No. 249, October 2010

Asymptomatic Endometrial Thickening

This Clinical Practice Guideline has been prepared by the Clinical Practice Gynaecology Committee and approved by the Executive and Council of the Society of Obstetricians and Gynaecologists of Canada.

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Key Words: Asymptomatic endometrial thickening, asymptomatic endometrial polyp, endometrial cancer, transvaginal ultrasonography, hysteroscopy, endometrial biopsy tamoxifen, postmenopausal polyps

Abstract

Objective: To formulate clinical recommendations for the assessment of endometrial thickening when it is found on ultrasound in a postmenopausal patient without bleeding.

Outcomes: Ensure that women with asymptomatic thickening and endometrial polyps found on ultrasound are managed appropriately.

Evidence: Published literature was retrieved through searches of English language articles from the EMBASE, Cochrane, and PubMed databases for relevant peer-reviewed articles dating from 1970 to 2009, using appropriate controlled vocabulary (e.g., "asymptomatic endometrial thickness," "endometrial cancer," "postmenopausal bleeding," "transvaginal ultrasonography," "endometrial biopsy" and "endometrial polyp"). Results were restricted to systematic reviews, randomized control trials/controlled clinical trials, and observational studies. Searches were updated on a regular basis and incorporated in the guideline to April 2010. Grey (unpublished) literature was identified through searching the websites of health technology assessment and health technology assessment-related agencies, clinical practice guideline collections, clinical trial registries, and national and international medical specialty societies.

Values: The level of evidence was determined according to the criteria established by the Canadian Task Force on Preventative Health Care (Table). Recommendations are ranked according to this method.

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

Key Words: Asymptomatic endometrial thickening, asymptomatic endometrial polyp, endometrial cancer, transvaginal ultrasonography, hysteroscopy, endometrial biopsy tamoxifen, postmenopausal polyps

Recommendations

1. Transvaginal ultrasound should not be used as screening for endometrial cancer. (II-1E)
2. Endometrial sampling in a postmenopausal woman without bleeding should not be routinely performed. (II-1E)
3. Indications for tissue sampling of the endometrium in bleeding postmenopausal women with an endometrial thickness of greater than 4 to 5 mm should not be extrapolated to asymptomatic women. (II-2E)
4. A woman who has endometrial thickening and other positive findings on ultrasound, such as increased vascularity, inhomogeneity of endometrium, particulate fluid, or thickened endometrium over 11 mm, should be referred to a gynaecologist for further investigations. (II-1A)
5. Decisions about further investigations should be made on a case-by-case basis in asymptomatic women with increased

Key to evidence statements and grading of recommendations, using the ranking of the Canadian Task Force on Preventive Health Care

Quality of evidence assessment*	Classification of recommendations†
I: Evidence obtained from at least one properly randomized controlled trial	A. There is good evidence to recommend the clinical preventive action
II-1: Evidence from well-designed controlled trials without randomization	B. There is fair evidence to recommend the clinical preventive action
II-2: Evidence from well-designed cohort (prospective or retrospective) or case–control studies, preferably from more than one centre or research group	C. The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making
II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category	D. There is fair evidence to recommend against the clinical preventive action
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	E. There is good evidence to recommend against the clinical preventive action
	L. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making

*The quality of evidence reported in these guidelines has been adapted from The Evaluation of Evidence criteria described in the Canadian Task Force on Preventive Health Care.[71]
†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the The Canadian Task Force on Preventive Health Care.[71]

endometrial thickening and risk factors for endometrial cancer such as obesity, hypertension, and late menopause. (II-1B)

6. In asymptomatic women on tamoxifen, a routine ultrasound for endometrial thickening should not be performed. (II-2E)
7. Not all postmenopausal women who have asymptomatic endometrial polyps require surgery. Women found to have asymptomatic polyps on ultrasound should be triaged for intervention according to size of the polyp, age, and other risk factors. (II-1A)

