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When You Don't Look But You Do Find: Pragmatic Approach To Management Of Asymptomatic Endometrial Thickening In Postmenopausal Patients

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Introduction

The endometrium varies in thickness through the menstrual cycle, largely in response to estrogen and progesterone stimulation. Following menopause, the endometrium should remain homogenously atrophied due to the relatively low circulating levels of estrogen. In postmenopausal women, the endometrium is considered thickened when it measures greater than 5 mm.[1] Measuring endometrial thickness includes assessing the width of the anterior and posterior layers of the endometrium made on the midline sagittal image obtained by transvaginal ultrasound. The principal objective of investigating a thickened endometrial lining is to diagnose endometrial hyperplasia or cancer. Patients who experience postmenopausal bleeding and are found to have an endometrial thickness greater than 5 mm necessitate endometrial sampling. However, whether endometrial sampling is required in the absence of symptoms, namely postmenopausal bleeding, is a more nuanced clinical decision. This article provides an approach to evaluating patients presenting with asymptomatic endometrial thickening, including a review of guidelines for when further testing is warranted. It will specifically address unique populations, namely patients using menopausal hormonal therapies as well as those on tamoxifen.

- Increasing age
- Obesity
- Diabetes
- Hypertension
- Polycystic ovarian syndrome
- Tamoxifen use
- Unopposed estrogen use
- Nulliparity
- Prolonged menstrual history (early menarche, late menopause)
- Genetic predisposition (i.e., Lynch syndrome)

Table 1. Risk factors for endometrial cancer; *courtesy of Olga Bougie, MD, FRCSC, MPH*

Differential Diagnosis Of Endometrial Thickness

Although the primary goal of investigating asymptomatic endometrial thickening is to exclude a malignant process, it is helpful to consider the different diagnoses of this finding. Most common causes of endometrial thickness include endometrial polyps, submucosal fibroids, intrauterine adhesions or septum, adenomyosis, proliferative endometrium, endometrial hyperplasia, and endometrial cancer. Additional ultrasound descriptors, such as whether the thickening is global or focal, the presence of fluid collections, increased vascularity, and the identification of a feeding vessel are all valuable features to help tailor the differential diagnosis and direct further investigations.

Certain sonographic features may be highly suspicious for an endometrial polyp, such as a hyperechoic focal endometrial mass with or without vascularity and distortion of the endometrial contour. The application of power doppler on transvaginal ultrasound, as well as the use of 3D imaging, may aid diagnostic accuracy. Saline-infused sonohysterography provides high diagnostic accuracy. Alternatively, hysteroscopy can offer concurrent diagnosis and treatment. The risk of malignancy within an endometrial polyp is estimated to be between 0.5% and 3.4-5.4% in high risk populations.[2] The strongest risk factors for malignancy in endometrial polyps are age greater than 60 years, postmenopausal status, and the presence of bleeding.[3,4] Other risk factors include polyp size, obesity, hypertension, and diabetes mellitus.[3,4]

Endometrial histopathological assessment can yield a number of findings including atrophic endometrium, proliferative endometrium, secretory endometrium, polyps, endometritis, endometrial hyperplasia, and cancer. While proliferative endometrium is generally regarded as a benign entity, this pathological finding is associated with an 11.9% risk of developing endometrial cancer in postmenopausal patients, compared to a 2.9% risk of cancer in those with atrophic endometrium.[5] Proliferative endometrium typically develops from unopposed estrogen stimulation and should prompt an evaluation to identify and address the underlying cause. Ongoing monitoring through repeat endometrial sampling should be considered in patients with this diagnosis. Although not standard practice, progesterone treatment may be considered in certain high risk patients on an individualized basis to reverse proliferative endometrium and prevent further development of endometrial hyperplasia or cancer.

Etiology Of Endometrial Cancer

Endometrial cancer is the most common gynecologic malignancy in developed countries, and its incidence continues to rise. There are 2 main subtypes of endometrial cancer: endometrioid, accounting for 80% of the cases, and non-endometrioid.[6] Endometrioid cancers arise from endometrial hyperplasia due to overstimulation of the endometrial lining from estrogen. Non-endometrioid cancer subtypes do not have a precursor and importantly may not result in a thickened endometrium. In the postmenopausal population, over 90% of patients who are ultimately diagnosed with endometrial cancer will experience bleeding.[7] Although we typically aim to diagnose and treat cancer early, it is unclear whether diagnosing endometrial cancer in asymptomatic patients provides a survival advantage.[8] Current guidelines recommend offering treatment to patients at the time of diagnosis. The main risk factors for endometrioid typical cancers are related to estrogen stimulation and include obesity, metabolic syndrome (diabetes, polycystic ovarian syndrome,

hypertension), tamoxifen use, and nulliparity **(Table 1)**. While more than 50% of all cancers are attributable to obesity, endometrial cancer has the strongest associated risk with this diagnosis. Patients with a normal body mass index (BMI) carry a 3% lifetime risk of developing endometrial cancer; however, for every 5-unit increase in BMI, the risk of developing cancer increases by 50%.[9]

Approach To Evaluation Of Thickened Endometrial Lining

Depending on the baseline characteristics of the population studied, up to 3-15% of postmenopausal women will have asymptomatic endometrial thickness. If this finding is noted on a CT scan, an ultrasound should be performed to confirm it.

