the whole group. Drafts were distributed electronically to the whole group, and monthly face-to-face meetings were used to obtain feedback from each of the members of the committee. For this major revision, all members of the AUBWG were involved in the review and revision process with two face-to-face meetings and teleconferences as appropriate.

Literature searches were performed in MEDLINE and The Cochrane Database of Systematic Reviews between January 1, 2005 and November 19, 2012, using the following search terms: postmenopausal uterine bleeding, transvaginal ultrasound, sonohysterography, saline infusion sonography, hysteroscopy, endometrial biopsy, tamoxifen, and hormone replacement therapy (see Sidebar: Evidence Tables [available from: www.thepermanentejournal.org/files/Winter2014/EvidenceSearch.pdf]). Also searched were the Web sites of the American College of Obstetricians and Gynecologists (www.acog.org/Resources_And_Publications), the Society of Obstetricians and Gynecologists of Canada (<http://sogc.org/clinical-practice-guidelines/>), the New Zealand Guidelines Group (www.health.govt.nz/about-ministry/ministry-health-websites/new-zealand-guidelines-group), the National Institute for Health

Table 3. Support for recommendations^a

Strength of Evidence	Language	Evidence
A	Guideline Development Team (GDT) strongly recommends that clinicians routinely provide the intervention to eligible patients	Intervention improves important health outcomes, based on good evidence, and the GDT concludes that benefits substantially outweigh harms and costs
B	GDT recommends that clinicians routinely provide the intervention to eligible patients	Intervention improves important health outcomes, based on 1) good evidence that benefits outweigh harms and costs or 2) fair evidence that benefits substantially outweigh harms and costs
C	GDT makes no recommendation for or against routine provision of the intervention. At the discretion of the GDT, the recommendation may use the language "option," but must list all the equivalent options.	Evidence is sufficient to determine the benefits, harms, and costs of an intervention, and there is at least fair evidence that the intervention improves important health outcomes. However, the GDT concludes that the balance of the benefits, harms, and costs is too close to justify a general recommendation.
D	GDT recommends against routinely providing the intervention to eligible patients	GDT found at least fair evidence that the intervention is ineffective, or that harms or costs outweigh benefits
I	GDT concludes that the evidence is insufficient to recommend for or against routinely providing the intervention. At the discretion of the GDT, the recommendation may use the language "option" but must list all the equivalent options.	Evidence that the intervention is effective is lacking, of poor quality, or conflicting, and the balance of benefits, harms, and costs cannot be determined

^a Source: Kaiser Foundation Guideline Development Group, Edition 3, September 1, 2004.

and Clinical Excellence (www.nice.org.uk), and the Geneva Foundation for Medical Education and Research (www.gfmer.ch/000_Homepage_En.htm). Each Web site was a repository of evidence-based and consensus-based guidelines.

The original postmenopausal bleeding guidelines and subsequent revisions were developed using the identified evidence and, where deemed necessary by the participants, a consensus process with which to classify, interpret, and develop components of the guideline not evaluated adequately by the literature. Evidence was classified using a modification of the system adopted by the US Preventive Services Task Force of the Agency for Healthcare Research and Quality (Table 2), adding a subgroup for Class 1

evidence to allow for meta-analysis of randomized controlled trials, such as a Cochrane review. An additional modification was to include the creation of a Class 7 grouping that isolated expert opinion, including that from guidelines or other consensus documents from national or international organizations or from the collective opinion of the AUBWG members. The recommendations were created and classified according to the strength of the evidence and classified according to the system used by KPSC Guideline Development teams (Table 3). The term *good evidence* used in the text or tables indicates that either Grade A or Grade B evidence was available to support the recommendations (Table 4). The process was designed to be a continuous one, allowing for ongoing modifications and revisions as new, higher quality or otherwise clarifying evidence becomes available.

The original consensus document was created, approved by the members of the AUBWG in October 2004, and then submitted to the SCPMG Regional Chiefs for review, comment, and approval. Specifically, the Chiefs selected the 5-mm endometrial echo complex (EEC) thickness as the evidence-based threshold above which endometrial sampling is recommended. Following the 2012 review of the available evidence, the recommended threshold was changed to 4 mm. Minor modifications of the guideline were made following presentation to the SCPMG Regional Chiefs of Obstetrics and Gynecology. The revised guidelines were unanimously approved by the Regional Chiefs of Obstetrics and Gynecology on March 20, 2013.

Rationale

Introduction

Postmenopausal bleeding is a common patient complaint that is encountered by all physicians and other clinicians of gynecologic care. The clinician faces the possibility that there exists an underlying malignancy, while knowing that, in most instances, the bleeding comes from a benign source. In years past, the gold standard of clinical investigation was the institution-based dilation and curettage (D&C), but there now exists a number of office-based methods for the evaluation of women with this complaint. The postmenopausal use of gonadal steroids for

the treatment of menopausal symptoms (HRT) is often associated with endometrial bleeding. Although the number of women using these agents decreased in the first decade of the 21st century, reevaluation of the literature and the release of new studies have collectively suggested that such therapy may provide benefit in at least selected instances.¹⁻³

As a result, clinicians will continue to be challenged by the issue of HRT-associated postmenopausal bleeding in the near future. It is known that tamoxifen and other SERMs may increase the chance of endometrial neoplasia developing. However, the proportion of postmenopausal women using such agents as adjuvant treatment of breast cancer is decreasing with the introduction of aromatase inhibitors³ (Grade C). Nevertheless, there will continue to exist a number of women in their late reproductive years with unknown or uncertain ovarian endocrine status who experience abnormal bleeding in association with the use of these agents. Such women may have to be considered to have postmenopausal bleeding associated with the use of a SERM.

The clinician should appreciate that although the focus of investigation of postmenopausal bleeding is on the endometrium, bleeding in the postmenopausal woman may arise from a number of extraendometrial gynecologic and nongynecologic sites, such as the cervix, vagina, and urologic and gastrointestinal tracts. As a result, it is incumbent on the clinician to consider all these possibilities when evaluating a patient with postmenopausal bleeding or apparent unscheduled (“breakthrough”) bleeding who is receiving HRT. Consequently, should the results of appropriately indicated and performed evaluation of the endometrium be normal, reevaluation for these potential causes is a prudent approach.

Definition of Postmenopausal Bleeding

The World Health Organization defines menopause as the permanent cessation of menstruation resulting from the loss of ovarian follicular activity.⁴ Because anovulatory “cycles” with episodes of multimonth amenorrhea frequently precede menopause, there is no consensus regarding the appropriate interval of

Problem Formulation

Intended use of the guideline

To assist physicians and other health care professionals in the evaluation and management of uterine bleeding in postmenopausal women (postmenopausal uterine bleeding)

Health problem

Postmenopausal uterine bleeding

Health interventions

Strategies and techniques for investigation of women with postmenopausal uterine bleeding

Population

Postmenopausal women

Practitioners

Physicians, physician assistants, nurse practitioners, and other health care professionals in the Departments of Emergency Medicine, Family Medicine, Internal Medicine, and Obstetrics and Gynecology

Medical setting

Offices, clinics, Emergency Departments, and hospital inpatients

Most important health outcomes

Outcomes of condition:

- Potential sign of endometrial or other uterine malignancy or premalignant condition such as atypical endometrial hyperplasia
- May reflect benign causes (including idiopathic, endometrial polyps) and iatrogenic sources

Outcomes of intervention:

- Identification of women with atypical endometrial hyperplasia and cancer
- Identification of women with usually benign lesions such as endometrial polyps

