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Guideline No. 451: Asymptomatic Endometrial Thickening in Postmenopausal Women

The English document is the original version; translation may introduce small differences in the French version.

This clinical practice guideline was prepared by the authors and overseen by the SOGC Clinical Practice Gynaecology committee. It was reviewed by the SOGC Clinical Gynaecology Committee and The Society of Gynaecologic Oncologists of Canada (GOC) and approved by the SOGC Guideline Management and Oversight Committee.
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RECOMMENDED CHANGES IN PRACTICE

1. Postmenopausal women without bleeding or risk factors do not need investigations if they are found to have endometrial thickness <11 mm on ultrasound.
2. Further endometrial investigations should be decided on an individual basis, based on specific ultrasound findings and the patient's personal risk for endometrial cancer.

KEY MESSAGES

1. Routine pelvic ultrasound is not recommended to screen for endometrial cancer.
2. Most patients who have endometrial cancer present with postmenopausal bleeding.
3. Asymptomatic endometrial thickening is common, and an endometrium <11 mm is associated with an extremely low risk of malignancy.
4. Patients who have endometrial thickening and other risk factors may be considered for further endometrial assessments based on their individual risk factors and ultrasound findings.
5. Hormone therapies, if given in a continuous combined formulation, do not increase the risk of endometrial cancer.
6. Patients on tamoxifen should not have routine ultrasound assessment if they are asymptomatic.
7. Endometrial biopsy in a patient with global thickening on ultrasound has a high rate of accuracy, if an adequate sample and pathological result is obtained.
8. Invasive endometrial procedures have a low but not insignificant complication risk.

ABSTRACT

Objective: To formulate strategies for clinical assessments for endometrial thickening on ultrasound in a postmenopausal woman without bleeding.

Target population: Postmenopausal women of any age.

Outcomes: To reduce unnecessary invasive interventions and investigations in women with asymptomatic endometrial thickening while selectively investigating women at risk for endometrial cancer.

Benefits, harms, and costs: It is anticipated that the adoption of these recommendations would save postmenopausal women unnecessary anxiety, pain, and risk of procedural complications. It is also expected to decrease the cost to the health care system by eliminating unnecessary interventions.

Evidence: English language articles from Medline, Cochrane, and PubMed databases for relevant peer-reviewed articles dating from 1995 to 2022 (e.g., asymptomatic endometrial thickness, endometrial cancer, postmenopausal bleeding, transvaginal ultrasound, endometrial biopsy, cervical stenosis, hormone therapies and the endometrium, tamoxifen, tibolone, aromatase inhibitors). Results were restricted to systematic reviews and meta-analyses, randomized controlled trials/controlled clinical trials, and observational studies.

Validation Methods: The authors rated the quality of evidence and strength of recommendations using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. See Appendix A (Tables A1 for definitions and A2 for interpretations of strong and conditional [weak] recommendations).

Intended Audience: Physicians, including gynaecologists, obstetricians, family physicians, radiologists, pathologists, and internists; nurse practitioners and nurses; medical trainees, including medical students, residents, and fellows; and other providers of health care of the postmenopausal population.

Social Media Abstract: Postmenopausal women often have a thickening of the lining of the uterus found during ultrasound. Without bleeding, an endometrium <11 mm is rarely a serious problem but should be evaluated by a health care provider.

SUMMARY STATEMENTS

1. Asymptomatic endometrial thickening >5 mm is found in 3%–15% of postmenopausal women depending on the population studied (*moderate*).
2. Ninety percent of postmenopausal women with endometrial cancer present with bleeding (*high*).
3. In postmenopausal women without bleeding and an endometrium <11 mm, the incidence of endometrial cancer is approximately 1% (*high*).
4. Endometrial biopsy is an accurate procedure if an adequate tissue sample is obtained in a patient with global thickening (*high*).
5. Hormone replacement therapies, if used in a continuous combined formulation, do not increase the risk of uterine cancer (*high*).
6. Women prescribed tamoxifen do not require screening ultrasound examinations (*high*).
7. Cervical stenosis may complicate the ability to obtain an adequate endometrial pathological sample (*high*).

RECOMMENDATIONS:

1. Indications for endometrial tissue sampling in patients presenting with postmenopausal bleeding should not be extrapolated to asymptomatic women (*strong, high*).
2. A woman who has an endometrial thickness >11 mm and/or other positive findings on ultrasound, such as increased vascularity, inhomogeneity of the endometrium, or particulate fluid, should have endometrial sampling or be referred to a gynaecologist for further investigations (*strong, moderate*).