J Obstet Gynaecol Can 2010;32(10):990–999

INTRODUCTION

In this guideline, asymptomatic endometrial thickening is defined as an endometrium of > 5 mm discovered on ultrasound in a postmenopausal woman who is not bleeding.[1–3] Current ultrasound literature suggests that asymptomatic endometrial thickness of 8 to 11 mm in a postmenopausal women is not abnormal.[4–8] The measurement of the endometrium is made at its maximal thickness on a midline sagittal image of the uterus obtained by transvaginal ultrasound. It is a bilayer measurement combining the width of both the anterior and the posterior layers of the endometrium. It has been suggested that the normal endometrial thickness in a postmenopausal woman is 5 mm. There is controversy about the normal measurement in women on hormone therapy. Studies have shown a normal range from 5.4 to 10.8 mm.[4–6,9] An endometrium 2 mm thicker in women who use sequential therapy may be normal.[10] The endometrium may normally be thicker in the first year after the last menstrual period, reflecting some residual hormonal activity.[11]

ABBREVIATIONS

HT	hormone therapy
TVUS	transvaginal ultrasound

The finding of asymptomatic endometrial thickening on ultrasound presents a clinical management dilemma and is a frequent reason for referral by family physicians. Concern is raised when an endometrium of > 5 mm is discovered during an ultrasound examination, often one that is undertaken for non-gynaecologic reasons. Subsequent radiologic reports prompt interventions that can be invasive and involve risk. The incidence of endometrial thickening (≥ 4.5 mm) in postmenopausal women ranges from 3% to 17%,[1–3] while the incidence of endometrial cancer in an unselected postmenopausal population is 1.3 to 1.7/1000.[12–14]

The American Cancer Society does not recommend routine screening of asymptomatic patients for endometrial cancer.[15] The Canadian Cancer Society reports that there is inadequate evidence that screening by ultrasonography or endometrial sampling would reduce the mortality from endometrial cancer.[16] The 2001 consensus statement on bleeding published by the Society of Radiologists in Ultrasound included a caveat that the 5 mm threshold does not apply to asymptomatic women with incidentally observed thickened endometrium.[17] In 2009, the American College of Obstetricians and Gynecologists stated that there was

no evidence to recommend routine investigations for asymptomatic endometrial thickening.[18] Despite this recommendation, clinicians are concerned when the ultrasound report states that endometrial cancer cannot be ruled out because of endometrial thickening found in an asymptomatic postmenopausal woman. Goldstein, in 2010,[19] recommended postmenopausal asymptomatic endometrial thickening be evaluated on a case-by-case basis. The clinician must consider risk factors for endometrial cancer including obesity, polycystic ovary syndrome, and diabetes mellitus in their decision making. Goldstein[19] emphasized that it is inappropriate to investigate every asymptomatic patient with thickened endometrium > 5 mm.

ENDOMETRIAL CANCER AND RISK FACTORS

Endometrial cancer is the most common gynaecologic malignancy.[20] The incidence in Canada is 19/100 000 women. The Canadian Cancer Society estimated that in 2009 there would be 4400 cases of endometrial cancer and 720 deaths due to the disease in Canada.[16] Approximately 80% of endometrial cancers occur in postmenopausal women.[21] Ninety percent of women with endometrial cancer present with bleeding.[22] Most women (72%) have stage I cancer when diagnosis is made,[22] and the survival rate depends on the stage, grade, and type of cancer. Five-year survival rates for localized, regional, and metastatic endometrial cancer are 95%, 67%, and 23%, respectively, and the overall 5-year survival rate is 86%.[20]

Individual risk factors are obesity, high-fat diet, reproductive factors such as nulliparity and polycystic ovary syndrome, early menarche, and late menopause.[23] Tamoxifen use also increases the risk of developing endometrial cancer by 2.3 per 1000 women.[24]

Women with hereditary nonpolyposis colorectal cancer syndrome have an estimated cumulative incidence of endometrial cancer ranging from 20% to 60% by the age of 70 years. The mean age of developing cancer is 47 in carriers versus 60 years in those with non-inherited endometrial cancer.[25] No studies have yet shown the benefit of screening for endometrial cancer in female carriers of hereditary nonpolyposis colorectal cancer syndrome.[26]

The incidence of endometrial cancer is lower in Black women. However, the overall mortality due to the disease is higher among this group.[27]

A Swedish longitudinal evaluation of postmenopausal women found that a history of bleeding incurs a 64-fold increased risk of endometrial cancer.[28,29] For any woman presenting with postmenopausal bleeding there is approximately a 10% risk of endometrial carcinoma.[29] If the woman is on hormone therapy and bleeds, the risk is 1%.[29]

It is unknown how many women who have endometrial cancer are diagnosed in the absence of bleeding. Diagnosis of cancer in asymptomatic women has been estimated by Smith-Bindman to be 5% to 10% of all cases.[30] It is also unknown if diagnosing endometrial cancer before a woman bleeds would improve overall survival.

