# EMAS clinical guide: Assessment of the endometrium in peri and postmenopausal women

Eva Dreisler [a], Lars Grønlund Poulsen [a], Sofie Leisby Antonsen [a], Iuliana Ceausu [b,c], Herman Depypere [d], C. Tamer Erel [e], Irene Lambrinoudaki [f], Faustino R. Pérez-López [g], Tommaso Simoncini [h], Florence Tremollieres [i], Margaret Rees [j], Lian G. Ulrich [a,*]

[a] Department of Gynaecology and Obstetrics, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark
[b] Department of Obstetrics and Gynecology, 'Carol Davila' University of Medicine and Pharmacy, Bucharest, Romania
[c] Department of Obstetrics and Gynecology, 'Dr. I. Cantacuzino' Hospital, Bucharest, Romania
[d] Breast Clinic and Menopause Clinic, University Hospital, De Pintelaan 185, 9000 Gent, Belgium
[e] Department of Obstetrics and Gynecology, Istanbul University, Cerrahpasa School of Medicine, Valikonagi Cad. No: 93/4, Nisantasi, 34365 Istanbul, Turkey
[f] 2nd Department of Obstetrics and Gynecology, University of Athens, Aretaieio Hospital, GR-11528 Athens, Greece
[g] Department of Obstetrics and Gynecology, Zaragoza University Facultad de Medicina, Hospital Clínico, Zaragoza 50009, Spain
[h] Tommaso Simoncini, Department of Clinical and Experimental Medicine, University of Pisa, Via Roma, 67, 56100, Pisa, Italy
[i] Menopause and Metabolic Bone Disease Unit, Hôpital Paule de Viguier, F-31059 Toulouse cedex 09, France
[j] Women's Centre, John Radcliffe Hospital, Oxford OX3 9DU, UK

## ARTICLE INFO

## ABSTRACT

*Introduction:* Invasive as well as non-invasive methods are available for assessment of the endometrium.
*Aims:* The purpose of this clinical guide is to provide evidence-based advice on endometrial assessment in peri and postmenopausal women.
*Material and methods:* Literature review and consensus of expert opinion.
*Results and conclusions:* Presuming speculum examination and cervical cytology are assessed, transvaginal ultrasound should be undertaken initially as it is non-invasive and will not only measure endometrial thickness, but will also detect other pelvic pathology such as leiomyomas and ovarian tumours.

The main indication for invasive methods is to obtain endometrial tissue to diagnose or exclude the presence of endometrial cancer or pre-malignancies. Biopsy is mainly undertaken as an outpatient procedure, but sampling is 'blind'. Hysteroscopy is used when focal lesions affecting the uterine cavity are suspected such as endometrial polyps or sub-mucous fibroids.

None of the available methods are perfect. Ultrasound evaluation is dependent on the experience of the examiner, the equipment and the quality of visualization. Hysteroscopy too is dependent on the examiner and fibroids may obstruct visualization. Blind endometrial biopsy procedures often miss focal lesions. Thus re-examination is necessary when symptoms persist and no explanation for these has been identified.

This clinical guide will evaluate the different methods of endometrial assessment, their indications and limitations. Guidance is also given about dealing with inconclusive investigations and persistent symptoms.

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## 1. Introduction

Methods to investigate the endometrium include non-invasive and invasive procedures. Speculum examination and palpation should always be done first to exclude non-endometrial gynaecological pathology. The main purpose of invasive methods is to obtain endometrial tissue for histological or cytological examination. The classic dilatation and curettage (D&C) has been used since the mid 19th century [1]. More modern methods, with different vacuum equipment to blindly obtain endometrial tissue and hysteroscopy visualizing the uterine cavity to obtain guided endometrial biopsies, have to some extent replaced D&C. Non-invasive procedures relate to imaging and include ultrasonic evaluation with or without saline, computerized tomography (CT) and Magnetic Resonance Imaging (MRI) with or without injection

of contrast or glucose Positron Emission Tomography (PET). The advantage of these methods in addition to being non-invasive is the possibility to assess also structures outside of the endometrial cavity and visualize focal lesions, which are often missed by blind biopsy. Accurate diagnosis in most cases requires histology; hence the methods are often combined.

Endometrial assessment is primarily indicated to diagnose or exclude endometrial cancer and its precursors: endometrial hyperplasia with or without atypia and the intra-epithelial neoplasia. Diagnosing malignant and premalignant changes in the endometrium requires histology. However endometrial assessment is also required in various benign conditions such as investigation of abnormal uterine bleeding (AUB) and monitoring treatment of hyperplasia without atypia.

The initial patient contact resulting in need of endometrial assessment is often prompted by abnormal uterine bleeding (AUB) (such as intermenstrual or postcoital bleeding or breakthrough bleeding in users of hormone therapy (HT)), postmenopausal bleeding (PMB), or pain. Incidental findings during other routine examinations, including risk factors for endometrial cancer may also indicate the need for endometrial assessment. Risk factors for endometrial cancer include unopposed oestrogen use, tamoxifen treatment, obesity, polycystic ovary syndrome (PCOS) and genetic factors e.g. families with hereditary non-polypoid cancer of the colon (HNPCC) [2].

When investigating the endometrium, factors such as patient history, age and menopausal age should be taken into account. Endometrial cancer is rare before the menopause, but when it occurs it is often found in the above mentioned risk groups. Of 4718 women with endometrial cancer in Denmark from 2005 to 2011 only 0.9% were less than 40 years and 4.4% were 40 to 49 years [3].

This clinical guide will evaluate the different methods of endometrial assessment, their indications and limitations. Guidance is also given about dealing with inconclusive investigations when symptoms persist.