3. Further investigations should be made on an individual basis in asymptomatic women with increased endometrial thickening and risk factors for endometrial cancer, such as obesity, hypertension, late menopause, unopposed estrogen use, and genetic cancer risks (*conditional, moderate*).
4. Postmenopausal women without bleeding, no risk factors, and a global endometrial thickening of $<$11 mm do not require invasive investigations (*strong, moderate*).
5. Transvaginal ultrasound should not be used as a screening tool for endometrial cancer (*strong, moderate*).
6. In asymptomatic women with endometrial thickening $>$11 mm and insufficient endometrial sampling, further investigations should include hysterosonogram, diagnostic hysteroscopy, dilation and curettage, or watchful monitoring (*conditional, low*).
7. Women taking hormone therapy in a continuous combined formulation without bleeding do not require screening ultrasounds (*strong, high*).
8. Women who are amenorrheic on hormone therapies and develop new bleeding should be investigated (*strong, low*).
9. Asymptomatic women on tamoxifen should not receive routine/screening ultrasound (*strong, high*).
10. Women with cervical stenosis and no bleeding should be managed individually depending on the endometrial thickness, appearance of the endometrium on ultrasound, and the patient's individual risk factors (*strong, low*).

INTRODUCTION

SOGC guideline no. 249, Asymptomatic Endometrial Thickening, was published in the JOGC in October 2010[1] and updated in 2018.[2] This guideline has been one of the most requested SOGC guidelines because of widespread use of pelvic and abdominal ultrasound for investigation of common clinical scenarios, such as lower abdominal pain, bloating and evaluation of the adnexa, and the prevalence of asymptomatic thickening (>4−5 mm) in the general postmenopausal population[3,4] (3%−15% or higher, depending on the study).

The finding of asymptomatic endometrial thickening on ultrasound represents a clinical management dilemma and constitutes a frequent reason for referral to gynaecologists. The primary reason to conduct further investigations in women with asymptomatic endometrial thickening is to rule out endometrial malignancy. The 2018 guideline[2] concluded that the risk of malignancy in women who are not bleeding with an endometrium thickness <11 mm was extremely low and that further investigations should be individualized based on patient risk factors.[5,6]

This current guideline was developed to re-evaluate the literature on asymptomatic thickening since the publication of the 2010 guideline and its re-approval in 2018. As endometrial polyps account for a large proportion of thickening, a separate new document has been written for this clinical entity.[7]

Definition

Asymptomatic endometrial thickening is defined as an endometrial thickness >5 mm discovered in a postmenopausal woman who is not experiencing vaginal bleeding. The measurement combines the width of the anterior and posterior layers of the endometrium of the midline sagittal image on transvaginal ultrasound.

In a menstruating woman, this thickness reflects the endometrial changes associated with the phase of the menstrual cycle that occur due to hormonal fluctuations. The endometrium ranges from 3 mm after menses to 15 mm in the luteal phase. In the first year after the last menstrual period, the normal endometrium is often thicker than it will be several years after menopause, reflecting declining residual levels of estrogen.[8] In a postmenopausal woman several years after the last menstrual period, the endometrium is typically less than 4−5 mm thick.[9,10]

Ultrasound Characterization, Anatomy, and Pathology of Endometrial Thickening in Postmenopausal Women

Characteristics of the endometrium on ultrasound examination include global or diffuse thickening, heterogeneity, fluid collections, increased vascularity, and focal areas of thickening with or without feeding vessels.

Ultrasound measurement over 4−5 mm may also reflect structural abnormalities such as a uterine septum, submucous myomas, polyps, synechiae or scars, or adenomyosis. Ultrasound technology, by identifying vascular flow, allows differentiation of polyps from other abnormalities.[11] Findings of increased vascularity and fluid accumulation (especially particulate) in association with endometrial thickening may warrant further investigations.[11]

After menopause, the range of biopsy results for endometrial thickening include atrophic endometrium, proliferative endometrium, secretory endometrium, polyps, endometritis, cystic atrophy, cystic hyperplasia, complex hyperplasia, atypical hyperplasia, or carcinoma of the endometrium.[12]

RISK FACTORS FOR ENDOMETRIAL CANCER/ HYPERPLASIA IN WOMEN WITH ASYMPTOMATIC ENDOMETRIAL THICKENING

Certain clinical characteristics, namely BMI>30, use of antihypertensive medication, and use of estrogen and progesterone therapy are associated with endometrial thickening.[13−16]

In patients presenting with endometrial thickening, several risk factors for endometrial hyperplasia and cancer should be considered. Increasing age,[17,18] nulliparity,[19,20] obesity,[17−19,21,22] hypertension,[19,20,22,23] diabetes,[17,19,20,22] and tamoxifen use[19,22,24] have consistently been associated with increased risk of hyperplasia. Other clinical characteristics, such as menopausal status,[17] polycystic ovary syndrome,[25] a long menstrual history (early menarche, late menopause),[22] and infertility[22] may also increase the risk of hyperplasia, based on results from select studies. Lynch syndrome (also called hereditary nonpolyposis colorectal cancer) is an inherited risk factor for hyperplasia and endometrial cancer,[26] and patients with this syndrome should be managed in clinics with special expertise, as these guidelines do not apply to them.[26] Exposure to estrogen and progesterone hormone therapy post menopause has been demonstrated to increase the risk of hyperplasia in some studies[19,22] but not in others.[27] Regimens for hormone therapy including long

cycle use of progestins (i.e., every 2−3 months in a sequential formulation) have been associated with a higher risk of endometrial cancer.[28] In the Women's Health Initiative randomized trial, women receiving hormone therapy demonstrated a nonsignificant lower incidence of endometrial cancer diagnoses, compared with those not receiving hormone therapy (13 fewer cases per 10 000).[27]