In 1981 Koss et al.[2] initiated a screening study of 1280 asymptomatic women aged 45 and older via endometrial sampling in a New York Medical Center. Carcinoma was found in only 8 patients (6/1000).

In 1997 Korhonen et al.[31] published their results of pathologic findings for endometrial biopsy in 2964 perimenopausal and postmenopausal women who were candidates for hormone therapy. Endometrial biopsy findings were 68.7% atrophic, 23.5% proliferative, 0.5% secretory, 0% hyperplastic, and < 0.07% malignant. Of the biopsy samples, 6.6 % were insufficient for classification, reflecting the low incidence of pathology in the general population.

A necropsy study found an occult incidence of endometrial cancer of 22 to 31/10 000 women (0.22% to 0.31%).[32] These studies indicate a background incidence of endometrial cancer of 0.6 to 6/1000 women (0.2% to 0.6%).[2,32]

SIGNIFICANCE OF ASYMPTOMATIC ENDOMETRIAL THICKENING

In a menstruating woman the endometrium changes with the phase of the menstrual cycle. It ranges from 3 mm after menses to a thickness of 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 fluctuating levels of estrogen.

Descriptions of the endometrium on ultrasound examination include global thickening, heterogeneity, thickening, focal areas of thickening, fluid collections, increased vascularity, and myometrial associated findings such as myometrial cysts, and submucosal fibroids. After menopause, endometrial thickening may reflect proliferative endometrium, cystic hyperplasia, complex hyperplasia, atypical hyperplasia, or carcinoma of the endometrium. Ultrasound evidence of thickened endometrium may also indicate structural abnormalities such as a uterine septum, submucous myomas, polyps, or adenomyosis. Ultrasound technology, by identifying vascular flow, now allows differentiation of polyps from other abnormalities.[33] Increased vascularity and fluid accumulation in association with endometrial thickening are cause for greater concern than other findings.[34]

SCREENING STUDIES OF ASYMPTOMATIC WOMEN

The purpose of performing ultrasound in non-bleeding postmenopausal women may be to investigate abdominal pain or masses or to delineate the adnexae when pelvic examination is inadequate. Screening studies have been undertaken to assess whether ultrasound can detect endometrial cancer in large populations of asymptomatic women.[3,35,36]

The American Cancer Society concluded that there was insufficient evidence to recommend any routine screening for endometrial cancer with TVUS or endometrial biopsy.[37] Screening asymptomatic women will result in unnecessary additional examinations because of low specificity. Most cases of endometrial cancer are diagnosed as a result of symptoms reported by patients, and a high proportion of these cases are diagnosed at an early stage, with high rates of survival.

In 1995, Ciatto and colleagues[35] performed TVUS on 2025 women to evaluate the feasibility of using this modality to screen for endometrial carcinoma solely on the basis of endometrial thickness. In this study, 117 women (5.8%) showed abnormal thickness of > 4 mm. Of these, 98 underwent endometrial biopsy, but 32 had impassable cervical stenosis. It was decided that evaluation of the endometrium by dilatation and curettage was not warranted. These women underwent repeat transvaginal ultrasound examination. The positive predictive value was 3.3%, with 3 endometrial carcinomas found out of 66 biopsies.

A 1999 study by Vuento et al.[3] focused on the feasibility of TVUS to screen for endometrial cancer in asymptomatic postmenopausal women using multiple criteria, one of which was endometrial thickness. In this study, 291 of 1074 women (29%) had an abnormal thickness > 4 mm, uterine artery pulsatility index < 1.0, or fluid accumulation in the endometrial cavity. However, after biopsy, only 23 women were found to have endometrial pathology, and only 3 were found to have endometrial cancer. Endometrial fluid was found in 12%. Another case of carcinoma was found 2.5 years later in a patient who had refused biopsy. The authors concluded that TVUS, while sensitive for detecting early endometrial cancer, has a low specificity that precludes its utility as a screening modality. Doppler ultrasound did not improve detection of abnormal endometrial pathology.

A study by Fleischer et al.[36] of 1926 women who underwent ultrasound examination as part of the workup for an osteoporosis prevention trial found that 93 women had an endometrium > 6 mm. When endometrial aspiration of 42 of these women was undertaken, there were abnormal findings in only 1 case. A further 1750 of 1833 women with endometrial thickness of < 6 mm underwent sampling, yielding 5 abnormal results (1 endometrial cancer). The sensitivity was 17% for 6 mm and 33% using 5 mm as a threshold. The positive predictive value was 2%. The negative predictive value at < 6 mm was 99%.