No.	Recommendation	Method	Strength of evidence ^b
1	Women with spontaneous postmenopausal bleeding should be primarily evaluated with either endometrial biopsy (EB), or transvaginal ultrasound (TVUS) to measure the thickness of the endometrial echo complex (EEC)	E	A
2	When TVUS or contrast sonography such as saline infusion sonography (SIS) are used as techniques for assessing the endometrium of women with postmenopausal bleeding, a detailed description of the evaluation should be placed in the patient record with or without representative photographs of the sagittal and transverse planes	C	N/A
3	Practitioners without adequate training in either office-based EB or TVUS should refer patients with postmenopausal bleeding or breakthrough bleeding to an individual, usually a gynecologist, appropriately trained in these techniques	C	N/A
4	Women with spontaneous postmenopausal bleeding and an EEC > 4 mm should be further evaluated with endometrial sampling	E	A
5	If clear endometrial fluid is identified on TVUS, the EEC is determined by subtracting the measured thickness of the fluid from the EEC measurement	E	B
6	In the presence of sonolucent fluid, women with a measurement of ≤ 3 mm may be managed expectantly. In the presence of postmenopausal bleeding, cervical carcinoma should be considered and evaluated appropriately	E	B
7	Women with persistent spontaneous postmenopausal bleeding require further evaluation of the endometrial cavity for focal lesions with one or a combination of office-based contrast sonography (eg, SIS) and hysteroscopy. Such an approach is necessary even if there is a satisfactory or adequate EB without evidence of hyperplasia, and regardless of the EEC thickness	E	B
8	Operating room-based dilation and curettage (D&C) of women with postmenopausal bleeding should be performed only when office-based EB is indicated, cannot be performed for patient comfort or technical reasons, or when it is inconclusive and results of sonographic techniques (TVUS, SIS) are not reassuring	E	B
9	Women taken to the operating room for D&C should have concomitant hysteroscopy with ancillary instruments that allow for the removal of focal lesions such as endometrial polyps	C	N/A
10	In the presence of endometrial carcinoma, hysteroscopy does not appear to affect short- or long-term prognosis. Consequently, hysteroscopy is not contraindicated in the evaluation of women with postmenopausal bleeding, including cases suggestive of cancer	E	A
11	Only selected women with bleeding associated with estrogen and progestin-containing hormone replacement therapy (HRT) require assessment of the endometrium. Uterine bleeding or spotting may be expected depending in part on the dose of HRT administered, in part on the schedule of progestin administration, and in part on the duration of therapy	E	B
12	It is not necessary to routinely evaluate the endometrium of women with uterine spotting or light uterine bleeding in the first six months of continuous estrogen and progestin HRT. Endometrial assessment of such women is recommended if spotting or bleeding persists beyond six months, although there is a very low incidence of endometrial hyperplasia or neoplasia	E	B
13	Women receiving doses of unopposed estrogen have a much higher incidence of endometrial hyperplasia and carcinoma, and require appropriate investigation of the endometrium	E	A
14	Women receiving estrogen and cyclical progestins can be expected to have indefinite progestin withdrawal bleeding and require no further investigation provided that the dose and duration of cyclic progestins is adequate	E	A
15	For women using cyclic progestins, bleeding outside the time of progestin withdrawal is considered abnormal and requires appropriate investigation	E	B
16	It is apparent that EEC thresholds used for spontaneous bleeding can be applied to patients with HRT-related bleeding, but with a higher incidence of false-positive findings	E	B
17	Women experiencing uterine bleeding while receiving tamoxifen (usually used as an adjuvant therapy for breast cancer) should be assessed primarily with endometrial sampling because, in such patients, TVUS is neither sensitive nor specific for neoplasia	E	A
18	Women with persistent bleeding during tamoxifen therapy, and who have already undergone endometrial sampling, should be assessed with one or a combination of contrast sonography (such as SIS) and hysteroscopy with appropriate sampling or excision of polyps if found	C	N/A
19	Women with repeated bleeding during tamoxifen therapy, and who have been demonstrated to have normal histologic findings and a structurally normal endometrial cavity, should have EB repeated annually	E	B
20	Postmenopausal bleeding can be a presenting symptom of cancer in the cervical canal. Consequently, if there is no endometrial explanation for postmenopausal bleeding, appropriate steps to evaluate patients for cervical cancer should be undertaken considering the results of a Papanicolaou test, colposcopy, and curettage of the endocervical canal	C	N/A

^a Recommendations are evidence based (E) unless sufficient evidence is not available and consensus-based (C) recommendations are provided.

^b See Table 2; strength of evidence is not applicable (N/A) to consensus-based recommendations.

amenorrhea preceding an episode of bleeding that would allow for the definition of postmenopausal uterine bleeding. For the purposes of this guideline, an episode of bleeding 12 months after the last menstrual period will be deemed to constitute postmenopausal bleeding. However, and especially in the perimenopausal years, the definition of "last period" may be difficult to ascertain, so liberal use of assays for estradiol and follicle stimulating hormone will help to determine when bleeding is occurring absent measurable ovarian function.

For women receiving HRT, bleeding is common, and its frequency and timing depends in part on the scheduling of the gonadal steroids used, particularly the progestational agent⁵ (Class 5). *Breakthrough bleeding* is unscheduled uterine bleeding that occurs in women receiving either estrogen alone or both estrogen and progestin therapy, which does *not* include the withdrawal bleeding that occurs following the cyclic withdrawal of

progestin treatment. About 50% of women using continuous estrogen-progestin combined replacement regimens experience breakthrough bleeding, with most cases resolving 6 months after initiation of therapy⁶ (Class 4).

The following definitions of abnormal bleeding during HRT are suggested^b:

- For women using cyclically administered progestins in combination with a cyclical or continuous estrogen: 1) occurs at an unscheduled time or 2) occurs at the anticipated time after progestin withdrawal but is heavy or prolonged.
- For women using continuous combined estrogen and progestin-containing regimens: 1) commences six months or more after initiation or 2) commences after amenorrhea has been established.

Risk of Endometrial Cancer

In the US, endometrial cancer is the most commonly diagnosed reproductive tract malignancy and is the fourth

most common cancer among women, trailing only cancers of the breast, lung, and colorectal origin⁷ (Class 5). Although endometrial cancer accounts for 6% of all female cancers, a number of intrinsic clinical features, including a propensity for early diagnosis (because of investigation of abnormal or postmenopausal bleeding) and the prompt use of effective therapy, it causes only about 3% of all cancer-related deaths.

There are 2 distinct types of endometrial cancer; most are Type 1, which develops secondary to unopposed estrogen-induced endometrial hyperplasia with an endometrioid appearance on histopathologic evaluation. Type 2 lesions comprise the minority, are of serous or clear cell origin, are not related to estrogen exposure, and are associated with a relatively poor prognosis. Older literature would suggest that Type 2 endometrial cancers comprise between 16% and 35% of endometrial cancer cases^{8,9} (Class 5), but more recent data from the US reveal that approximately 90% are Type 1 and about 10% are Type 2 lesions¹⁰ (Class 5).

For women with postmenopausal bleeding who do not use HRT, the incidence of endometrial cancer ranges from 4.9% to 11.5%¹¹⁻¹⁴ (Class 5). There appears to be a greater risk of endometrial cancer in women who present with postmenopausal bleeding 10 or more years following menopause. One relatively large study found that postmenopausal bleeding over the age of 60 years was associated with a 13% risk of endometrial cancer¹¹ (Class 5). Another large cohort study of slightly more than 3000 women with postmenopausal bleeding identified a peak in the age group from 60 through 64 years, of whom 7% were found to have endometrial cancer; the risk was lower for those in the younger and older age groups¹⁴ (Class 5).