Endometrial cancer is the most common gynaecologic malignancy. The incidence and mortality of endometrial cancer in Canada is 36.8 and 5.9 per 100 000.[29] Endometrial cancer is typically diagnosed in postmenopausal women, who usually present with postmenopausal bleeding. The incidence of endometrial cancer in women between ages 30 and 49 years who present with irregular bleeding is on the rise in Ontario, consistent with trends in other countries[30] (see SOGC guidelines 390 and 291).[31,32] Approximately 90% of women with endometrial cancer will present with postmenopausal (or abnormal) uterine bleeding.[27,33] In postmenopausal women without bleeding, the absolute risk of endometrial cancer or atypical hyperplasia is low (0.62% and 0.59%, respectively).[34] For asymptomatic endometrial thickness, an individualized risk assessment that considers patient and imaging risk factors balanced against the possible complications and cost of investigations, is necessary. Endometrial cancer typically presents with significantly elevated endometrial thickness (mean = 20 ± 4 mm compared to mean = 4 ± 1 mm in women with normal endometrium).[35] These estimates are for women presenting with bleeding. A recent retrospective study involving non-bleeding women with endometrial thicknesses >10 mm and <10 mm found that the prevalence of endometrial malignancy was 6.3% and 1.7%, respectively ($P = 0.023$).[7] It is important to consider that type 2 endometrial cancer, which is more virulent (e.g., papillary serous, clear cell, mucinous, carcinosarcoma, and poorly differentiated subtypes), tends to arise from atrophic endometrium and is not associated with hormonal stimulation.

There does not appear to be a survival advantage in diagnosing endometrial cancer in women who are asymptomatic versus those who are bleeding.[36]

Summary Statements 1 and 2 and Recommendations 1, 2, and 3

INCIDENCE OF ASYMPTOMATIC ENDOMETRIAL THICKENING ON ULTRASOUND

An incidental finding of thickened endometrium (>4 mm) may be detected in approximately 3%−15% of postmenopausal women,[3,37−39] though figures vary widely depending on patient selection in the research and clinical setting. While an incidental finding of a thickened endometrium is not uncommon, it is not on its own diagnostic of endometrial pathology, and endometrial sampling is required for precise pathologic diagnosis.

The American Cancer Society; European Society for Medical Oncology; European Society for Radiotherapy and Oncology and European Society of Gynaecological Oncology;[40] and American College of Obstetricians and Gynecologists[10] do not recommend routine endometrial cancer screening for average-risk asymptomatic patients. There is no evidence that this screening reduces mortality from endometrial cancer. Screening asymptomatic women increases anxiety and complications from biopsies.

Most cases of endometrial cancer are identified because of symptoms, especially bleeding. A high proportion of these cases are diagnosed at an early stage, with high rates of survival.

STUDIES ON THE SIGNIFICANCE OF ASYMPTOMATIC ENDOMETRIAL THICKENING

There is a lack of consensus on the significance and management of an incidental finding of endometrial thickening in asymptomatic postmenopausal women, and studies have sought to determine the ideal threshold for endometrial thickness at which additional investigation with endometrial sampling is recommended.[41]

Smith-Bindman et al. performed a decision analysis to estimate the endometrial thickness threshold that should be considered abnormal in asymptomatic postmenopausal women, incorporating published and unpublished data to model outcomes in a theoretical cohort of postmenopausal women aged 50 years or older, not receiving hormone therapy.[5] They calculated that in postmenopausal women without vaginal bleeding, the risk of cancer is approximately 0.002% when the endometrium is ≤11 mm thick and 6.7% when the endometrium is thicker than 11 mm. This is similar to the risk differential in the setting of postmenopausal bleeding when the endometrial thickness cutoff of 5 mm is used.

Alcazar et al. published a systematic review and meta-analysis that included 9 studies and 4751 postmenopausal women not on hormone replacement therapy, tamoxifen, or aromatase inhibitors. The mean prevalence of endometrial cancer or hyperplasia with atypia among women with endometrial thicknesses ≥11 mm was 6.5% (range 0%−15%), while the mean prevalence in women

with an endometrial thickness <11 mm was 1.7% (range 0.1%–5.1%). Compared with women with an endometrial thickness <11 mm, those with a thickness >11 mm had a 2.59-fold increased risk of endometrial cancer or hyperplasia with atypia.[42]