Smith-Bindman et al.[30] calculated a 6.7% risk of endometrial cancer if the endometrium was > 11 mm, and a 0.002 % risk if the endometrium was thin (< 11 mm). This theoretical risk was calculated on the basis of a review of published and unpublished data and an estimate of 15% of total cases of endometrial cancer occurring in women who have no bleeding. The risk is also related to age, with women > 70 years, with a thicker endometrium having a higher risk (9.3% with 11 mm endometrium).

Gambacciani et al.[1] undertook a retrospective review of 850 postmenopausal women who were investigated with outpatient hysteroscopy for various causes of thickening. The authors focused on the 148 asymptomatic postmenopausal women with endometrium > 4 to 5 mm, and found 1 case of adenocarcinoma (0.7%) (endometrium 16 mm) and 9 cases of hyperplasia (6.1%). In this study 24/27 cases of adenocarcinoma presented with bleeding, 2/27 had an abnormal Papanicolaou smear, and 1/27 (3.7%) had thickened endometrium. One hundred forty-seven hysteroscopies were performed for benign pathology; the false positive rate was 93.2%.

Gerber et al.[38] in a retrospective analysis discovered 16 patients (13%) had endometrial cancer when an endometrial thickening of 10 mm was used as a cut-off in the investigation of 123 asymptomatic women; 21 of the women (17%) had hyperplasia. Asymptomatic women without symptoms had no prognostic advantage over the symptomatic women if bleeding had occurred for < 8 weeks. Duration of postmenopausal bleeding was correlated with increasing tumour stage and reduced survival time. Endometrial screening often resulted in unnecessary operations with increased morbidity and cost.

Archer et al.[12] attempted to obtain endometrial samples in 801 asymptomatic perimenopausal and postmenopausal women prior to enrolment in a multicentre hormone replacement therapy study. Of the samples, 75% contained sufficient tissue for diagnosis. One endometrial cancer was diagnosed, illustrating the low incidence of disease in asymptomatic women and the low incidence of disease in asymptomatic women. The endometrium was atrophic in 46.9%, proliferative in 16.7%, secretory in 6.8%, and hyperplastic in 5.2%.

Tsuda et al.[39] screened 1400 asymptomatic postmenopausal Japanese women and found a prevalence of endometrial disease of 2.3% in asymptomatic and 21% in symptomatic women. At a cut-off of 3 mm in non-bleeding women, sensitivity was 90%, specificity 84%, and positive predictive

value 12%. With an endometrial thickness < 3 mm, the probability that endometrial disease would be missed was 0.003.

A review of the literature therefore does not indicate that routine screening via transvaginal ultrasound for endometrial cancer is recommended. There is a baseline incidence of thickening (≥ 4.5 mm) of up to 17%, with a low incidence of cancer < 1%.[1,12,36–38]

WOMEN WITH RISK FACTORS

Increased lifetime estrogen exposure has been associated with an increased risk of endometrial cancer. Early menarche, late menopause, obesity, and unopposed estrogen use have been linked to an increased risk. Should endometrial thickening on ultrasound be more aggressively investigated in women with risk factors?

A regression analysis by Maatela et al.[40] of endometrial thickening in asymptomatic postmenopausal women found an increased risk of pathological findings in the presence of obesity (BMI > 26) and late menopause.

In a 1993 study of ultrasonic thickness of the endometrium in 300 asymptomatic postmenopausal women, Andolf et al.[41] found that endometrial thickness correlated significantly with BMI. In the same study, Andolf and colleagues found a non-significant trend towards a higher prevalence of predisposing factors (hypertension, nulliparity, diabetes) in women with a thick endometrium.

The Women's Health Initiative data, however, showed that the interactions of age, race/ethnicity, BMI, hypertension, smoking status, pack-years of smoking, prior use of unopposed estrogen, or prior use of estrogen and progesterone had no significant effect on the observed incidence rate of endometrial cancer.[42] There was a insignificant decrease in the number of endometrial cancer cases in women taking HT rather than placebo (13 fewer cases per 10 000).