There are no reliable data regarding the incidence of endometrial carcinoma in women using estrogen and progestin-containing HRT regimens. However, the estimated proportions range from 0.02% to 0.05% per annum¹⁵⁻¹⁷ (Class 5). For women receiving tamoxifen, the risk of endometrial cancer is likely above 10% depending in part on the dose and in part on the duration of therapy¹⁸⁻²¹ (Class 4).

Suggested Contents for Report of Endometrial Echo Complex (EEC) Evaluation

Normally Configured Uterus, EEC well seen

The uterus measures ___ . ___ cm in length; the corpus ___ . ___ cm in width, and ___ . ___ cm in anterior-posterior thickness. The EEC is seen in its entirety in both the sagittal and transverse planes, is consistent in thickness and echogenicity, and measures ___ . ___ mm throughout.

Comment: _____

Uterus with EEC well seen, endometrial cavity containing sonolucent fluid

The uterus measures ___ . ___ cm in length; the corpus ___ . ___ cm in width, and ___ . ___ cm in anterior-posterior thickness. The EEC is seen in its entirety in both the sagittal and transverse planes, and contains sonolucent fluid. The endometrium on both sides of this fluid is consistent in thickness. The two-layer endometrial thickness calculated by subtracting the thickness of the fluid from the total endometrial echo complex thickness is ___ . ___ mm.

Comment: _____

Generic

Uterine length: ___ . ___ cm

Corpus width: ___ . ___ cm

Corpus thickness: ___ . ___ cm

Endometrial fluid: Yes No

If Yes: Sonolucent? Yes No

Thickness of sonolucent fluid (sagittal): ___ . ___ mm

Thickness of sonolucent fluid (transverse): ___ . ___ mm

Entire EEC seen: Yes No

EEC consistent throughout: Yes No

Double-layer endometrial thickness: Sagittal plane: ___ . ___ mm

Transverse plane: ___ . ___ mm

Net endometrial thickness if sonolucent fluid subtracted: Sagittal plane: ___ . ___ mm

Transverse plane: ___ . ___ mm

Comment: _____

Relationship to Age

The national registries of nations with government-supported health care programs provide information regarding demographic variables associated with the risk of endometrial carcinoma. The incidence of endometrial cancer is very low below the age of 50 years, and especially before 40 years. The Scottish national data suggest that the incidence of endometrial carcinoma is about 6 to 8/100,000 women each year after the age of 50 years²² (Class 4). However, these data do not describe the risk of endometrial cancer in women presenting with postmenopausal bleeding. Swedish data demonstrate that the incidence of postmenopausal bleeding declines with succeeding years after menopause and that the incidence of endometrial carcinoma increases as the age of the patient with postmenopausal bleeding increases¹² (Class 4).

Hormone Replacement Therapy

The relative risk of development of endometrial cancer for a woman receiving unopposed estrogen preparations in historically typical doses is about 5 times that for nonusers¹⁷ (Class 4). This increased risk is almost, if not totally, eliminated if appropriate cyclic or continuous progestins are added to the regimen¹⁷ (Class 4),²³ (Class 1a),²⁴ (Class 1b). However, a number of features may affect these risks, including the dose of the estrogen, and the dose, route, and regimen used to administer the progestin.

Most of the high-quality evidence relating to estrogen and progestin type and dosing and the risks of endometrial neoplasia has been obtained from randomized trials using endometrial hyperplasia as a surrogate outcome, studies that are well summarized in The Cochrane Database of Systematic Reviews²⁵ (Class 1a). Unopposed estrogen, compared with placebo, is associated with an odds ratio (OR) for the short-term (18- to 24-months) development of endometrial hyperplasia that is 2.42 (95% confidence interval [CI], 1.19-4.92), 11.86 (CI, 7.76-18.14), and 13.06 (CI, 5.88-29.02) for low-, moderate-, and high-dose formulations, respectively. When estrogen is administered in conjunction with a progestin, these risks are reduced substantially if an adequate dose is administered for an appropriate time.

When the progestin of a combined HRT regimen is administered cyclically, optimal results are obtained with 10 to 14 days/month because there is evidence that for women who use cyclic progestin therapy for less than 10 days per cycle, the risk of endometrial cancer is raised (OR, 2.9; CI, 1.8-4.6)¹⁷ (Class 4). The minimum cycle duration has generally been considered to be 1 month. However, there is fair evidence that quarterly or even semiannual cycling for 14 days of medroxyprogesterone acetate (10 mg/day) is adequate to prevent most cases of endometrial hyperplasia or neoplasia, at least with conjugated equine estrogen (or equivalent) doses up to 0.625 mg/day²⁶ (Class 1b),^{27,28} (Class 3). Nevertheless, in the best available case-control study evaluating the role of cyclical therapy, long-cycle progestin replacement was associated with a 1.63 OR (CI, 1.12-2.38) at 5 to 10 years and a 2.95 OR (CI, 2.42-3.62) at 10 or more years compared with women not receiving HRT²⁹ (Class 4). These increases were not seen with continuous progestin regimens, including the use of the intra-uterine progestin releasing system. There is relatively recent evidence that ultralow doses of unopposed estrogen may not increase the incidence of endometrial carcinoma, but these preparations are not yet in widespread use^{30,31} (Class 3). Furthermore, there is good evidence that even doses as low as 0.3 mg/day of unopposed equine estrogens are associated with an increased risk of endometrial hyperplasia²⁵ (Class 1a).

The addition of a progestin to an estrogen-based HRT regimen is frequently associated with bleeding—generally predictable with cyclic progestin therapy and unpredictable for women receiving continuous treatment with progestin preparations^{32,33} (Class 4). As a result, the proportion of women having underlying endometrial carcinoma can be expected to be much lower in women using combined HRT regimens than it is for those using estrogen alone or, depending on the formulation and schedule, for those receiving no HRT at all³⁴ (Class 4).

Endometrial Cancer and Tamoxifen

Tamoxifen is a nonsteroidal compound in the family of SERM³⁵ that possesses weak estrogen activity similar to clomiphene citrate. Each of these agents is used to flood estrogen receptors with relatively inactive hormones, an approach designed to diminish estrogen-related cellular function. For those women using tamoxifen as adjuvant therapy for breast cancer, there is a substantial reduction in the rate of recurrence of breast cancer, but there is also a 3 to 6 times increase in the incidence of endometrial carcinoma¹⁸⁻²¹ (Class 4). This risk is proportional both to the dose of the drug and the duration of therapy, with those women treated for 5 or more years experiencing a fourfold risk^{36,37} (Class 4). Some evidence exists that, for women in whom endometrial carcinoma develops following prolonged tamoxifen use, both the grade and stage of the tumor may be

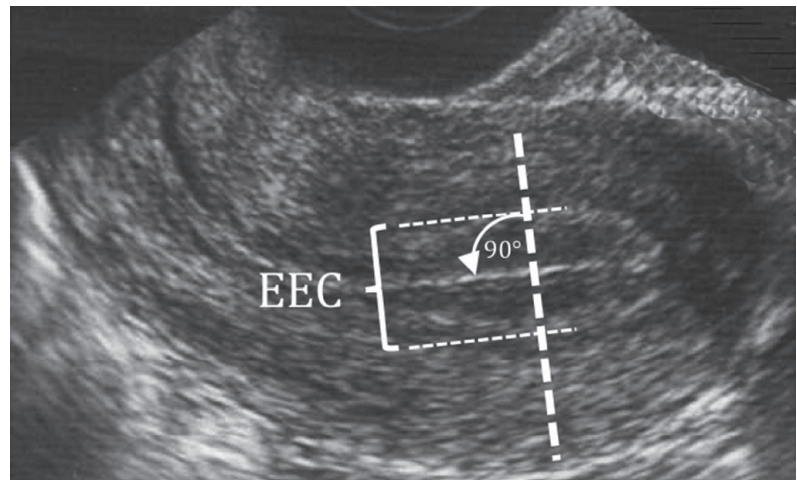


Figure 1. Endometrial echo complex (EEC) measurement in the sagittal plane.