Since the publication of this systematic review, additional studies have proposed similar endometrial thickness thresholds for endometrial sampling. Using receiver operating characteristic (ROC) curves, thresholds of ≥10 mm (n = 1995)[38] and ≥12 mm (n = 488)[43] have been separately proposed, with no conclusive threshold found in another study.[39]

Another study involved 602 postmenopausal women with vaginal bleeding or asymptomatic thickened endometrium who were evaluated and divided into 2 groups of symptomatic or bleeding women (n = 274) and asymptomatic or non-bleeding women with an incidental finding of thickened endometrium (>5 mm; n = 328). Women in both groups underwent endometrial biopsy for histopathologic examination. Endometrial carcinoma was detected in 8 women (2.9%) in group 1 and in 3 (0.9%) in group 2. The best cutoff point for endometrial thickness in predicting endometrial carcinoma in group 1 was 8.2 mm, which provided 75% sensitivity (95% CI 40.9%–92.9%) and 74% specificity (95% CI 68%–78.5%). In group 2, the area under the ROC curve (AUC) was 0.76 (95% CI 0.46–1.00; $P = 0.114$); the evidence was inconclusive as to the relationship between endometrial thickness and malignancy.[39]

Another recent systematic review re-examined the optimal endometrial thickness threshold for diagnosing endometrial cancer.[44] Although the authors of that study cautioned that there are significant limitations in the studies currently available, a review of 7 studies (n = 2986), found that 12 mm was the optimal diagnosis threshold for endometrial cancer in asymptomatic postmenopausal women (AUC 0.716; 95% CI 0.534–0.897, $P = 0.019$).

An observational study of 1024 women in Austria not on tamoxifen and without Lynch syndrome with thickened endometrium on ultrasound who underwent histological assessment surgically confirmed this thickness cutoff of 11 mm. [45]

While asymptomatic endometrial thickening may be reported as an isolated incidental finding, several studies have suggested increased risk for endometrial cancer or hyperplasia with atypia when increased vascularity is present.[43]

In summary, women with endometrial thickening ≥11 mm or increased vascularity on ultrasound warrant additional investigation by a gynaecologist for consideration of endometrial biopsy.

Summary Statement 3 and Recommendations 4 and 5

INVESTIGATIONS: ACCURACY OF BLIND ENDOMETRIAL BIOPSY

Endometrial biopsy is required for assessment of endometrial tissue, and options include blind outpatient endometrial biopsy, dilation and curettage, or preferably hysteroscopy-guided biopsy. Advantages of blind outpatient endometrial biopsy compared with dilation and curettage and hysteroscopy include cost savings and its minimally invasive nature. Interestingly, agreement rate on tumour grade from preoperative endometrial sampling to final diagnosis in patients found to have endometrial carcinoma was not significantly higher in hysteroscopic biopsy versus office endometrial biopsy in one systemic review.[46]

The Pipelle suction-piston device was found to be the best and most frequently evaluated device in several systemic reviews and meta-analyses, with a sensitivity of 99.6% in detecting endometrial carcinoma and a 81% sensitivity in detecting atypical endometrial hyperplasia (specificity >98%).[47,48] Diagnostic accuracy was higher in postmenopausal women compared with premenopausal women (sensitivity 99.6% vs. 91%, respectively).[47] In a systematic review of 1013 patients, the overall failure rate of outpatient biopsy was 7% (95% CI 5%–8%) with 6 devices tested (Accurette, Gynoscann, Novak curette, Vabra aspirator, Z-sampler, and Pipelle), compared with 8% (95% CI 6%–11%) in studies using only the Pipelle.[48] Overall, 15% of samples procured with all devices were histologically inadequate (95% CI 12%–17%), compared with 13% of samples procured with the Pipelle (95% CI 10%–16%).[48] Postmenopausal women had increased failure rates for outpatient biopsy along with increased rates of inadequate tissue samples (12% and 22%, respectively).[48] With the Pipelle device, the post-test probability of endometrial cancer in postmenopausal women was calculated to be 82.7% for a positive test and 0.8% for a negative test (pretest probability 6.9%, (CI 4.4–10)). [48] Hence, a negative test result has high negative predictive value in someone with low pretest probability.

Endometrial biopsy is a successful procedure with a high overall accuracy for detecting endometrial cancer when

adequate specimens are obtained from patients with global endometrial thickening. If inadequate tissue is found (i.e., determined by the pathologist to be insufficient for evaluation) or scant tissue is retrieved after several Pipelle passes, additional diagnostic tests or watchful evaluation with repeat ultrasound imaging after 4 months may be necessary, depending on the clinical scenario, the concern on initial ultrasound appearance, and the patient's wishes, if the risk of malignancy is calculated to be low.[44] See Figure 1 for an algorithm of suggested management.