## 2. Ultrasound examination of the endometrium

In the peri and post menopause AUB and PMB are indications for sonographic assessment of the endometrium. The endometrium is best visualized by trans-vaginal sonography, with the probe close to the endometrium. Alternatively trans-rectal or trans-abdominal examination is performed. The International Endometrial Tumour Group has proposed terms and definitions to describe sonographic features of the endometrium and intrauterine lesions [4]. Excellent inter- and intra-observer reproducibility has been demonstrated in measurement of endometrial thickness (ET) [5]. Measurement of ET is documented to be a cost-effective first-line investigation in populations with prevalence of endometrial cancer $\leq 15\%$ [6]. In high-risk populations initial investigation with endometrial biopsy is more cost-effective; although patient discomfort is higher [7].

ET, homogeneity, and endo-myometrial borders are evaluated. When adding colour or power Doppler to the examination, focal growing lesions e.g. endometrial polyps or sub-mucous myomas may be suspected, but for final diagnosis histology is necessary [8,9]. For the detection of focal lesions measurement of ET alone is insufficient [10].

In PMB the measurement of ET can subdivide patients into cancer high and low risk groups. When the endometrium is less than 4 mm, endometrial cancer is rare. In a review including 5 studies of 2752 patients with ET $\leq 4$ mm only 3 cases of EC were detected, resulting in a risk of 1/917 for EC [11]. A meta-analysis of 2896 patients including 259 cases of EC, suggests a lower cut-off value

of $\leq 3$ mm, improving sensitivity to 97.9% (95% CI 90.1–99.6%), but decreasing specificity to 35.4% (95% CI 29.3–41.9%), leading to more invasive procedures [12]. At 4 mm sensitivity is 95% and specificity 47%. At 5 mm the figures are 90% and 54%, respectively. Increasing sensitivity is always a trade-of the specificity. The acceptable level of false positive tests varies between different national guidelines [7,13]. In Scotland the SIGN guideline suggesting a 3 mm cut-off for non-HT users was published in 2003 [14].

When the endometrium is not measurable or irregular, second stage diagnostic procedures are necessary as the odds ratio (OR) for endometrial cancer in women with immeasurable endometrium is 5.23 comparable to with the risk in women with postmenopausal bleeding and endometrial thickness 5–9 mm [15]. Endometrial cancer is unlikely in cases with a thin and regular endometrium, however it is important that the measurement is made before endometrial sampling [16].

In early studies of ultrasound investigation in endometrial cancer patients, diagnostic performance was excellent in expert hands when evaluating myometrial involvement [17]. Unfortunately these results were not reproducible, when less experienced examiners were involved [18,19]. Among reasons for misclassifications are; adenomyosis, focal growing cancer, and small clusters of cells invading the myometrium, resembling normal tissue. Ultrasound has been demonstrated to have high diagnostic performance (positive predictive value (PPV) 72-86% and negative predictive value (NPV) 98%) for evaluation of cervical involvement [17,20].

Saline contrast sonohysterography with the installation of saline in the uterine cavity is suggested in women with PMB and endometrium $\geq 5$ mm (or not measurable/not clearly defined endometrium) for detection of focal lesions. Saline contrast sonohysterography is also relevant when investigating the cause of AUB, and useful for triage of patients for either blind biopsy or hysterocopic biopsies/resection. Fluid contrast sonohysterography is easily performed as an out-patient procedure since only equipment normally used for gynaecological examination, a baby-feeding tube connected with a syringe or an insemination catheter are needed. Even so, it is often not generally available in hospitals, where ultrasound evaluation is undertaken by radiologists or radiographers rather than by gynaecologists. Fluid installation sonography enhances the endometrial lining, and sensitivity and specificity for diagnosing focal lesions are in line with hysteroscopy. In a meta-analysis including 2278 procedures, a sensitivity of 95% (95%CI 93–97%) and specificity 88% (95%CI 85–91%) for identifying focal lesions was reported [21]. The feasibility of the procedure was significantly better in pre-menopausal (successful in 95% (95%CI 94–96%) compared to postmenopausal women (successful in 86.5% (95%CI 83.2–89.8%). Compared to hysteroscopy saline contrast sonohysterography is less expensive, less painful, and complications rarely occur [22]. The contrast media can either be saline or gel. Fewer technical failures are reported with gel compared to saline contrast sonohysterography (1.8% vs. 5%) [23]. Endometrial sampling during saline contrast sonohysterography is a method to improve the sampling compared to the blind procedures [24]. In women with cervical stenosis ultrasound guided fine-needle aspiration is also possibility when histology is mandatory [25].

Implementation of 3D ultrasound has so far not increased the diagnostic performance of ultrasound in ruling out endometrial malignancy or in the specific diagnosis of focal lesions [26,27]. The combination of 3D and power Doppler analysis allows an estimation of the vascularized endometrial volume and has been demonstrated to be superior to ET alone in ruling out endometrial malignancy however, future studies to confirm the usefulness among non-expert examiners and in larger populations are warranted [28].

## 3. Endometrial sampling

For decades, dilatation and curettage (D&C) has been used for endometrial sampling. While it is a simple procedure, it typically requires hospital admission and general anaesthesia. Since the 1970s it has been largely superseded by outpatient biopsy not requiring general anaesthesia using disposable devices such as the Pipelle de Cornier®, Vabra® and Novak® curettes. Both D&C and outpatient biopsy are "blind procedures", do not sample the whole cavity and can miss focal lesions. Diagnostic performance of these procedures is detailed below.