Martinez-Rubio and Alcazar[43] prospectively compared the prevalence of abnormal endometrium in 187 postmenopausal asymptomatic, normotensive women and 182 asymptomatic postmenopausal women receiving anti-hypertensive drugs. The endometrium was assessed via office endometrial biopsy and TVUS when the definition of abnormal ultrasound was > 5 mm. Women taking antihypertensive medications were significantly more likely than normotensive women to have endometrial thickness > 5 mm (26.9% vs. 12.8%; *P* 0.001), heterogeneous endometrial polyps (23.1 vs. 12.8%; $P < 0.001$), and endometrial polyps (17.6 vs. 9.6%; $P < 0.001$). These results were independent of body mass index.

Sit et al.[44] evaluated asymptomatic thickening as an estrogen biomarker as a part of the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial in 1271 women. Thickness ranged from 1 to 32 mm (median 3 mm). Frequency of thicker endometrium was independently associated with increasing BMI and current use of HT.

The time from menopause is a factor in investigating the significance of the findings. Tsuda et al.[11] found histologic findings of a proliferative endometrium in 28% of women < 5 years post-menopause and in 4.8% in women ≥ 5 years post-menopause. Andolf and colleagues[41] found only an insignificant trend towards decreasing endometrial thickness with time after menopause.

ENDOMETRIAL THICKENING IN WOMEN ON HT

Hänggi et al.[10] compared TVUS with histological findings in endometrial evaluation of postmenopausal women using hormone therapy to evaluate the safety of 3 hormone therapy regimens versus no therapy. Patients on oral micronized 17β-estradiol/oral sequential dydrogesterone were compared with those using transdermal 17β-estradiol/oral sequential dydrogesterone, or oral tibolone. If endometrial thickness was < 5 mm, endometrial biopsy sample was either inactive/atrophic or insufficient for diagnosis. Hyperplastic or malignant change was not reported. After 24 months, endometrial thickness was increased both in the oral and the transdermal 17β-estradiol/dydrogesterone groups. The tibolone group showed no difference from the control group.

In the Postmenopausal Estrogen and Progestin Interventions Trial, 448 participants underwent both TVUS and endometrial biopsy over 4 years.[45] They were randomized to placebo or to cyclic or sequential HT. Langer et al.[45] found that at a threshold value of 5 mm for endometrial thickness, TVUS had 90% sensitivity and 48% specificity. No cancer or atypical hyperplasia was found in 261 women with endometrial thickness of < 5 mm. Two cases of atypical hyperplasia and 1 case of cancer were found in 307 women with endometrial thickness ≥ 5 mm. The majority of serious disease cases were found in women with endometrial thickness > 10 mm. Eight cases of complex hyperplasia, 3 cases of atypical hyperplasia, and 1 case of adenocarcinoma were found in the study population. Using this threshold, more than one half of the women would undergo a biopsy, while only 4% had serious disease.

Gull et al.[46] evaluated a random sample of 1000 women between the ages of 45 and 80 who underwent screening ultrasound in Sweden; 559 were postmenopausal. The current use of HT was associated with increasing endometrial thickness.

Kurtay et al.[47] assessed the effects of hormone therapy on endometrial thickness in asymptomatic postmenopausal

women between 1997 and 2001. Three hundred seven women received oral equine HT, oral equine estrogen, oral 17β-estradiol, or oral tibolone. All women on estrogen also received a progestin. Patients with endometrial thickness > 7 mm underwent a biopsy. Patients taking tibolone did not have a statistically significant increased thickness of endometrium compared with those in the other arms of the study. The authors suggested that tibolone closely mimics the natural atrophic state of the postmenopausal endometrium and could be considered as an alternative to HT.

In a 10-year (1991 to 2001) study undertaken in by Mossa et al.,[48] the threshold of endometrial thickness was investigated in 587 women on HT. An increased endometrial thickness and increased incidence of bleeding was found in the HT group. However, no difference in the prevalence of endometrial cancer was found between the HT and control groups. The authors recommended that women with bleeding on HT undergo hysteroscopy and biopsy only if endometrial thickness is > 8 mm.