Summary Statement 4 and Recommendation 6

ENDOMETRIAL EFFECTS OF MENOPAUSAL HORMONE THERAPIES

Systemic Menopausal Hormone Treatments

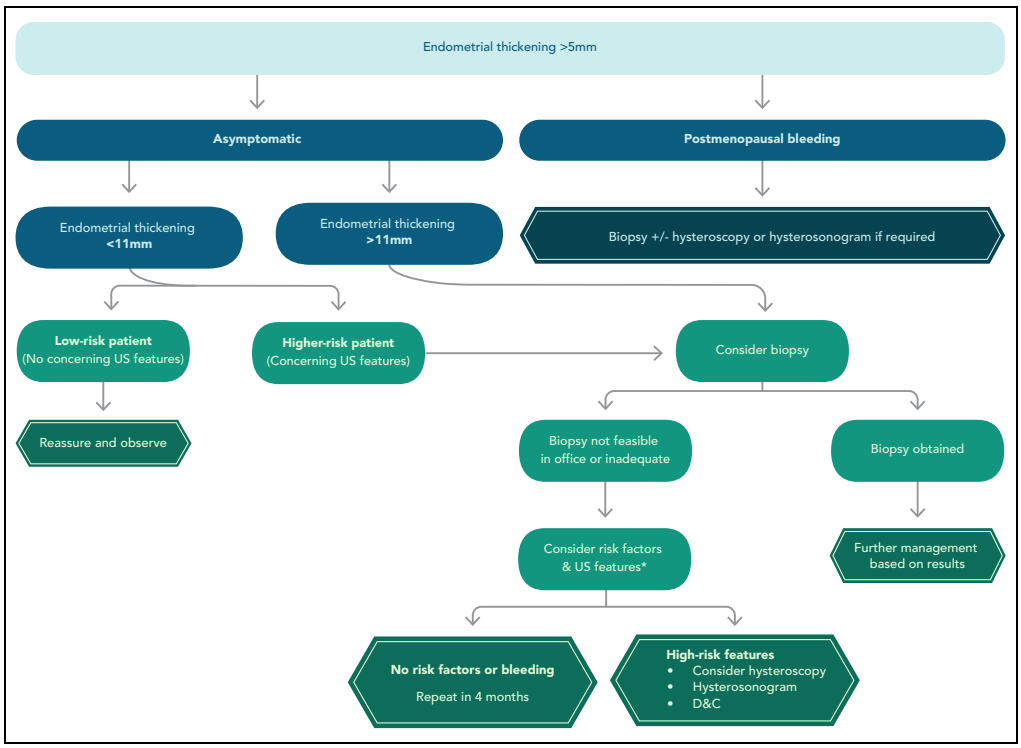
The thickness of the endometrium in a postmenopausal woman should be <4−5 mm. Various menopausal hormone products have been shown to affect endometrial thickness, depending on the type, dosage, and regimen.

The use of unopposed systemic estrogen has been shown to increase endometrial thickness.[49,50] One prospective randomized controlled trial studying the effects of conjugated equine estrogen at a dosage of 0.625 mg daily reported an increase of 5.5 mm in endometrial thickness after 52 weeks of use.[50]

A Cochrane review[51,52] reported both a dose-response and duration-of-use-response relationship between the use of oral estrogen alone and the risk of hyperplasia over 1−3 years of use. With the lowest dose regimens (i.e., conjugated equine estrogens at 0.45 mg and estradiol at 1 mg) a marginally nonsignificant increase in hyperplasia was reported at 1 year; however, significant increases were seen at both years 2 and 3 in this group, and an even more striking increased risk was observed for the moderate- (odds ratio [OR] 11.86) and high-dose estrogen groups (OR 13.6). This same review reported no clinically significant increase in endometrial thickness or endometrial hyperplasia for both continuous and sequential estrogen-progestin therapy regimens, although there is mixed evidence for a variety of long cycle regimens.[28,51,52]

Newer estrogen-progestin therapies and related products continue to be developed for which either endometrial thickness or endometrial biopsy hyperplasia data have been collected. In prospective randomized controlled trials

Figure 1. Algorithm for the Investigation of Endometrial Thickening in Postmenopausal Women



*High-risk patient features include increasing age,[1,2] nulliparity,[3,4] obesity,[1–3,5,6] hypertension,[3,4,6,7] diabetes,[1,3,4,6] tamoxifen use,[3,6,8] and Lynch syndrome. High-risk US features include increased vascularity, heterogeneity, and fluid collection.
US: ultrasound; D&C: dilation and curettage.

of these newer products and combinations, no significant increases in endometrial thickness (i.e., a ≤1 mm increase) and/or endometrial hyperplasia (i.e., a <1% incidence of endometrial hyperplasia) were observed for the following:

- estradiol + progesterone (1/100, 0.5/100, 0.5/50 and 0.25/50) for 12 months[53];
- estradiol 1 mg + drospirenone 2 mg for 12 months;
- estradiol patch 25 μg + vaginal progesterone 100 mg 2/wk for 12 months[51,54];
- a levonorgestrel intrauterine system (average 14 μg/d) + estrogen gel 1.5 mg/d, estradiol patch 50 μg, or estradiol 2 mg, oral, once daily) for 1–2 cycles (5–10 y)[55];
- tibolone 2.5 mg, oral, once daily for 2 years[56–58]; and
- the tissue selective estrogen complex tablet containing conjugated equine estrogen 0.45 mg and bazedoxifene 20 mg once daily for 12 months.[59]