### 3.1. Dilatation and curettage

Publications investigating the diagnostic performance of this method have been available since 1958. In more than half of examinations D&C samples less than 50% of the endometrial surface, and fails to detect approximately half (43–66%) of cases with hyperplasia and almost three in four (40–90%) polyps [29–31].

In postmenopausal women presenting with bleeding and a transvaginally measured endometrium of ≥5 mm, D&C misses 11% of endometrial cancers, 50% of hyperplasia without atypia and 60% of hyperplasia with atypia [32]. The procedure frequently leaves part or the entire lesion behind (87%) and misses polyps in 58% of the cases [32,33]. However, 94% of non-focal pathology is correctly diagnosed.

In a prospective study, polyps were diagnosed in 22 of 51 patients and removed in 8% of the procedures yielding a sensitivity of 43% [34]. D&C failed to detect intrauterine disorders subsequently diagnosed by hysterectomy in 62.5% of 397 women resulting in a sensitivity of 46%, specificity of 100%, (PPV) of 100% and (NPV) of 7.1% [33].

In 496 women who underwent D&C, 32% of focal lesions were diagnosed. D&C accuracy was 62% for endometrial hyperplasia and 83% when atypia was present [35].

Complications include perforation of uterus in 6–13 per 1000, infections in 3–5 per 1000 and lacerations of cervix [36,37].

In conclusion, although D&C allows for histological examination of endometrial tissue, the diagnostic performance does not permit this procedure to stand alone. Consequently, the procedure has largely been replaced either by office based endometrial biopsy without anaesthesia or hysteroscopy.

### 3.2. Outpatient endometrial biopsy

Several comparative studies of the diagnostic performance of disposable devices have been published, but the majority have D&C as the gold standard with known diagnostic failure especially of focal lesions (see above) [38]. The sensitivity for outpatient biopsy ranges from 68 to 92% for endometrial cancer and 73 to 94% for atypical hyperplasia in studies with hysterectomy diagnosis as gold standard [39–41]. Unsuccessful sampling due to technical reasons (e.g. cervical stenosis) is frequent, occurring in 17% (25/149) and inadequate sampling (not enough tissue) was documented in 7% (9/124) of cases in one study [42]. In cases of an inadequate sample and a non-reassuring endometrial thickness further diagnostic workup is necessary, otherwise in approximately 6% endometrial pathology will be overlooked [43,44].

## 4. Hysteroscopy

The use of an instrument to visualize the uterine cavity was first proposed in 1869 by Pantaleoni but more than 100 years elapsed before the optical systems became available to permit the first hysteroscope to be developed [45].

Hysteroscopy has the advantage of making visually guided biopsies possible and allows identification and removal of focal lesions in the uterine cavity. Disadvantages are hospital admission, general anaesthesia, higher cost of equipment and, though rare, more serious complications such as perforation. Technical improvements and advances in instrumentation have made office based hysteroscopy with local or no anaesthesia possible.

In general the diagnostic specificity of hysteroscopy in cancer and other endometrial pathology is high (92% to 95.8%) as is sensitivity (78.4% to 98%) but in 3–5% of women with postmenopausal bleeding, the procedure cannot be performed due to technical and anatomical problems [42,46,47]. Approximately the same diagnostic performance is described with office hysteroscopy 5Fr [48]. The diagnostic performance of hysteroscopy is related to the ability of diagnosing rather than excluding cancer. Hysteroscopy without endometrial biopsy is insufficient in differentiating between benign, pre-malignant and malignant disease in the uterine cavity [49].

The procedure is generally safe, although concern about the risk of spreading malignant cells is under discussion. Spread of endometrial cells during hysteroscopy does occur and is associated with high inflation pressure [50,51]. However based upon small randomized studies and the revised FIGO guidelines for endometrial cancer staging, this spread does not seem to influence pelvic recurrence rate or survival in endometrial cancer patients [52–54]. Other complications (in total 8%) include perforation (3%), false passage (2%), bleeding (1%), infection (1%) and more serious, though seldom, bowel injury (0.25%) [55].

### 4.1. Further investigations

Computed tomography (CT) is not reliable for the evaluation of ET [56]. Prediction of cervical and parametrical spread and depth of myometrial invasion in endometrial cancer is also limited with a sensitivity of 10%, 9%, and 17%, for none, inner and outer half respectively [57]. CT findings are not specific for endometrial carcinoma, which can be mimicked by other conditions, including endometrial extension of cervical cancer, endometrial polyps, leiomyomas, and intrauterine fluid collections, including blood and/or necrotic material (e.g. from recent biopsy or curettage).

For endometrial cancer, MRI is considered the most accurate imaging technique in preoperative assessment because of excellent soft-tissue contrast-resolution [58]. For predicting myometrial invasion, sensitivity, specificity, (PPV) and (NPV) were 87%, 57%, 44%, and 92% respectively in a prospective multicenter study of 318 endometrial cancer patients [19]. An English national survey of UK practice showed overall concordance of MRI and histopathology findings of 82% for depth of myometrial invasion, 90% for cervical extension, and 94% for pelvic nodal involvement when individual patient data were analyzed [59]. However, only 35% of individual departments met the national target of 85% for assessing depth of myometrial invasion. Diagnostic performance of MRI seems to be dependent on patient volume as a factor of investigational performance.

MRI is not diagnostic in evaluating the endometrium. Adenomyosis can be diagnosed using MRI with a diagnostic accuracy of 85% [60], but may not be differentiated from endometrial polyps, secretory endometrium, stage 1A endometrial cancer, and endometrial hyperplasia [61].