Study should include coronal or transverse plane as well. For demonstration purposes, the image is from a premenopausal woman.

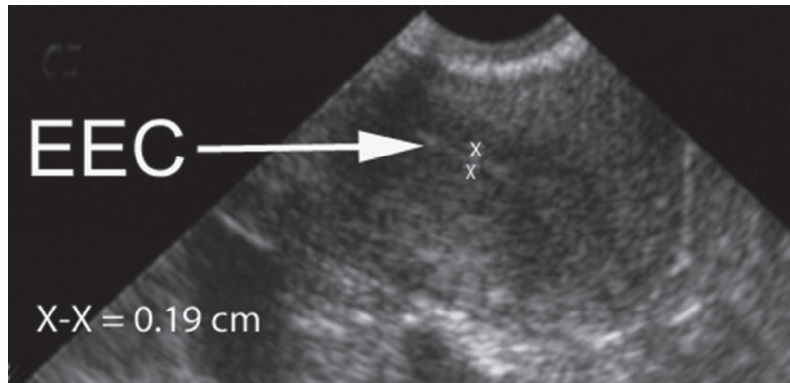


Figure 2. Typical measurement of normal postmenopausal endometrial echo complex (EEC) (< 4 mm) (arrowhead).

higher, thereby potentially compromising survival³⁸ (Class 4). Formerly there was controversy regarding the most appropriate approach to monitoring the endometrium in women using tamoxifen, with some investigators suggesting that routine endometrial sampling be performed on an annual basis. However, current evidence suggests that such an approach consumes resources without improving survival rates^{39,40} (Class 3). Consequently, and at least for the present, only women receiving tamoxifen who experience uterine bleeding should be investigated.

Although not strictly within the scope of this guideline, the management of nonbleeding women with a thickened endometrium (thick EEC) who are receiving tamoxifen is a potential issue. Evidence from studies evaluating this issue fails to support the notion of routine sonographic screening⁴¹ (Class 5), at least in part because there is no evidence for a clinically useful EEC threshold in tamoxifen-treated patients⁴⁰ (Class 3). These findings, often cystic in nature, represent a unique, reversible, tamoxifen-induced change⁴² (Class 5).

Relationship to Hereditary Nonpolyposis Colonic Cancer

A number of other factors are associated with an increased risk of endometrial cancer. Hereditary nonpolyposis colorectal cancer is a relatively common, autosomal dominant syndrome originally described by Henry Lynch, and it is still known in some quarters by the name Lynch syndrome, particularly if there is a known DNA mismatch pair. Endometrial cancer is the most common extracolonic cancer found in women with this syndrome. The estimated lifetime risk of

endometrial cancer in women with Lynch syndrome is 42% to 60%^{43,44} (Class 5) and, unlike spontaneous endometrial cancer, these malignancies often present in the premenopausal years⁴⁵ (Class 4).

Other Risk Factors for Endometrial Cancer

The evidence linking other risk factors to the development of endometrial cancer is relatively weak. These include obesity, hypertension, and a history of either endogenous or exogenous hyperestrogenism⁴⁶ (Class 5).

Clinical Investigation of Women with Postmenopausal Vaginal Bleeding

Physical Examination

Pelvic examination should be performed searching for visual evidence of lesions or bleeding from gynecologic (eg, vulva, vagina, exocervix) and non-gynecologic (eg, perineum, periurethral, perianal) sources.

Evaluation of the Endometrium

Histologic Assessment

Sampling of the endometrium can be accomplished by devices designed for office use, by D&C, or under hysteroscopic direction. Office-based sampling is usually performed with disposable catheters that allow for the application of suction to obtain a specimen. Any method of sampling the endometrial cavity misses a proportion of endometrial cancers²⁴ (Class 1b),^{47,48} (Class 3),⁴⁹ (Class 5).

Dilation and Curettage

D&C should no longer be the first method of sampling the endometrium in most cases. Comparison of office-based

endometrial sampling with the Pipelle (CooperSurgical Inc; Trumbull, CT; USA) device with combined curettage and hysteroscopy reveals that each blind procedure is an acceptable screening tool but does miss usually benign lesions such as endometrial polyps⁵⁰ (Class 2). However, it is not completely clear that D&C is equivalent to endometrial sampling with a suction catheter. One group of investigators from Sweden demonstrated that D&C was slightly superior to the Endorette endometrial sampler (CooperSurgical Inc; Trumbull, CT; USA), a suction catheter device similar to the Pipelle, for diagnosing endometrial cancer when the EEC measured 7 mm or more⁵¹ (Class 1b).

Procedure and Tissue Yield

Failure Rates of Office-Based Endometrial Sampling

When inadequate tissue is obtained to allow histologic assessment, the specimen is typically called “nondiagnostic.” Evidence suggests that such patients may have underlying intrauterine lesions, including malignancy, especially if results of transvaginal ultrasonography (TVUS) are nondiagnostic or in excess of an acceptable threshold value such as 5 mm⁵² (Class 5). Office-based sampling of the endometrium is associated with a procedure failure rate of approximately 10% and a tissue yield failure rate that is historically approximately also 10%^{34,49,53} (Class 3).

Collectively, these data would suggest that women with “nondiagnostic” endometrial biopsy specimens should have additional uterine evaluations with TVUS, contrast sonography, hysteroscopy, or a combination of any of these procedures.

Comparison of Office-Based Sampling Systems

There are a number of issues to consider when comparing office-based endometrial sampling catheters, including ease of use, procedure-associated pain, frequency of obtaining adequate samples, number of passes required to obtain those samples, and cost. The Pipelle device has been shown, in the context of a randomized trial, to be superior to the Vabra aspirator (Berkeley Medevices Inc; Richmond, CA; USA), with adequate tissue being found in 73.3% vs 52.4% of cases⁵⁴ (Class 1b). The Pipelle device has also been compared with the Explora catheter (CooperSurgical Inc; Trumbull, CT; USA) in a randomized

trial; results showed the Explora to be slightly superior regarding proportion of adequate samples (97% vs 91%)⁵⁵ (Class 1b). However, in randomized trials from Scotland, the Tao Brush (Cook Medical; Bloomington, IN; USA) was found to be superior to the Pipelle catheter in obtaining a satisfactory endometrial sample (72% to 43%)^{56,57} (Class 1b). Endometrial cytology with liquid-based techniques has also been described to have a high sensitivity for carcinoma, but it has not been compared with blind sampling⁵⁸ (Class 3). Clearly, more comparative trials are necessary to determine the optimum combination of effectiveness, cost, and procedure-related pain.

Blind Endometrial Sampling

Blind methods of endometrial sampling frequently fail to identify focal pathology of the endometrium. Although blind sampling, either by endometrial biopsy or D&C, is a satisfactory first-line technique for the detection of endometrial neoplasia that affects the entire endometrial surface, it is inadequate at detecting localized lesions such as endometrial polyps, which may be malignant⁵⁹⁻⁶¹ (Class 3). Indeed, a well-designed prospective study demonstrated that even D&C performed in the operating room missed endometrial polyps about half the time⁶⁰ (Class 3). This information would suggest that in the presence of symptoms or evidence of a focal lesion, or, following blind sampling, if symptoms of postmenopausal bleeding persist, imaging of the endometrial cavity should be performed with one or a combination of the following: TVUS, contrast sonography, or hysteroscopy.