A Cochrane review of studies involving tibolone users concluded that there was no clear evidence of differences in the risk of endometrial cancer between tibolone and placebo. A recent prospective cohort study from Denmark in a larger database of patients treated with tibolone between 1995 and 2009 did find an increased risk of endometrial cancer.[60,61]

Not all selective estrogen receptor modulator and estrogen combinations offer endometrial safety. A 1-year randomized controlled trial studying raloxifene 40 mg + estradiol 1 mg (oral, once daily) reported a significant increase in endometrial thickness of 0.74 mm ($P < 0.05$). In this trial, 2 patients were found to have endometrial hyperplasia, 1 with atypia.[62] One study on the use of conjugated equine estrogens 0.3 mg + raloxifene reported no change in endometrial thickness.[63]

The use of transdermal testosterone as an adjunct to estradiol has been studied, and no increase in endometrial thickness or endometrial hyperplasia were reported.[64,65]

Complementary Treatments

There are limited quality studies exploring the effect of herbal or complementary menopausal products on endometrial thickness, and most are of short duration. A meta-analysis of 30 randomized controlled trials related to a variety of phytoestrogens (isoflavone, genistein, daidzein, lignans, S-equol and equol) used for up to 104 weeks reported no increase in endometrial thickness. Data for endometrial hyperplasia were not reported.[66]

Treatments for Genitourinary Syndrome of Menopause

Local (vaginal) hormone therapies contain estradiol; conjugated equine estrogen or estrone; dehydroepiandrosterone (DHEA); or testosterone in a variety of preparations and delivery systems.

A 2020 systematic review of 22 trials assessing endometrial thickness and 15 trials with endometrial biopsies found no clear evidence of endometrial proliferation after vaginal estrogen therapy used for up to 52 weeks. No change in endometrial thickness was reported for vaginal tablets, ring or inserts with estradiol 4 μg, 10 μg or 25 μg, In head-to-head studies, although a higher percentage of conjugated equine estrogen cream users versus ring users were found to have an endometrial thickness >5 mm (12% vs. 6%); this difference was not statistically significant. A higher rate of proliferative endometrium was also reported with the use of vaginal conjugated equine estrogen cream; however, the authors opined that these differences were attributable to a higher dose of conjugated equine estrogen cream used in the studies (1.25 mg 3 × wk vs. 0.3–0.625 g 2 × wk). Overall, there was no clear finding of endometrial proliferation after vaginal estrogen therapy; however, not all studies included endometrial biopsy.[67]

Studies of a new low-dose vaginal estradiol soft gel (4 μg and 10 μg dosages) did not assess changes in endometrial thickness, but there was no hyperplasia.[68]

Studies of a DHEA vaginal insert, Prasterone 6.5 mg daily, and of intravaginal testosterone[69] also reported either no increase in endometrial thickness or endometrial hyperplasia.[70]

Ospemifene is an oral selective estrogen receptor modulator approved for the treatment of genitourinary syndrome of menopause. In studies, up to 52 weeks of ospemifene 60 mg daily, was associated with a modest mean increase in endometrial thickness of 0.62–0.81 mm, but this finding was deemed clinically insignificant. The incidence of endometrial hyperplasia was found to be <1%, with no cases of endometrial hyperplasia with atypia reported.[71]

Nonhormonal Options for Vasomotor Symptoms

In a phase 2b randomized controlled trial, fezolinetant, a neurokinin-3 receptor antagonist, at a variety of doses was shown to have no impact on endometrial thickness, based on 12 weeks of data.[72]

Tamoxifen

First reported in the 1990s, postmenopausal patients on tamoxifen therapy were found to have a thicker endometrium (10.4 [SD 5.2] mm vs. 4.2 [SD 2.8] mm; $P = 0.0001$) compared with controls.[73] These findings were rapidly confirmed in other studies.[73–76]Average endometrial thickness was 11.5 (SD 5.2) mm after 2.8 years of therapy with tamoxifen 20 mg daily.[77]

The percentage of patients on tamoxifen having an endometrial thickness >5 mm on transvaginal ultrasound was found to be 53%–71% in women taking tamoxifen compared with 12% in a control group.[76,78,79] Increase in endometrial thickness was only significant in postmenopausal or amenorrheic patients and not in premenopausal ones.[75,76,80]

On transvaginal ultrasound examination, the endometrium of patients on tamoxifen is often described as irregular and containing multiple cystic areas resembling "swiss cheese" or as a cystically thickened endometrium. In 50%–90% of patients, this ultrasound finding is not associated with any cavitary lesion, with both endometrial biopsy and hysteroscopy confirming an atrophic endometrium and histology showing a condensated stroma and fluid-filled, cystically dilated glands lined with flattened epithelium.[80–82] In most studies, transvaginal ultrasound was unable to differentiate between significant endometrial pathology and endometrial glandulocystic atrophy.[80,82]