MRI is contraindicated in patients who have metallic biomedical devices or metallic objects in strategic anatomical regions. It is more costly and less readily available than CT and requires long image acquisition times.

When PET/CT is used in pre-menopausal women, normal endometrial ^{18}F-fluorodeoxyglucose (FDG) uptake changes cyclically, and increases during the ovulatory and menstrual phases.

The uptake is not dependent on postmenopausal hormone therapy or hormonal contraceptives, but increases with oligomenorrhea and benign endometrial abnormalities [62]. FDG-PET/CT has gained widespread use in the workup of cancer patients. For predicting myometrial invasion of endometrial cancer, sensitivity, specificity, PPV, NPV, and accuracy for PET/CT were 93%, 49%, 41%, 95% and 61%, respectively in a multicentre study [19]. PET/CT was found to be the best imaging modality overall compared to MRI and 2D ultrasonography in the preoperative evaluation of EC, however the overall performance of MRI in this particular study was inferior to findings in other large scale studies [59].

Several factors such as variable physiologic uptake of FDG by normal tissues, FDG uptake related to inflammation or infection, occasional malignant lesions with low avidity for FDG, unusual tumour sites, limited resolution of small lesions, altered bio-distribution of FDG related to hyperglycaemia or hyper-insulinaemia and bone marrow activation are commonly encountered in cancer patients and in addition motion artefacts make the interpretation of PET studies challenging [61].

The fusion of PET with MRI in the PET/MRI scan can compensate for their individual disadvantages and therefore offers several advantages in comparison to PET or MRI alone. The combination of these two diagnostic imaging modalities into a single scanner improves the diagnostic accuracy by facilitating the accurate registration of molecular aspects and metabolic alterations of the diseases with exact correlation to anatomical findings and morphological information. Whole-body PET/MRI is a promising diagnostic modality for oncological imaging due to the high soft tissue resolution of MRI and considerably lower radiation exposure compared to PET/CT [63].

In summary whole body imaging is primarily recommended in staging of endometrial cancer when evaluation of myometrial invasion and dissemination is crucial to subsequent treatment planning.

### 4.2. Endometrial assessment in women with AUB or PMB

The most important aspect of endometrial assessment is to diagnose or exclude endometrial cancer or pre-malignancy, but benign causes of AUB such as infection, fibroids and polyps also need identification and treatment.

However international guidelines do not agree on the sequence of investigations in PMB [64]. The recent ACOG recommendation state that endometrial tissue sampling is a first-line option in women > 45 years [65]. However AUB is very frequent in women in their forties, and endometrial cancer is rare. Thus investigation of 260 women under the age of 50 years identified no case of endometrial cancer or complex hyperplasia even in women with endometrial thickness greater than 4 mm and but three cases of simple hyperplasia without atypia, which is a frequent finding in peri-menopausal women [66,67].

Due to anovulation irregular bleeding is the rule rather than the exception in women in their forties, and the risk of cancer is small even if hyperplasia without atypia is a common finding seen in up to 10% of women up to five years after menopause [67]. We would recommend that in pre-menopausal women, ultrasound evaluation is first-line investigation. In women without risk factors, if the endometrium is clearly visible and no polyps or fibroids are seen and if cervical pathology is ruled out, medical management may be an option without endometrial biopsy prior to treatment. If AUB cannot be regulated by medical treatment, histological assessment is warranted.

PMB is the most important indication for endometrial assessment. Although a common finding will be atrophy, the risk of endometrial cancer as the cause of bleeding increases with age up to one in four by age 80 [68]. Ultrasound evaluation is the first-line investigation and if the whole endometrium is clearly visualized with a sharp demarcation and the thickness is no more than 4 mm, endometrial biopsy may be omitted even in a post-menopausal woman. However speculum examination and cervical cytology should be assessed to ensure that other sources of bleeding are detected. In all other cases histological evaluation is mandatory in women with PMB, including cases where the endometrium is not fully visualized. A suggested flow of investigations in women with PMB can be seen in Fig. 1.

### 4.3. Endometrial assessment in asymptomatic women

The need for endometrial assessment is not limited to women with bleeding since endometrial cancer can occur without bleeding [69]. Based on a theoretical cohort it has been suggested that incident findings of increased endometrial diameter in a woman without bleeding and without other risk factors might not require endometrial histological assessment if the thickness is less than 11 mm [70]. However a recent review of published studies reports a mean endometrial thickness of 2.9 mm in 2952 postmenopausal women and finds no valid cut-off on which to base a recommendation for endometrial histological examination in asymptomatic women [71]. Thus with a prevalence of endometrial cancer and pre-malignancy both in the order of 0.6%, the results from this systematic review could not justify the use of endometrial thickness as screening for endometrial cancer or hyperplasia in asymptomatic postmenopausal women.