Transvaginal Ultrasonography

Compared with premenopausal women, the measured thickness of the endometrium (by convention a double layer in the midsagittal view; Figure 1) should be thinner in postmenopausal women not receiving HRT (Figure 2). This double-thickness layer is called the EEC. If there is uniformly sonolucent fluid—generally a nonconcerning finding—the thickness of the fluid echo is subtracted from the measurement from baseline to baseline to obtain the EEC (Figure 3). The morphologic features should be uniform and, if there are irregularities, or if the EEC cannot be

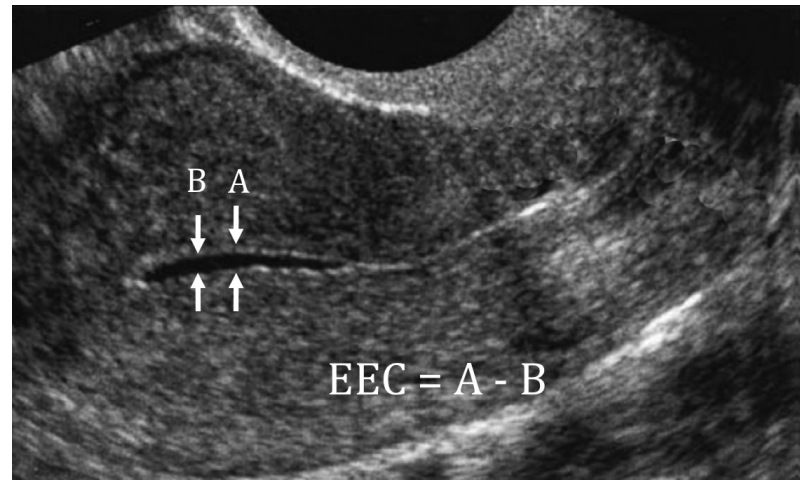


Figure 3. Measurement of endometrial echo complex (EEC) when there is fluid in the cavity. Thickness of fluid (B) is subtracted from distance between base of opposing layers of endometrium (A). These should be in the same plane; they are separated slightly here for demonstration purposes.

adequately evaluated (Figure 4), other investigations are warranted, such as contrast sonography, hysteroscopy, and/or endometrial sampling. At this time, available evidence suggests that there are no advantages offered by the use of 3-dimensional ultrasonography, as compared with standard 2-dimensional ultrasonography⁶² (Class 3).

In general, thicker EECs are associated with a greater likelihood of endometrial or intracavitary pathology, including endometrial polyps, hyperplasia, and cancer⁶³ (Class 3). On the other hand, the reliability of TVUS allows the clinician to identify a group of women with postmenopausal bleeding who have a thin endometrium and thus a very low likelihood of hyperplasia or neoplasia. Unless there is a recurrence of bleeding, this group of women with postmenopausal bleeding and a thin EEC generally require no more investigation⁶⁴⁻⁶⁶ (Class 2). There is some evidence that TVUS may be less sensitive for the detection of Type 2 endometrial carcinomas regardless of the EEC threshold. A cohort study demonstrated that 17% of patients with postmenopausal bleeding and Type 2 endometrial cancer had an EEC of less than 4 mm⁶⁷ (Class 5).

A number of EEC thickness thresholds have been published to guide clinicians in discriminating between women who require endometrial sampling and those who do not, at least for the first episode of postmenopausal bleeding (Table 5). The

thinner the threshold, the fewer cases of hyperplasia and cancer missed, but with higher sensitivity, specificity is reduced and more endometrial sampling must be performed. Furthermore, the use of HRT can have a variable impact on the measurements depending on the use of a progestin. Continuous estrogen-progestin regimens tend to cause a hypotrophic and sonographically thin endometrium, whereas the EEC in women receiving regimens of continuous estrogen and cyclically administered progestins will vary according to the date of the TVUS and the cycle date in the HRT regimen. Available evidence suggests that women with postmenopausal bleeding and a thickened endometrium are less likely to have endometrial pathology when they are receiving HRT than when they are not^{65,68} (Class 2). Presumably, the endometrial thickness in women receiving estrogen and cyclic progestin therapy would be lowest shortly after the cessation of the progestins, a time that might be best suited for measurement of EEC thickness in women who experience unscheduled bleeding.

Normal Thickness of Endometrial Echo Complex

Meta-analytic research using “summary data” has been performed using high-quality studies evaluating the utility of TVUS-obtained EEC thickness for the assessment of women with postmenopausal bleeding. The authors of the largest meta-analysis to date, with just more

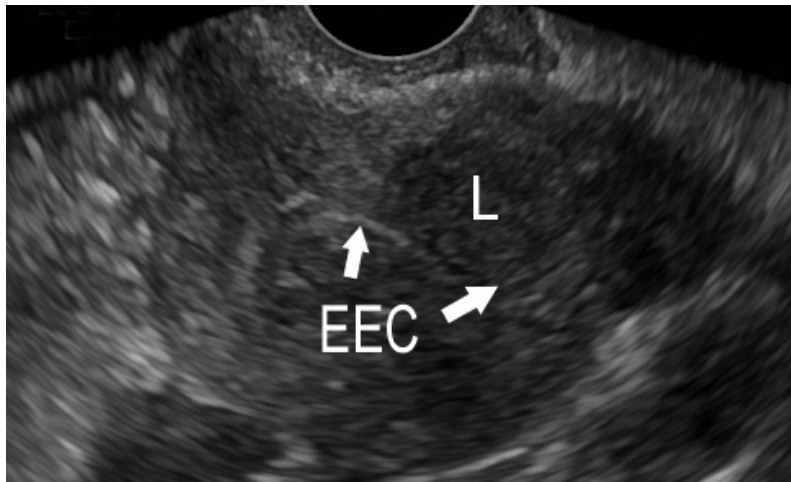


Figure 4. Inadequate measurement of endometrial echo complex (EEC) (between symbols).

than 9000 patients, demonstrated that an EEC of 3 mm or less would provide a posttest probability of 0.4% for endometrial cancer; a 4-mm threshold, 1.2%; and a 5-mm threshold, 2.3%⁶⁶ (Class 2). In this study, the best quality evidence was that for the 5-mm threshold.⁶⁶ The authors of a second large meta-analysis of nearly 6000 women reported that an EEC of 5 mm or less was associated with a 4% chance of endometrial cancer. This sensitivity did not vary in women using HRT⁶⁵ (Class 2).

Meta-analysis using the original datasets is thought to provide more accurate conclusions than using the summary data provided in the published manuscript because of a number of factors, including publication bias, method of analysis, and length of follow-up^{69,70} (technical descriptions). One such analysis employed this technique but, rather than using fixed cutoffs for EEC, used multiples of the mean

for each different study and determined that if the median EEC thickness was used, the sensitivity would be approximately 96% and specificity would be 50%. However, such an approach is difficult to evaluate and implement because it does not provide guidance about EEC thickness overall⁷¹ (Class 2). Consequently, Timmermans et al⁷² (Class 2) performed a re-analysis of the data using original datasets, rather than summary data, and were able to evaluate 2896 cases from 13 authors (259 with endometrial carcinoma), only 2 of which were from the original 90-author group reported in the publication by Smith-Bindman et al⁶⁵ (Class 2). The conclusions from this analysis suggested that a threshold of 5 mm for the EEC would have sensitivity for endometrial cancer of only 90%; 4 mm, a sensitivity of 95%; and 3 mm, a sensitivity of 98%—thresholds that are different from those found in the previously published meta-analyses. No

original dataset analyses were reported considering the impact on EEC thickness.