STUDIES IN WOMEN WITH ENDOMETRIAL POLYPS

The estimated prevalence of polyps in women with postmenopausal bleeding ranges from 13% to 50%.[49] Several studies have also shown that polyps are highly prevalent in asymptomatic postmenopausal women.[49–52] The molecular and pathological etiology of endometrial polyps is evolving. Most lesions are benign, but some may be pre-malignant (simple or complex hyperplasia with cytological atypia) or malignant.[53] Malignant pathology is identified in 0.5% to 4.8% of polyps found in postmenopausal women.[53,54] However, polyps are a known risk factor for the subsequent development of endometrial cancer.[49–53]

Fernández-Parra et al.[55] conducted a retrospective chart review to determine the incidence of malignant polyps in postmenopausal women. Of 1870 hysteroscopies conducted at the study centre, 653 had confirmed polyps. The majority of women had postmenopausal bleeding, and only 117 women were asymptomatic. No cases of cancer in a polyp were found in asymptomatic women.

In a Norwegian study of 411 pre- and postmenopausal patients, pathological analysis of hysteroscopically resected endometrial polyps was conducted.[49] Thirty-one percent of study participants were symptomatic in postmenopause, and 18.5% were asymptomatic in postmenopause. In the group of postmenopausal women with symptoms, 5.5% of polyps were malignant or had atypical hyperplasia compared with 2.6% in women with no symptoms. The authors concluded that hysteroscopic resection of both symptomatic and asymptomatic polyps should be performed since the natural course of malignant polyps is still unknown.

Antunes et al.[53] sought to determine factors associated with malignancy in endometrial polyps in their 2007 study. A retrospective chart review of 475 surgical patients of any age who underwent hysteroscopy for endometrial polyp removal were included in the study. Overall, 78.53% of the polyps were benign, 13.47% had simple or complex hyperplasia, and 2.74% were malignant. Statistical subanalysis showed that women over 60 years of age were 3.28 times more likely than their younger counterparts to have malignant endometrial polyps. Women over 60 with postmenopausal bleeding were 5.31 times more likely than asymptomatic younger women to have malignant polyps. The authors did not find a significant difference in the prevalence of malignant polyps associated with arterial hypertension, diabetes mellitus, obesity, HT, or tamoxifen use. Antunes et al.[53] concluded that older women with postmenopausal bleeding are at greatest risk for malignancy and should have hysteroscopic resection of the polyps.

In 2009, Ferrazzi et al.[54] sought to elucidate the risk of malignancy in endometrial polyps in a large sample of asymptomatic and symptomatic postmenopausal women. A total of 1155 asymptomatic women and 770 bleeding women who had undergone polypectomy were included in the retrospective clinical chart review study. The authors found only one case of a cancerous polyp in the asymptomatic group. The polyp in this case was large, with a mean diameter of 40 mm. There was a significantly ($P < 0.001$) higher prevalence of malignant polyps in the symptomatic group. The authors concluded that women with incidentally found polyps do not require polypectomy unless the polyps have a large diameter.

In 2009, Gregoriou et al.[56] published a retrospective analysis of 516 cases of women who underwent hysteroscopic polypectomy to determine risk factors for malignancy. The final pathology report after polyp resection was compared with each patient chart. The majority of polyps were benign (96.9%), and a small percentage were premalignant (1.2%) or malignant (1.9%). Obesity (BMI > 30) ($P = 0.001$), diabetes mellitus ($P = 0.04$), menopause ($P = 0.005$), and age > 60 years ($P = 0.001$) were all significant risk factors for the development of malignant polyps. Gregoriou et al.[56] suggested that all clinical parameters must be considered to assess the risk of the malignancy potential of a polyp in a postmenopausal woman.

Baiocchi et al.[57] also conducted a large-scale retrospective study to determine the clinical factors associated with malignant polyps. Inclusion criteria for this study were diagnosis of an endometrial polyp or endometrial postmenopausal thickening of ≥ 5 mm. In total, 1242 cases were included in this study run from January 1995 to December 2006. The majority of patients (95.2%) had

benign polyps. Hyperplastic polyps with atypia occurred in 1.3% of patients and cancer in 3.5%. Postmenopausal status, age > 60, and hypertension were all significantly correlated with cancer in the polyp. Other clinical factors such as diabetes mellitus, HT, tamoxifen, and bleeding symptoms were not significantly different between the benign and cancerous polyp groups. In fact, the 2 most important factors appear to be advanced age and postmenopausal status. Baiocci et al.[57] concluded that older menopausal patients with hypertension are at the greatest risk of developing a malignant polyp. However, in both the Gregoriou et al.[56] and Baiocci et al.[57] studies the incidence of cancer in polyps was low (1.9% and 3.5% respectively).