The prevalence of endometrial cancer in asymptomatic women is extremely low. Screening of 801 postmenopausal American women revealed one cancer (0.13%) and four cases of atypical hyperplasia (0.63%) and in 661 biopsies obtained from treatment naïve British postmenopausal women, no cancers and one case of atypical hyperplasia (0.15%) were identified [72,73]. These figures do not justify invasive endometrial procedures unless other risk factors indicate the need for such investigation. In accordance with this, ultrasound screening in asymptomatic postmenopausal women is also not recommended in ACOG guidelines [7].
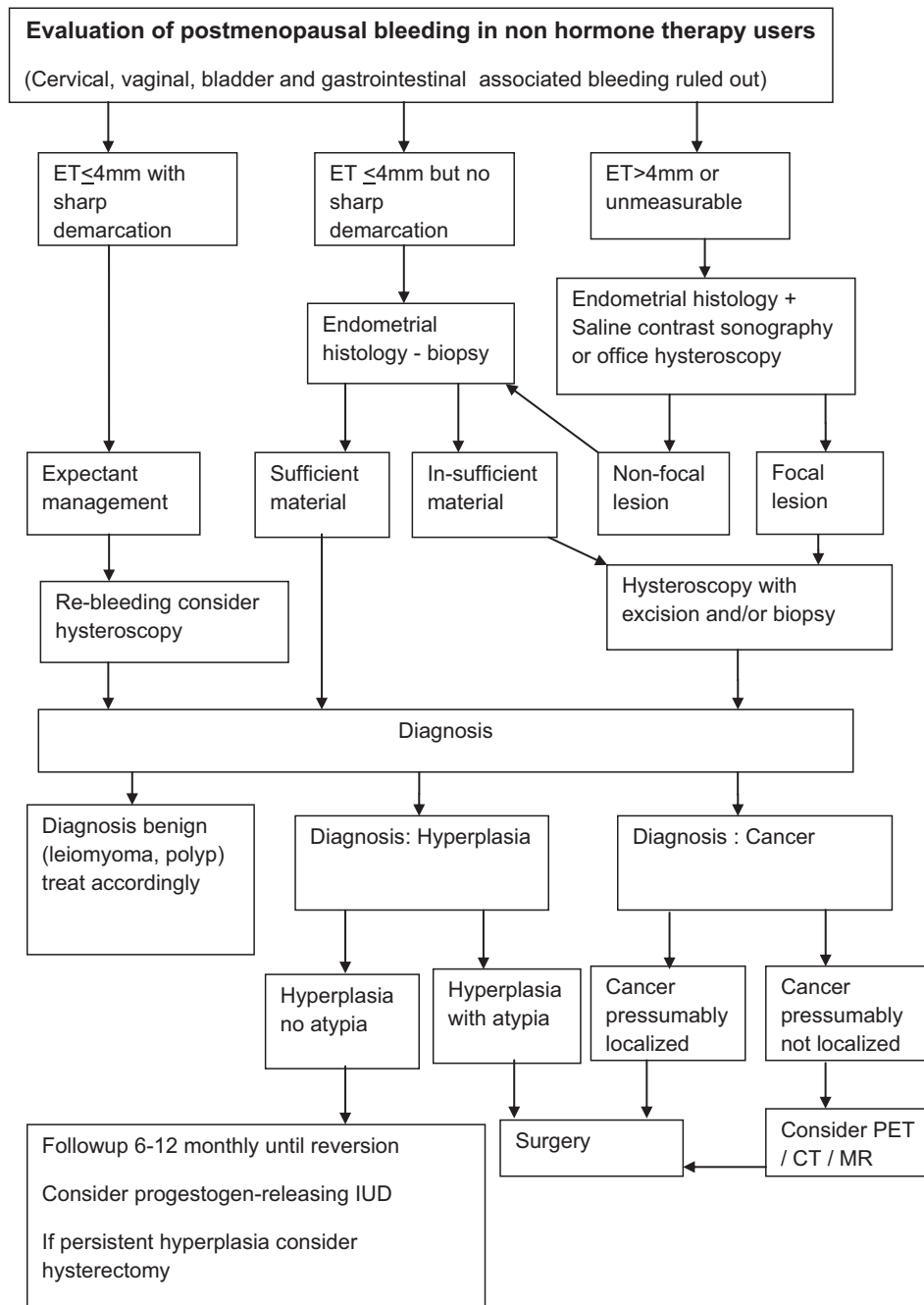
Women with risk factors, such as those from HNPCC families, with PCOS or grossly overweight, should be investigated more rigorously. Whereas screening for endometrial cancer is generally not indicated, The American Cancer Society recommend that women who have (or may have) HNPCC are offered yearly testing for endometrial cancer with endometrial biopsy beginning at age 35 [74]. In Denmark women with genetic disposition in HNPCC families are offered gynaecological examination every second year from age 25 with endometrial biopsies if ultrasonic evaluation or symptoms raise suspicion of endometrial pathology.

However even though endometrial cancer risk is increased in women in HNPCC families, in the Danish cancer database from 2005 to 11 incl. there was only one case of uterine cancer in a woman less than 20 years, four below 30 and 35 below 40 in a total of 4718 cases [3] The one who was less than 20 years had a family history of bowel cancer, but was not diagnosed as a HNPCC family member, and the four cancer patients who were less than 30 years were not known with hereditary disposition. Furthermore based on 189 women from the Danish HNPCC registry, the median age for endometrial cancer is 50 with a range 32 to 79 years compared to 65 years in the general population [75]. Thus routine endometrial biopsy may not be indicated even in young women with genetic disposition less than 30 years..