Before this individual dataset-based meta-analysis, the Scottish Intercollegiate Guidelines Network chose the 3-mm thickness for the following 3 groups of postmenopausal women with postmenopausal bleeding⁷³ (evidence-based guideline): 1) never used HRT, 2) discontinued HRT a year or more earlier, and 3) using continuous combined HRT. The Scottish Intercollegiate Guidelines Network also set a different threshold for women receiving estrogen and cyclic progestin therapy and estimated that, in the context of unscheduled bleeding, the risk of endometrial cancer for such women was 0.2% if the EEC was 5 mm or less.

The American College of Obstetricians and Gynecologists has published a practice bulletin that recommended an EEC threshold of 4 mm, above which other techniques of endometrial assessment should be employed.⁷⁴ The issue of HRT and its impact on EEC thresholds is not dealt with in that guideline (evidence-based guideline).

Endometrial Fluid Found with Transvaginal Ultrasonography

As described previously in this section, fluid may be identified between the sonographically determined endometrial layers in both symptomatic and asymptomatic women⁷⁵ (Class 5; Figure 3). Such a finding had previously been thought to be a predictor of malignancy, but more recent evidence challenges such a conclusion. The issue may be particularly relevant in the presence of cervical stenosis, when access to the endometrial cavity for endometrial sampling or hysteroscopy may be limited. Although there remains a relative paucity of studies evaluating this finding, existing con-

Table 5. Meta-analyses of sensitivity and specificity of endometrial echo complex for detection of endometrial cancer in women with postmenopausal bleeding

Author, year	Method	Number of included studies	Number of subjects	Number with EEC	Sensitivity by EEC thickness (95% CI)			Specificity by EEC thickness (95% CI)		
					3 mm	4 mm	5 mm	3 mm	4 mm	5 mm
Timmermans et al, ⁷² 2010	Original dataset	13	2896	259	97.9 (90.1-99.6)	94.8 (86.1-98.2)	90.3 (80.0-95.5)	35.4 (29.3-41.9)	46.7 (38.3-55.2)	54.0 (46.7-61.2)
Gupta et al, ⁶⁶ 2002	Summary data	57	8890	1243	99.3 (96.8-99.8)	98.9 (97.1-99.6)	97.7 (95.2-98.8)	25.3 (22.8-27.9)	24.2 (19.7-29.2)	26.1 (21.1-31.6)
Smith-Bindman et al, ⁶⁵ 1998	Summary data	35	5892	759	100 (89-100)	96 (93-98)	96 (94-98)	38 (32-45)	53 (51-55)	61 (59-63)

CI = confidence interval; EEC = endometrial echo complex.

temporary studies are remarkably consistent demonstrating that if the fluid is sonolucent and if the EEC, which is the combined thickness of the 2 separated endometrial layers, is 3 mm or less (see Figure 3), the finding is highly likely to be benign⁷⁶⁻⁷⁸ (Class 3). On the other hand, if the EEC is greater than threshold (3.0-4.5 mm depending on the study) or if the fluid is echogenic⁷⁹ (Class 3), there is a risk of malignancy and immediate further investigation aimed at obtaining a tissue sample is warranted⁸⁰ (Class 3). Women with postmenopausal bleeding, intrauterine sonolucent fluid, and an EEC of 3 mm or less could still harbor a carcinoma in the cervical canal, so such a diagnosis should be considered⁷⁹ (Class 3).

Documentation

If TVUS or contrast sonography is used to evaluate women with postmenopausal bleeding or unscheduled bleeding who are receiving HRT, documentation ideally comprises both a midline sagittal image and a transverse fundal image documenting the thickest measurement of the EEC. A suitable note describing the findings should be included in the patient record⁸¹ (Class 7). The addition to the record of selected images is desirable but not considered mandatory provided that the note describes the endometrial findings in sufficient detail.

Contrast Sonography

Transcervical instillation of saline (saline infusion sonography), or other sonographic contrast media such as gel, into the endometrial cavity allows for contrast-enhanced sonographic evaluation that is designed to improve diagnostic utility for lesions involving the endometrial cavity such as polyps or submucous leiomyomas⁸² (Class 5). The procedure is performed in an office setting with a small-caliber catheter positioned in the endometrial cavity while imaging is performed with simultaneous TVUS. In addition to saline infusion sonography, such fluid contrast-enhanced ultrasonography of the endometrial cavity is known as *sonohysterography* and *hysterosonography*, although the latter two terms may create confusion with the contrast-enhanced radiographic evaluation of the endometrial cavity and fallopian tubes that is called a hysterosalpingogram. Consequently, for purposes of this document, the term *contrast sonography* or saline infusion sonography will be used.

The procedure appears to accurately evaluate the endometrial cavity and can be successfully performed in more than 85% of postmenopausal women in an office setting⁸³ (Class 2). Saline infusion sonography seems superior to TVUS in defining intrauterine lesions in women with postmenopausal bleeding and a measured EEC greater than 5 mm, particularly for the delineation of endometrial polyps, for which it seems as accurate as hysteroscopy⁸⁴ (Class 2). Another observer-blinded comparison demonstrated that saline infusion sonography was essentially equivalent to hysteroscopy and superior to TVUS for the diagnosis of endometrial cavity abnormalities in women with postmenopausal bleeding⁸⁵ (Class 3). There is no current evidence suggesting that saline infusion sonography enhances the diagnosis of malignancy. However, by virtue of its ability to identify postmenopausal women with endometrial polyps, saline infusion sonography may facilitate diagnosis, targeted removal, and resolution of symptoms, thereby reducing resource utilization and improving patient satisfaction with the overall process (Class 7).

Hysteroscopy with Curettage and Directed Biopsy

Hysteroscopy is an endoscopic technique that allows direct visualization of the endometrial cavity. It can be performed in an office setting with local or no anesthesia, with or without sedation, or in a procedure room or operating room. To accomplish the procedure, it is often necessary to first dilate the cervix adequately to accommodate the external diameter of the outer sheath of the hysteroscope assembly, which generally ranges from 4.0 to 5.5 mm. A number of small-caliber fiberoptic devices exist that are approximately the diameter of some biopsy catheters (3-4 mm). With such instrumentation, dilation of the cervix may not be necessary. One inherent advantage of hysteroscopy is that endoscopically guided removal of lesions may be performed immediately after diagnosis, during the same procedure. Provided that the lesions are relatively small, such excisions may even be performed in an office setting. Despite the seemingly obvious advantages of the technique, the data supporting the use of hysteroscopy for management of women with postmeno-

pausal bleeding are relatively sparse and generally of relatively poor quality.

As described previously, hysteroscopy is superior to endometrial biopsy^{60,61,67} (Class 3), D&C⁶⁰ (Class 3), and ultrasonography^{84,85} (Class 3) for the identification of structural lesions of the endometrium such as endometrial polyps. Hysteroscopy has good diagnostic accuracy for structural lesions, such as polyps and leiomyomas, whether or not performed in an office setting, and good patient acceptability in either setting^{24,86} (Class 1b). Indeed, in a study designed to determine the desires of women regarding a primary assessment tool for evaluation of postmenopausal bleeding, 95% preferred to undergo office hysterectomy rather than experience a 5% chance that a lesion could be missed⁸⁷ (Class 6). However, it should be noted that hysteroscopic visualization alone is relatively inaccurate in the diagnosis of atypical hyperplasia and carcinoma^{84,88,89} (Class 3). Consequently, hysteroscopy should not be performed in women with postmenopausal bleeding who have not undergone antecedent or concurrent endometrial sampling by suction or sharp curettage.