IMPLICATIONS OF TAMOXIFEN FOR ENDOMETRIAL THICKENING

Women taking tamoxifen have a greater risk of endometrial cancer. This risk is augmented further if those women were previously taking estrogen replacement therapy.[58]

Routine endometrial biopsy is not necessary in asymptomatic women who are taking tamoxifen.[24] Endometrial thickening can be confused with stromal hypertrophy in these women. However, any abnormal bleeding should be evaluated. Endometrial cancers that occur in these women are similar to endometrial cancers occurring in the general population with respect to stage, grade, and histology. Prognosis tends to be good. To date there have been no published studies evaluating the effect of endometrial cancer screening modalities on mortality among women taking tamoxifen for the treatment or prevention of breast cancer.

Fishman et al.[59] found that endometrial thickness increased with increasing duration of tamoxifen use at a rate of 0.75 mm/yr. The mean endometrial thickness after 5 years of tamoxifen use was 12 mm (range 6 to 21 mm). After discontinuation of tamoxifen treatment the endometrium decreased by 1.27 mm/yr.

Gerber et al.[60] investigated the effect on the endometrium in women with breast cancer when they switched from tamoxifen to an aromatase inhibitor, anastrozole. A total of 226 postmenopausal women who had received tamoxifen 20 mg/d for ≥ 12 months, ≤ 48 months and had developed abnormal vaginal bleeding and/or asymptomatic endometrial thickness >10 mm underwent hysteroscopy and dilatation and curettage. One hundred seventy-one were randomized to continue tamoxifen (88) or changed to anastrozole (83). Patients were monitored for ≤ 42 months via TVUS at 6-monthly intervals. There was no difference in recurrent vaginal bleeding between groups: 4/83 on tamoxifen and 9/88 on anastrozole. Mean endometrial thickness for patients who switched to anastrozole was significantly less than for those on tamoxifen. Repeat hysteroscopy and dilatation and curettage revealed endometrial atrophy in all 4 cases in the anastrozole group, and there were 14 polyps, 8 hyperplasias, and 7 atrophies in the tamoxifen group.

Women on long-term tamoxifen therapy are thought to have higher risk of developing endometrial cancer. Berlière et al.[61] enrolled 575 women with estrogen receptor-positive breast cancer into a prospective study of endometrial pathology. Prior to tamoxifen treatment, all women had TVUS, and if endometrial thickness was > 5 mm, hysteroscopy was performed to remove polyps or lesions. In the study by Berlière et al.,[61] women who had lesions before initiating tamoxifen therapy were found at 2-year follow-up to be at significantly higher risk ($P < 0.001$) of developing atypical lesions. The lesions in the women who had lesions originally were also more severe than any developed in the women who were initially lesion-free. The authors concluded that women with initial lesions may be at greater risk for the oncologic effects of tamoxifen on their endometrium.

Garuti et al.[62] also conducted a prospective study of estrogen-positive breast cancer patients who were being prescribed tamoxifen adjuvant therapy. The authors enrolled 99 asymptomatic patients and evaluated the endometrium using hysteroscopy if their endometrial thickness was > 4 mm. Thirty-four women had thickness > 4 mm, 10 had polyps, 4 had simple hyperplasia, and 3 had complex hyperplasia. Thus, 18.6% of the patients had asymptomatic endometrial pathology before tamoxifen treatment. Garuti et al.[62] suggested routine endometrial screening for all women before initiation of tamoxifen therapy since subclinical endometrial pathology is prevalent in this group of women.

The most recent American College of Obstetricians and Gynecologists guideline for tamoxifen use and endometrial cancer risk has several recommendations for postmenopausal women.[24] Women may be stratified into 2 risk groups based on whether they have initial endometrial lesions. Women with initial lesions are at higher risk for developing endometrial cancers on tamoxifen therapy. Routine endometrial screening is not recommended for women taking tamoxifen because of the costs incurred and risk of unnecessary further investigation. Instead, women should be educated regarding the symptoms of endometrial cancer and instructed to consult their doctor if they develop any spotting or postmenopausal bleeding. If a woman develops endometrial hyperplasia, the use of tamoxifen should be re-assessed.