Endometrial thickening on transvaginal ultrasound was significantly associated with postmenopausal bleeding[79] as well as endometrial pathology, particularly endometrial cancer.[73,77,83] No correlation between endometrial thickness and duration of tamoxifen treatment was found.[76]

In multiple studies using 5 mm as the cutoff for further investigation in women taking tamoxifen, the sensitivity and specificity for positive histological findings varied from 87.5% to 91% and from 19% to 96%, respectively.[79,84,85] Other studies have recommended against the use of a single cutoff based on transvaginal ultrasound alone, since some patients with thicknesses <5 mm were found to have significant endometrial pathology, including endometrial cancer.[86]

Endometrial thickness significantly decreased 6 months after tamoxifen was ceased, and no difference in endometrial thickness was noted between women on tamoxifen and controls 1 year after the end of tamoxifen treatment.[81,87]

As stated in the American College of Obstetricians and Gynecologists' 2014 committee opinion, routine screening of asymptomatic women on tamoxifen with transvaginal ultrasound and/or endometrial sampling demonstrated no benefits, and it is not currently recommended.[88,89] Women on tamoxifen should promptly report any abnormal vaginal bleeding. Symptomatic women should be investigated, and transvaginal ultrasound alone is not sufficient to eliminate significant endometrial pathology in this higher risk population.[76,90] Therefore, the management of endometrial thickening, if found in an asymptomatic patient on tamoxifen, should be determined by a case-by-case evaluation.

Aromatase Inhibitors

In one study, postmenopausal patients treated with fulvestrant were found to have significantly lower endometrial thicknesses than patients receiving placebo, even after a 14-day course of ethinyl estradiol.[91]

In a study comparing endometrial thickness in patients taking exemestane versus tamoxifen, patients on tamoxifen were twice as likely to have endometrial thicknesses >5 mm compared with patients on exemestane after 24 months of treatment (35.5% vs. 61.8%; $P = 0.004$). This difference appeared as early as 6 months of treatment and was no longer visible 12 months after treatment completion. Patients who switched from tamoxifen to exemestane had a rapid decrease in endometrial thickness within 6 months, mostly due to losing the stimulatory effect of tamoxifen.[92]

Summary Statements 5 and 6 and Recommendations 7, 8, and 9

APPROACH TO A STENOTIC CERVIX

An endometrial biopsy may be challenging to obtain in the presence of a stenotic, tortuous cervix; extremes of uterine flexion or version; congenital anomalies; or scarring of the cervix from previous surgery or radiation.[93] In these situations, it may be difficult to obtain an adequate sample, and attempts at biopsy may lead to increased patient discomfort, as well as complications such as creation of false passage, uterine perforation, and bleeding.[94] Cervical stenosis is characterized as narrowing of the endocervical canal preventing passage of a 2.5 mm Hegar or Pratt dilator.[93] Stenosis of the external cervical os is described as an external os diameter <4.5 mm.[93,95] Common risk factors for cervical stenosis include nulliparity and

postmenopausal status, as well as a history of previous endometrial curettage and treatment of cervical dysplasia.[96,97]

Medical Management

Prostaglandin E_1 (misoprostol) has been suggested as a treatment option for cervical stenosis. Although its mechanism of action is not completely understood, it is thought to be mediated by estrogen.[93] Misoprostol dosages of 400 μg orally or 200 μg vaginally 9 to 12 hours prior to hysteroscopy may be of benefit, as evidenced by shorter procedure times and use of fewer dilators.[98,99] Alternatively, 10 mg of vaginal prostaglandin E_2 (dinoprostone) can be considered.[100] Studies examining use of misoprostol prior to attempted office endometrial biopsy or IUD insertion have not demonstrated a benefit.[47,101,102] Furthermore, misoprostol is associated with several adverse effects, including nausea, vomiting, vaginal bleeding, and abdominal/pelvic pain.[103,104] It is important to consider that misoprostol may also be ineffective as a cervical-ripening agent in postmenopausal women and those treated with gonadotropin-releasing hormone analogs because of the hypoestrogenic state in these patients,[105] unless they have been pretreated with systematic estrogen for 2 weeks prior.[106]

Osmotic dilators (laminaria tents) may facilitate cervical dilation during operative hysteroscopy; however, placement of laminaria requires some degree of cervical os dilation, thereby limiting their use.[107]

Operative Techniques

Cervical dilation may be associated with a few complications. The overall risk of dilation and curettage and hysteroscopy is less than 1%, with uterine perforation reported in 0.12%–0.76% of cases, depending on the series reviewed.[108–110]