In the past, there were concerns that the pressurized distending media used with hysteroscopy could result in retrograde dissemination of malignant cells into the peritoneal cavity sufficient to alter the prognosis of endometrial carcinoma^{90,91} (Class 5). However, although some investigators have shown a low incidence of peritoneal washings testing positive for endometrial cells⁹² (Class 5), others have compared the incidence of positive peritoneal cytologic findings associated with hysteroscopy to that associated with D&C and have found the frequency to be similar—about 9% to 10%⁹³ (Class 1b),⁹⁴ (Class 4). Overall, there seems to be a slightly increased risk of positive peritoneal cytologic findings associated with the use of hysteroscopy (OR, 1.78; CI, 1.13-2.79)⁹⁵ (Class 1b). However, available high-quality evidence suggests that the prognosis associated with a hysteroscopic diagnosis of endometrial cancer is not different from that with other diagnostic methods⁹³ (Class 1b),^{92,96-98} (Class 3).

Sequencing of Investigations

The exact sequencing of investigations for women with postmenopausal bleeding will necessarily vary somewhat depending

on the local resources and expertise, the judgment of the clinician, and patient preference. There is evidence that resource utilization is reduced if the practitioner is able to perform the TVUS examination in the office without adding additional charges as opposed to having the procedure performed by a radiologist⁹⁹ (Class 3), and this would be presumably true for contrast sonography as well. The same can be said for hysteroscopy, for which in-office performance using local anesthesia is logically cheaper than any hospital or surgical center-based procedure.

Primary Assessment of Spontaneous Postmenopausal Bleeding

For women with spontaneous bleeding 12 or more months following the last menstrual period, the endometrium can be primarily assessed by either office-based endometrial biopsy (Figure 5) or TVUS (Figure 6). For those who undergo TVUS and have an EEC greater than 4 mm, localized thickening, or an indistinct or nonvisible EEC, endometrial sampling is a reasonable next step.

These approaches were compared by Weber et al¹⁰⁰ (Class 3) from the Cleveland Clinic in a cost-modeling exercise, with primary TVUS predicted as being slightly less expensive. However, in that study, the assumptions were based on a charge mod-

el and included performance of the TVUS in a Radiology Department. In another study, Medverd and Dubinsky¹⁰¹ (Class 3) demonstrated that TVUS as a primary assessment modality utilized approximately 11% fewer resources than did an endometrial biopsy-originated evaluation paradigm. It is unclear whether charges or costs were considered in their analysis, but it is presumed that the imaging was performed in a Radiology Department and was interpreted by a radiologist. A cost modeling analysis from the UK, which assumed that a gynecologist performed all procedures, suggested that endometrial biopsy- and TVUS-initiated investigational paradigms were similar regarding their cost-effectiveness when 5 mm was used as the EEC threshold¹⁰² (Class 3). How this analysis translates to US fee-for-service or prepaid models is unclear, and the impact of changing the EEC threshold to 4 mm was not evaluated.

Primary Assessment of Hormone Replacement Therapy-Related Postmenopausal Bleeding (Breakthrough Bleeding)

The increased risk of endometrial cancer for women with postmenopausal bleeding who are receiving unopposed estrogen requires assessment in all cir-

cumstances. For women with postmenopausal bleeding while receiving combined estrogen-progestin HRT regimens, the approach is less clear, as it is apparent that such women are at significantly reduced risk of endometrial carcinoma compared with women not receiving HRT¹⁰³ (Class 5). Furthermore, women using estrogen and cyclic progestin therapy and who have cyclic bleeding near to or following the end of the progestogenic component of the regimen require no investigation. In addition, those women who use estrogen and continuous progestin regimens will frequently experience breakthrough bleeding in the first 6 months of therapy and generally require no investigation. However, women receiving cyclic progestin regimens who have unscheduled bleeding, or for those receiving continuous progestin therapy who have breakthrough bleeding beyond 6 months and especially following a period of amenorrhea, the endometrium should be assessed. Available evidence suggests that either endometrial biopsy or TVUS can be used in a fashion similar to that recommended for spontaneous bleeding using a similar EEC threshold for endometrial sampling⁶⁵ (Class 2),⁶⁸ (Class 5). Although it is possible that a higher EEC threshold might apply to women receiving sequential HRT, the committee could

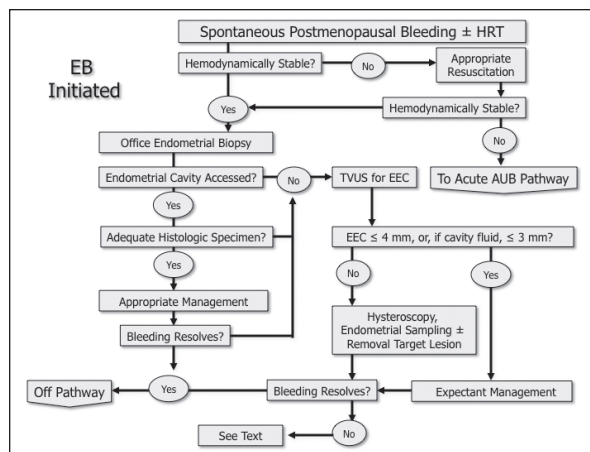


Figure 5. Investigation of postmenopausal uterine bleeding with initial investigation of endometrial echo complex (EEC).

Entire EEC should be seen, allowing demonstration of a consistent 2-layer thickness in both the sagittal and transverse planes that is less than or equal to 4 mm. If there is clear (sonolucent) fluid, the bilaminar endometrial thickness should be less than or equal to 3 mm.

AUB = abnormal uterine bleeding; HRT = hormone replacement therapy; TVUS = transvaginal ultrasonography; ± = with or without.

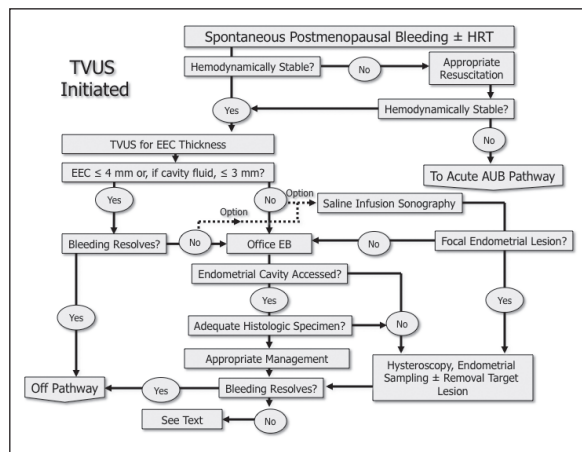


Figure 6. Endometrial biopsy (EB) as initial investigation of postmenopausal uterine bleeding.

A satisfactory EB comprises perceptible passage of the sampling device through the cervical canal into the endometrial cavity and appropriate functioning of the aspiration mechanism. Adequacy of the specimen for histologic interpretation is determined by the pathologist.

AUB = abnormal uterine bleeding; EEC = endometrial echo complex; HRT = hormone replacement therapy; TVUS = transvaginal ultrasonography; ± = with or without.

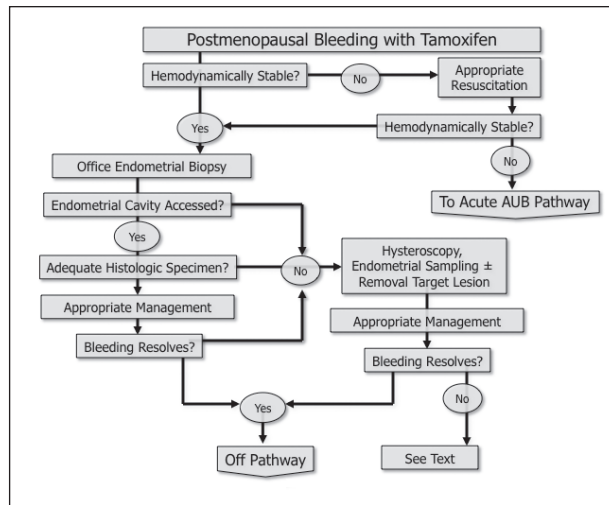


Figure 7. Investigation of postmenopausal uterine bleeding in women receiving tamoxifen.