### 4.4. Endometrial assessment in HT users

The risk of endometrial hyperplasia and cancer is related to oestrogen dose as well as duration and dose of progestogen addition [76–81]. Thus the risk of cancer with unopposed oestrogen treatment is increased by a factor of 2–3 for ever use and the odds

**Evaluation of postmenopausal bleeding in non hormone therapy users**

(Cervical, vaginal, bladder and gastrointestinal associated bleeding ruled out)

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ET≤4mm with          ET ≤4mm but no      ET>4mm or
sharp                sharp               unmeasurable
demarcation          demarcation
                                         Endometrial histology +
                                         Saline contrast sonography
                     Endometrial         or office hysteroscopy
                     histology - biopsy

Expectant   Sufficient   In-sufficient   Non-focal   Focal
management  material     material        lesion      lesion

Re-bleeding consider              Hysteroscopy with
hysteroscopy                      excision and/or biopsy

                     Diagnosis

Diagnosis benign      Diagnosis: Hyperplasia    Diagnosis : Cancer
(leiomyoma, polyp)
treat accordingly

            Hyperplasia   Hyperplasia    Cancer        Cancer
            no atypia      with atypia    pressumably   pressumably
                                          localized     not localized

Followup 6-12 monthly until reversion        Surgery      Consider PET
                                                          / CT / MR
Consider progestogen-releasing IUD

If persistent hyperplasia consider
hysterectomy
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**Fig. 1.** Suggested flowchart of investigations in untreated women with postmenopausal bleeding. Ultrasonic evaluation (US). Endometrial thickness (ET).

ratio for oestrogen intake for more than 5 years is in the order of 7–8. Sequential oestrogen and progestogen increases the risk of cancer if progestogen is added for less than 10 days per month but, even with 10 days or more the risk may be increased with long term use. Continuous combined oestrogen and progestogen does not increase risk of endometrial cancer and may in fact reduce or even revert endometrial hyperplasia [73,82]. Use of tibolone may increase endometrial cancer risk [79]. Local vaginal oestrogen is not known to increase the risk of endometrial cancer, and women using this therapy should be handled as untreated postmenopausal women [83,84].

Unscheduled uterine bleeding is common in the first months following HT initiation. The frequency depends on the oestrogen dose and the type of HT. In women using continuous combined

HT, unscheduled bleeding occurs more frequently during their first postmenopausal years [85].

When deciding on endometrial investigation in HT users, consideration to risk of treatment should be included and the indication for endometrial histology thus is stronger in users of unopposed oestrogen compared to combination therapy. Unfortunately bleeding is not a predictor of endometrial pathology in users of unopposed oestrogen. In a group of 287 users of unopposed conjugated estrogens, 20% developed hyperplasia within one year of treatment, but, 7 of these 56 women did not have any bleeding in the 90 days preceding biopsy [86].

For this reason we recommend yearly endometrial histology in users of unopposed oestrogen regardless of bleeding, if endometrial thickness is more than 4 mm. Unopposed oestrogen therapy is

of course not recommended to non-hysterectomized women, but even so this population exists especially after the publication of the WHI studies because of women's and doctor's concerns of increased breast cancer risk related to progestogen use [77,78]. These women have an increased risk of endometrial cancer up to 10–15 years after treatment has stopped, and it is important to agree on how to manage these women,

No solid data exist on when to investigate women taking sequential therapy, but the absolute risk of endometrial cancer is low. In a UK survey of 1312 women who had been taking sequential therapy for an average of 3.29 years representing approximately 4300 patient-years, biopsies were obtained from 84% revealing 59 cases of complex hyperplasia and 6 with atypia, but no cases of carcinoma [73]. There was no relationship between histology and bleeding pattern. Irregular bleeding is common in users of sequential HT of whom approximately 40% experience more than three days of variation between onset of bleeding in different cycles [87]. Thus the best option is probably to investigate if bleeding pattern changes substantially, although data are fragile.

Another option is to take additional risk factors into consideration such as obesity [79]. Finally a shift to continuous combined therapy will revert complex hyperplasia without atypia in virtually all cases [73,82].

Bleeding and spotting with continuous combined oestrogen and progestogen normally declines after the first 3 months treatment; and thus bleeding on continuous combined HT that persists beyond or that appears after the first 6–12 months of therapy requires the same evaluation as PMB in on HT users [85].

Documentation for need of other endometrial thickness cut-off values for HT users has not been published. This is supported by the finding of no substantial difference in endometrial thickness in women taking sequential versus continuous combined HT (3.6 mm vs. 3.2 mm), if the ET measurement is taken approximately on the fifth day following the last progestogen pill [88]. With sequential therapy the ET is smallest after shedding of the endometrium and this is an ideal time for measurement to avoid false-positive findings. A meta-analysis of 35 studies comprising 5.892 women with PMB identified 96% of women with endometrial cancer and 92% of women with endometrial disease, with a false positive rate of 39% and 19% respectively. There was no significant difference in the sensitivity between HT users and non-HT users, but the number of women with false-positive results was 23% for HT users compared to 8% in women on no treatment [89]. Tibolone and continuous combined therapy as well as sequential therapy give rise to a small increase in ET but to a lesser extent. It is impossible to get sufficient measurements of ET, when an intrauterine levonorgestrel system is located in the uterus because of acoustic shadowing.

Considering the limitations of ultrasound in HT users, the strength of the indication for endometrial histological evaluation is dependent on the type of HT and the risk of hyperplasia and cancer associated with the specific therapy. Unopposed oestrogen treatment may require yearly biopsies whereas women on low dose combination therapies only require endometrial investigation when symptomatic and can be assessed with ultrasound as the primary tool of investigation.

## 5. Endometrial assessment in users of tamoxifen, raloxifene and aromatase inhibitors

In women treated with tamoxifen, the risk of endometrial malignancy is increased and polyps are often found [90]. Two out of three have an ultrasonic endometrial thickness of more than 8 mm even though half of these women will have endometrial atrophy [91]. The apparent increased ET in these women is due to sub-endometrial changes rather than true endometrial growth.

Ultrasound, D&C or blind endometrial biopsy is less valuable in these cases and hysteroscopy is recommended.

Recommendations for screening before, during and after tamoxifen treatment differ between different countries.