COMPLICATIONS OF INVESTIGATION

Endometrial biopsy may result in pain, bleeding, infection, and uterine perforation, and office-based endometrial biopsy has false negative rates of 5% to 15%.[63] Dilatation

and curettage has false negative rates of 2% to 6%.[46] Endometrial sampling may be limited or impossible because of virginal status, cervical stenosis, small introitus, pain, or anatomical abnormalities such as fibroids aberrating the canal. The finding of insufficient tissue in the face of endometrial thickening prompts further investigations such as hysterosonogram, office hysteroscopy, dilatation and curettage, and diagnostic and therapeutic hysteroscopy under general anaesthetic.[63–66] Each of these procedures has its own complications, including untimely hysterectomy. In a study designed to compare blind biopsy, hysteroscopy with biopsy, and ultrasound in 683 women who were experiencing bleeding, discomfort and distress was reported in 16% of women who had hysteroscopy and in 10% who had blind biopsy.[67]

No major complications were reported in the Shushan et al.[68] study of 300 women who underwent hysteroscopic polyp removal. Minor complications reported in the study included bradycardia during general anaesthetic and postoperative hemorrhage that was treated conservatively with uterine tamponade for 8 hours. Two of the 300 patients were readmitted to hospital with postoperative fever and treated with antibiotic combination therapy for pelvic inflammatory disease. Lev-Sagie et al.[69] reported a complication rate of 3.6% in a retrospective study of women who underwent hysteroscopy after incidental finding of endometrial polyp on ultrasound examination. The complications reported in the study were uterine perforation in 2 women and complication of general anaesthetic due to difficult intubation. Ferrazzi et al.[54] reported a particularly low rate of complications in the literature. Only the minor complications of cervical tears and false passages were reported in 0.6% and 0.3% of asymptomatic patients respectively. False passage complications were reported in 0.8% of symptomatic patients in the Ferrazzi et al. study.[54] In the 2007 Lieng et al.[70] study, 92.2% of hysteroscopies performed to remove endometrial polyps were complication-free. The complications that did occur included uterine perforation, creation of false passage, moderate bleeding, endometritis, failed procedure, and uterine perforation including bowel injury. Thus, some of the complications of hysteroscopy carry significant morbidity and possible mortality.

CONCLUSION

Asymptomatic endometrial thickening found on ultrasound examination in postmenopausal women often poses a clinical management dilemma. Although the prevalence of endometrial cancer is relatively low in women with no bleeding, the disease has the best outcome when it is found at an early stage. The disease is usually diagnosed at an early stage when postmenopausal women present with bleeding. Routine ultrasound screening for asymptomatic women is not recommended. Current evidence suggests that certain subsets of women at high risk of developing endometrial cancer who have endometrial thickening on ultrasound and other positive findings (increased vascularity, inhomogeneity of endometrium, particulate fluid, excessively thickened endometrium > 11 mm) should be referred to gynaecologists for further investigations. Women with risk factors for endometrial cancer and endometrial thickening such as tamoxifen use, obesity, hypertension, and late menopause should be triaged on an individual basis. Polyps found in asymptomatic postmenopausal women need not be removed routinely. However, factors such as polyp size and histopathology, and patient age must be incorporated into the decision for polypectomy. Investigations for asymptomatic endometrial thickening are not risk free, and serious complications such as bowel injury and uterine perforation have been reported in the literature. Thus, adoption of these recommendations may reduce anxiety, pain and risk of procedural complication to the postmenopausal patient.

Recommendations

1. Transvaginal ultrasound should not be used as screening for endometrial cancer. (II-1E)

2. Endometrial sampling in a postmenopausal woman without bleeding should not be routinely performed. (II-1E)

3. Indications for tissue sampling of the endometrium in bleeding postmenopausal women with an endometrial thickness of greater than 4 to 5 mm should not be extrapolated to asymptomatic women. (II-2E)

4. A woman who has endometrial thickening and other positive findings on ultrasound, such as increased vascularity, inhomogeneity of endometrium, particulate fluid, or thickened endometrium over 11 mm, should be referred to a gynaecologist for further investigations. (II-1A)

5. Decisions about further investigations should be made on a case-by-case basis in asymptomatic women with increased endometrial thickening and risk factors for endometrial cancer such as obesity, hypertension, and late menopause. (II-1B)

6. In asymptomatic women on tamoxifen, a routine ultrasound for endometrial thickening should not be performed. (II-2E)

7. Not all postmenopausal women who have asymptomatic endometrial polyps require surgery. Women found to have asymptomatic polyps on ultrasound should be triaged for intervention according to size of the polyp, age, and other risk factors. (II-1A)

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