Transvaginal ultrasonography is not sufficient for the evaluation of women experiencing bleeding while receiving tamoxifen. Endometrial sampling is necessary. AUB = abnormal uterine bleeding; ± = with or without.

not find convincing evidence to support such a notion. Consequently, clinicians are encouraged to perform TVUS for EEC measurement in the early phase of the “cycle” shortly after the completion of the progestin component.

Unless appropriately trained in either endometrial sampling techniques or TVUS, the primary care provider should refer any patient whose postmenopausal bleeding fits within the criteria requiring endometrial assessment. The gynecologist should determine which patients, if any, require TVUS assessment, including those who should be referred to a radiologist or other individual with specialist training in ultrasound of the uterus.

Investigation of Postmenopausal Bleeding in Women Receiving Hormone Replacement Therapy

Evaluation of women with postmenopausal bleeding while using HRT is affected by a number of factors, including the type of regimen, the dose of estrogen, and, if used, the scheduling of progestin administration (cyclic or continuous). These and other factors have an effect on the nature and timing of anticipated and unscheduled bleeding and may have a role in the timing and interpretation of ultrasound findings.

Causes of Abnormal Uterine Bleeding

Causes of abnormal bleeding in women using HRT include the following:

- Poor compliance
- Poor gastrointestinal absorption (for oral preparations)
- Drug interactions
- Coagulation defects
- Liver disease
- Gynecologic disorders, including but not limited to endometrial cancer, endometrial polyps, and cervical or vaginal lesions
- Nonreproductive tract origins (eg, urinary tract, gastrointestinal tract).

Important Points in the Patient History

The clinician should determine if the bleeding pattern is within acceptable limits (see earlier section, Hormone Replacement Therapy). In addition, the provider should ascertain if there are any other factors or symptoms that may place the patient at increased risk of endometrial cancer. Pertinent questions to ask include the following:

- *When does the bleeding occur with respect to progestin administration?* Women receiving cyclical progestin therapy should have bleeding near the end of or shortly after discontinuation of the progestin component of the regimen.

- *How long does the bleeding last? How heavy is it?* Heavy bleeding, even when experienced in the context of a cyclically administered progestin, may suggest the presence of intrauterine pathology.
- *Was there a period of amenorrhea after HRT was started?* For continuous combined regimens, breakthrough bleeding is common, especially in the first six months, but should a period of amenorrhea be established initially, bleeding, even within the first six months, suggests intrauterine abnormalities.
- *Is there evidence of poor compliance?* The patient should understand the appropriate method for following her treatment regimen. Some women take their medications sporadically or use their progestin in an unconventional fashion.
- *Is there a reason to suspect poor gastrointestinal absorption?* A history of nausea, vomiting, or diarrhea is a potential explanation for incomplete absorption and resultant bleeding.
- *Is there any evidence of hepatocellular disease?* The liver is responsible for metabolizing estrogen. Should there be active or chronic hepatocellular disease, the circulating levels of estrogen may be higher than normal and abnormal bleeding may occur secondary to endometrial stimulation.
- *Is the patient receiving any other drugs?* The intentional or inadvertent use of other gonadal steroids (estrogens with or without progestins) may explain unexpected bleeding.

Discontinuation of Hormone Replacement Therapy before Clinical Investigation

There is no convincing reason to discontinue HRT before clinical investigation. If the primary physician is able to complete the required investigative steps, this issue is moot. However, if the physician will be referring the patient for clinical assessment by a gynecologist, there may be a time period between the referral and the actual consultation appointment. In such instances, women may continue their regimen (Class 7).

Recurrent Spontaneous or Breakthrough Bleeding

Spontaneous or HRT-related, recurrent postmenopausal bleeding can oc-

cur. In a prospective study of women with postmenopausal bleeding who were not receiving HRT and whose EEC measured 4 mm or less, the incidence of recurrent bleeding was 10% at a mean of 49 weeks following the original TVUS¹⁰⁴ (Class 5). Of these 25 patients, 8% (n = 2) had endometrial carcinoma and 4% (n = 1) had a malignant melanoma. In another retrospective study of 1536 women with postmenopausal bleeding evaluated over a period of almost 5 years with both TVUS and endometrial biopsy, the prevalence of endometrial cancer was 3% with primary assessment.¹⁰⁵ On the other hand, the prevalence was 4% in the 126 patients with normal results of the initial evaluation who presented with persistent postmenopausal bleeding¹⁰⁵ (Class 5).

There is no current evidence supporting any specific recommendations for reinvestigation in the face of a normal TVUS or satisfactory and normal endometrial biopsy specimen. However, considering the false-negative rates associated with either approach, the indications for reassessment should be rather liberal considering one or a combination of repeat TVUS, repeat endometrial biopsy, and contrast sonography or hysteroscopy^{64,106} (Class 5),⁴⁹ (Class 6),¹⁰⁷ (Class 7). Determination of the specific order and combinations of these investigations will depend on the clinical judgment of, and resources available to, the clinician.

Tamoxifen-Related Bleeding

As previously described, patients receiving tamoxifen who are postmenopausal experience an increased risk of endometrial neoplasia that is greatest after four years of exposure. Whereas there is no evidence to support the use of routine biopsy of such patients, any who present with bleeding while receiving tamoxifen should undergo office-based endometrial sampling if possible (Figure 7). If not feasible, such patients should undergo hysteroscopy and curettage.

The tamoxifen-induced impact on the endometrium frequently, if not usually, creates a thickened EEC, often with diffuse subendometrial cystic change that is in no way indicative of endometrial hyperplasia or malignancy¹⁰⁸⁻¹¹³ (Classes 2-4). As a result, TVUS for evaluation of EEC thickness

is not useful in the evaluation of tamoxifen-related postmenopausal bleeding.

Many patients with tamoxifen-related bleeding have endometrial polyps^{114,115} (Class 1b). Consequently, if bleeding persists, evaluation of the endometrial cavity is indicated, generally with hysteroscopy, with hysteroscopically guided excision of any identified polyps and curettage for reassessment of the endometrium. Contrast sonography may also be useful in this regard; however, there is evidence that saline infusion sonography is inferior to hysteroscopy in detecting focal lesions in these patients¹¹⁶ (Class 3).

For patients who are receiving tamoxifen, who have persistent episodes of postmenopausal bleeding, who have no evidence of focal lesions, and for whom both the cervical canal and endometrial cavity have been adequately evaluated with imaging and adequate endometrial sampling showing benign tissue, annual repeated sampling is indicated (Class 7). ♦

^a *The group also developed guidelines that apply to women with both acute and chronic abnormal uterine bleeding in the reproductive years.*

^b *Adapted from the Scottish Intercollegiate Guidelines Network⁷³*

Disclosure Statement

The author has no conflicts of interest to disclose.

Acknowledgment

Kathleen Loudon, ELS, of Loudon Health Communications provided editorial assistance.

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More Burdened

A determining point in the history of gynecology is to be found in the fact that sex plays a more important part in the life of woman than in that of man, and that she is more burdened by her sex.

—Henry E Sigerist, 1891-1957, Swiss-born American medical historian