US investigators have suggested baseline hysteroscopic evaluation of the endometrium before tamoxifen treatment, since oestrogen dependent breast cancer and endometrial cancer share many risk factors such as obesity [92]. Hysteroscopy in this study was possible in 118 of 130 women, of whom 34 had benign polyps, one had a polyp with simple hyperplasia and one additional woman had simple hyperplasia. No other pathology was identified. The prevalence of benign polyps is high, and other investigators have found no increased risk of endometrial cancer in untreated women with endometrial polyps compared to women without polyps [93].

Although endometrial pathology in tamoxifen treated women most often present with unscheduled bleeding, amenorrhea does not totally rule out the presence of endometrial pathology. However in 250 women with endometrial thickness of 10 mm or more but without symptoms, 1250 ultrasound evaluations only revealed one case of endometrial cancer compared to 2 cases in 20 women with bleeding [94].

In a study of 406 postmenopausal tamoxifen users, five cases of endometrial cancer were identified of which three were found in asymptomatic women followed for at least three years [95]. All five had taken tamoxifen for more than three years, and four had been treated for more than five years. A cut off value for endometrial thickness of 8 mm is suggested with no screening earlier than three years after starting treatment. However one cancer was found in a woman with endometrial thickness of 3.5 mm and no bleeding. In addition this was the only cancer which was not early stage. Even so lowering the cut off level to 5 mm would result in 50% of women on tamoxifen having to undergo hysteroscopy. In women with endometrial bleeding the risk of endometrial abnormalities was doubled compared to those without bleeding.

Screening of postmenopausal women treated with tamoxifen requires hysteroscopy, and with a cancer incidence between 0.1 and 1% screening with invasive methods is probably not justified in women without additional risk factors. Postmenopausal women with bleeding should be investigated immediately with hysteroscopy with biopsies and removal of polyps. In premenopausal women the evidence for recommendations for endometrial investigation is scant. Overall the risk of cancer in premenopausal women is extremely low and does not justify invasive methods of screening [3].

Users of raloxifene, a selective oestrogen receptor modulator seem to have a decreased risk of endometrial cancer with OR 0.50 (0.29–0.85) compared to non-treated whereas tamoxifen users had an OR of 3.0 (1.3–6.9) in a case control study of 547 cases and 1410 controls [96]. In agreement with this, eight years follow-up data in raloxifene users indicated no increased risk of any endometrial pathology [97] Women treated with raloxifene should be managed as untreated women. The available evidence suggests that the same pertains for bazedoxifene users [98].

Treatment with aromatase inhibitors has largely replaced long term adjuvant tamoxifen treatment (more than 2–3 years) for breast cancer in postmenopausal women. In general aromatase inhibitors have been compared to tamoxifen, and endometrial pathology has been reduced also in women pre-treated with tamoxifen. Endometrial thickening induced by long-term tamoxifen treatment in postmenopausal breast cancer patients is reversed and maintained throughout long-term treatment with aromatase inhibitors, and no increased risk of endometrial cancer has been identified. The reduction in endometrial pathology with aromatase inhibitors as compared to tamoxifen has not been significant in all studies, but the trend has been the same, implying

that women using aromatase inhibitors may be managed like other postmenopausal women [99–102].

## 5.1. Endometrial investigation after previous endometrial ablation or resection

Women who have previously undergone endometrial resection or ablation present with special challenges.

Hysteroscopy as well as ultrasonography is less reliable in identifying cases of hyperplasia in these women, as residual endometrium or endometrial regeneration may occur below fibrotic scarring or develop from adnomyosis foci. Adhesions have been shown to be more prominent in women after resection compared to roller ball ablation [103]. Fibrotic intrauterine adhesions develop in over half of women who have undergone microwave endometrial ablation [104]. In addition residual endometrium is often found especially in the uterine cornuae and adhesions following the previous ablation may prevent usual outpatient procedures to reach pathological foci [105,106].

Occult cancer although rare may occur and bleeding patterns are not predictive of endometrial pathology following previous resection/ablation [103].

Risk-factors for endometrial cancer are to some extend the same as for abnormal uterine bleeding as indication for endometrial ablation. Although recommendable, endometrial histology is not always checked prior to ablation.

Unopposed oestrogen treatment results in an increased number of cases with endometrial proliferation and hyperplasia compared to continuous combined therapy in women after endometrial resection, and consequently combined HT is recommended postoperatively if these women require treatment [105]. Whereas ultrasonic evaluation did reveal differences in endometrial thickness between these two treatment groups and no cases of endometrial hyperplasia were identified in women with endometrial thickness less than four mm, cases with residual endometrium have been missed by ultrasound as well as by hysteroscopy.

In this context postmenopausal bleeding in women who have undergone endometrial ablation still requires the same investigation as in non-treated women, but the usual procedures may be less reliable. Furthermore as endometrial pathology may develop deeper down in the myometrium, pelvic pain may also be the presenting symptom even without bleeding. Consequently normal outpatient procedures will often be insufficient. Thus hysteroscopy and possibly MRI may be first choice investigational methods, and hysterectomy indicated if symptoms persist even without a histopathological diagnosis of malignancy [106].

## 5.2. Inconclusive investigations and persisting symptoms/recurrent bleeding

Common scenarios include incomplete visualization of the endometrium, endometrial biopsy sample insufficient for diagnosis in the presence of an endometrial thickness of 5 mm or more and negative investigations with continuing AUB or PMB.

Because of concerns of sampling error and missed focal lesions reinvestigation is required as the onus to ensure that endometrial cancer or endometrial hyperplasia with cytological atypia is not missed.