Typically, cervical stenosis is managed with gradual dilation using successively larger rigid dilators. This method may lead to the creation of false passage or uterine perforation, especially if uterine orientation is unknown or with extremes of uterine flexion. Ultrasound guidance may mitigate this risk.[111] Use of intracervical dilute vasopressin (0.05 U/mL) has been reported to reduce the force required for cervical entry, but caution must be used, as systematic infiltration of vasopressin may result in cardiovascular compromise.[112]

In certain cases, blind dilation of the cervical canal may lead to cervical laceration, creation of false passage, or uterine perforation. A vaginoscopic approach may avoid these complications, in which a small diameter (preferably <5 mm) hysteroscope is used to directly visualize the vagina and cervical canal before entering the uterus. This approach may be used in an outpatient hysteroscopy setting or in the operating room. At times, it may be necessary to revise the cervical canal to gain access to the uterus. This may be done with sharp dissection using microscissors and/or blunt dissection with microgrаspers.[113] Other alternatives are using the cutting loop electrode or laser to excise a small segment of the internal os or using the hysteroscopic morcellator to access the uterine cavity.[113,114] Bettocchi et al. described successful approaches to accessing the uterine cavity in 98.5% of 10 156 cases of cervical stenosis, using hysteroscopic techniques such as the push/spread technique, the microscissor, micrograsper, and bipolar electrode.[96]

Hammoud et al. recently described ultrasound-guided endometrial biopsy for patients with cervical stenosis that involved bypassing the cervix.[115] Under general anesthetic, when cervical dilation failed, they describe access through the anterior uterine wall by a 20 cm, 18- or 20-gauge needle inserted through the vaginal vault. This technique is done under transabdominal ultrasound guidance. Once intrauterine access is confirmed, the endometrium is sampled.

Summary Statement 7 and Recommendation 10

CONCLUSION

The finding of endometrial thickening and the possibility of uterine cancer causes anxiety in patients. Asymptomatic endometrial thickening in postmenopausal women is commonly found on an ultrasound examination. Hyperplasia is a pathological diagnosis made after tissue biopsy, not a diagnosis that can be made on ultrasound. Although the risk of endometrial cancer is relatively low in women with no bleeding, the disease has the best outcomes when found at an early stage, usually when postmenopausal women present with bleeding. There is no evidence of improved outcomes before a woman presents with bleeding. Routine ultrasound screening for asymptomatic women is not recommended. Current evidence supports our previous guideline, which recommended a conservative approach with a 10–11mm endometrium in a non-bleeding woman. However, it is recommended that certain subsets of women with higher risks of developing endometrial cancer or who have other positive findings (e.g., increased vascularity, inhomogeneity of the endometrium, particulate fluid) as well as women with clinical

risk factors should be triaged on an individual basis. Investigations for asymptomatic endometrial thickening are not risk free, and serious complications such as infection, uterine perforation, and bowel injury have been reported in the literature. Endometrial biopsy should be a key first step in evaluating those suspected to have pathology or at high risk for cancer, though the finding of insufficient tissue necessitates more invasive testing. Watchful monitoring with repeat ultrasound over 4 months may be an option if the patient is counselled with respect to her individual endometrial cancer risk. Newer literature continues to support the extremely low risk of malignancy in women with asymptomatic global endometrial thickening <10−11 mm.

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APPENDIX A

Table A1. Key to Grading of Recommendations, Assessment, Development and Evaluation Quality of Evidence

Grade	Definition
Strength of recommendation	
Strong	High level of confidence that the desirable effects outweigh the undesirable effects (strong recommendation for) or the undesirable effects outweigh the desirable effects (strong recommendation against)
Conditional (weak)[a]	Desirable effects probably outweigh the undesirable effects (weak recommendation for) or the undesirable effects probably outweigh the desirable effects (weak recommendation against)
Quality of evidence	
High	High level of confidence that the true effect lies close to that of the estimate of the effect
Moderate	Moderate confidence in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Limited confidence in the effect estimate: The true effect may be substantially different from the estimate of the effect
Very low	Very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Adapted from GRADE Handbook (2013), Table 5.1.
[a]Do not interpret conditional (weak) recommendations to mean weak evidence or uncertainty of the recommendation.

Table A2. Implications of Strong and Conditional (Weak) recommendations, by guideline user

Perspective	Strong Recommendation • "We recommend that…" • "We recommend to not…"	Conditional (Weak) Recommendation • "We suggest…" • "We suggest to not…"
Authors	The net desirable effects of a course of action outweigh the effects of the alternative course of action.	It is less clear whether the net desirable consequences of a strategy outweigh the alternative strategy.
Patients	Most individuals in the situation would want the recommended course of action, while only a small proportion would not.	The majority of individuals in the situation would want the suggested course of action, but many would not.
Clinicians	Most individuals should receive the course of action. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Recognize that patient choices will vary by individual and that clinicians must help patients arrive at a care decision consistent with the patient's values and preferences.
Policy makers	The recommendation can be adapted as policy in most settings.	The recommendation can serve as a starting point for debate with the involvement of many stakeholders.

Adapted from GRADE Handbook (2013), Table 6.1.