A concerted effort has been made to determine the optimum cutoff for further testing, primarily through endometrial sampling, in this clinical presentation. It is estimated that the risk of cancer in patients without postmenopausal bleeding is 0.002% when the endometrium is ≤11 mm in thickness and 6.7% when it exceeds 11 mm. This distinction is similar to the risk stratification in patients with postmenopausal bleeding, where a ≤5mm cut off is used to determine the need for endometrial sampling. Increased vascularity observed on ultrasound has been associated with increased risks of endometrial hyperplasia or cancer.[10] Upon a comprehensive review of the evidence, the Society of Obstetricians and Gynecologists of Canada recommends that patients found to have endometrial thickening of ≥11 mm, or concerning sonographic features such as increased vascularity, heterogeneity, or fluid collection, should be considered for further investigations or be referred to a gynecologist.[11]

Endometrial Sampling

Endometrial sampling can be obtained using a pipelle biopsy, generally performed in an outpatient clinic setting or through dilation and curettage. Although an endometrial pipelle biopsy is a blind procedure, it has a high diagnostic accuracy for endometrial cancer (99.6% sensitivity), particularly in postmenopausal women. However, up to 20% of postmenopausal women will have an inadequate sample collected through office endometrial sampling. As such, office endometrial biopsy is considered a reliable and accurate test for diagnosing endometrial cancer, provided that the endometrial thickness is global in nature on ultrasound assessment and an adequate sample is obtained for histological evaluation. If an inadequate sample is obtained, monitoring and repeating imaging in approximately 4 months, or proceeding with further testing such as hysteroscopy and endometrial curettage can be considered. This decision is typically individualized for each patient, depending on their risk of endometrial pathology versus surgical risks. In cases where a stenotic cervix prevents obtaining office endometrial sampling, a similar balance of risks must be evaluated. Although prostaglandin E1 (misoprostol) pre-treatment is often employed in this setting to help with cervical dilation, there is no evidence to support its benefits prior to office endometrial biopsy.[12,13] A number of operative techniques may be used to safely access the endometrial cavity in individuals with a stenotic cervix, if necessary.

Directed hysteroscopic evaluation and sampling can be considered when focal endometrial thickness is identified on ultrasound, other ultrasound features suggest the presence of an endometrial polyp or distinct lesion, or when an inadequate sample is obtained from an office biopsy.[2] Hysteroscopic evaluation can be performed in an ambulatory setting, thereby decreasing the risk of anesthetic complications.

Specific Populations

Tamoxifen

Tamoxifen use is associated with a significant increase in endometrial cancer and endometrial hyperplasia, which is dose dependant. A systematic review of 26 studies, including 44,980 tamoxifen users and 193,414 non-tamoxifen users demonstrated a relative risk of 2.03 (95% confidence interval: 1.68–2.45; I^2: 76%) for endometrial cancer diagnosis in the tamoxifen group.[14]

There is a significant increase in endometrial thickness observed in patients using tamoxifen, with up to 70% of postmenopausal patients having an endometrial thickness greater than 5 mm while on this medication.[15] Additionally, the endometrium of patients on tamoxifen is often described as irregular and containing multiple cystic areas. Increased endometrial thickening is associated with a higher risk of bleeding. Endometrial polyps are the most common endometrial pathology

diagnosed in postmenopausal patients using tamoxifen, with a rate of 8–36.0%.[16]

Currently, there is a lack of evidence to support routine screening in the population.[17] Patients using tamoxifen should be counselled regarding the risks to the endometrium and to report any vaginal bleeding, which should be promptly investigated.

Menopausal Hormonal Treatment

Systemic estrogen use is associated with increased endometrial thickness, as well as the development of endometrial hyperplasia and cancer. A Cochrane review concluded that there is no clinically significant increased risk of endometrial thickness or endometrial pathology diagnosis with the use of combined estrogen and progesterone treatment, whether in continuous or sequential regimens.[18] The use of a tissue selective estrogen complex combination product containing CEE 0.45/bazedoxefine 20 mg daily has not been associated with a significant increase in endometrial thickness or hyperplasia.[19] Treating genitourinary symptoms of menopause with vaginal preparations of estradiol, conjugated equine estrogen or estrone, DHEA, or testosterone have not demonstrated an impact on the endometrium.[20]

Conclusion

Endometrial thickness greater than 5 mm is common in postmenopausal patients. The primary goal of assessment in this situation is to exclude endometrial cancer or hyperplasia, which are currently on the rise. Major risk factors for endometrial cancer include obesity, metabolic syndrome, and a history of anovulation. The majority of patients (>90%) with endometrial cancer will present with vaginal bleeding, at which point endometrial sampling should be performed.

If patients present with an incidental finding of endometrial thickness and deny vaginal bleeding, referral to a gynecologist or endometrial sampling should be performed when the endometrial thickness exceeds 11 mm or if concerning features are noted on ultrasound.

Although patients using tamoxifen are at an increased risk of endometrial pathologies, there is currently insufficient evidence to support routine sonographic screening.

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