Considering the sensitivity of the available methods for endometrial assessment re-evaluation of the endometrium is always necessary in postmenopausal women with recurrent bleeding even after an initial benign endometrial histology, as focal lesions may have been missed. If an obvious reason for bleeding is not found (e.g. atrophic vaginitis, cervical pathology, cystitis, rectal bleeding) or instituted treatment is not effective, hysteroscopy with endometrial biopsy should be considered.

The first question is when to reinvestigate. The urgency with which re-investigation should be done depends on the estimated risk level. Thus in an obese or oestrogen treated woman in her sixties or seventies with a thick endometrium and an insufficient endometrial sample blindly obtained, we suggest immediate hysteroscopy on the assumption that a focal lesion has been missed. In contrast an early postmenopausal woman may just have had a delayed menstruation and provided the endometrial lining is sharply demarcated, even if it is 6–8 mm, re-investigation may be less urgent. Recurrent bleeding within the first year after an episode of postmenopausal bleeding is common (21–33%), irrespective of the primary diagnosis. Recurrence rate is not reduced by hysteroscopy or polyp removal, but re-bleeding with endometrial growth is associated with increased risk of endometrial pathology [107,108].

In any case it is suggested that women insufficiently diagnosed or with recurrent or persistent symptoms should be followed up e.g. after 6 months.

The second question is what investigation is recommended: a combination of transvaginal ultrasound (as there may be new pelvic pathology) and hysteroscopy to directly visualize the uterine cavity with biopsy appears to be advisable. It is also important to ensure that other causes of bleeding are excluded such atrophic vaginitis, cervical lesions, urinary tract or rectal bleeding.

Regardless of the chosen cut-off level, endometrial cancer can never totally be ruled out by ultrasound and repeat investigation/assessment is recommended in the above mentioned cases and in other women at increased risk of cancer.

## 5.3. Follow up after diagnosis of endometrial hyperplasia

Endometrial hyperplasia with atypia carries a high risk of endometrial carcinoma and should be treated as such [109].

The cumulative risk of progression of hyperplasia was investigated in a nested case-control study of 138 cases of endometrial carcinoma in a cohort of 7947 women [110]. Cumulative 20-year progression risk among women who remained at risk for at least one year was less than 5% for non-atypical endometrial hyperplasia and 28% for atypical hyperplasia.

Endometrial hyperplasia is the result of endogenous (anovulation, obesity) or exogenous oestrogen dominance on the endometrium. Thus endometrial hyperplasia is a common finding in perimenopausal women with anovulatory cycles [67].

Endometrial hyperplasia without atypia often reverts spontaneously, but the most effective treatment if the causal factor (e.g. the source of oestrogen stimulation) cannot be removed is fitting of a levonorgestrel-releasing intrauterine device [111,112]. Endometrial hyperplasia should be expected to revert after 3–6 months. If unopposed postmenopausal oestrogen HT or sequential oestrogen-progestogen is the cause of hyperplasia, this is reversed by continuous combined treatment in the same time-frame [73,82].

In any case endometrial hyperplasia should be followed up at 6–12 months intervals until reversion – and in cases of persistent hyperplasia in elderly women, hysterectomy may be considered.

## 6. Summary

In conclusion, none of the available methods for endometrial evaluation are perfect and in particular insufficient biopsy material or inadequate examinations cannot be used to reassure patients that no pre-malignant or malignant change in the endometrium is present. In addition none of the methods are independent of the investigators performance and experience. Patient history, age, and co-morbidity are important factors and should be taken into account when the need for re-examination is considered. Thus

the suggested flowcharts should always be adjusted to individual patient factors. Whereas endometrial hyperplasia without atypia in a perimenopausal woman may be a normal finding which will often regress spontaneously with a negligible risk of malignancy, the same finding in an older woman is likely to signify an increased risk of or a missed endometrial cancer or possibly an oestrogen producing tumour if the patient is not obese or taking oestrogen.

Re-bleeding in a postmenopausal woman is always indication of re-investigation most likely with hysteroscopy and guided biopsies unless an obvious cause is known or this examination has been done within the last few months.

Consequently, it is necessary to be aware that the assessment of the endometrium might be inadequate, and investigation should be pursued.

## 7. Summary recommendations

The main onus of endometrial assessment is to exclude carcinoma of the endometrium and premalignant endometrial hyperplasia

- Transvaginal ultrasound scanning (TVS) is used for initial assessment.
- Endometrial biopsy should be undertaken as an outpatient procedure if possible.
- Hysteroscopy allows direct visualization of the endometrial cavity and any focal lesions.
- Should results be inconclusive and AUB or PMB persist transvaginal ultrasound should be repeated and hysteroscopy performed.
- In tamoxifen users, the endometrial thickness (ET) is increased, and hysteroscopy is recommended in cases of postmenopausal bleeding.
- Unopposed oestrogen therapy increases the risk of endometrial cancer during and several years after treatment is stopped, and continued assessment is recommended.
- Assessment of the endometrium in the absence of bleeding should be limited to women at high risk of endometrial cancer.
- In women with no clear diagnosis or with recurrent or persistent symptoms or with previous hyperplasia should be followed up e.g. after 6 months.

## Contributors

LU, ED, LGP and SLA prepared the initial draft which was circulated to EMAS board members for comment and approval. Production was coordinated by MR and LU.

## Competing interests

Lian Ulrich has been speaking at national and international meetings for Novo-Nordisk, Schering Plough MSD, AstraZeneca A/S, Novartis and Sanofi Pasteur MSD, and has been giving advice to Shionogi and to Danish health authorities.

Lars Grønlund Poulsen works as consultant for Bristol-Myers Squibb, Pfizer and AstraZeneca, primarily as advisor on local legislations regarding medical information.

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