Libyan Medical Journal
https://lmj.ly/index.php/ojs/index

Review article

Asymptomatic Thickened Endometrium; Are we Over-Diagnosing it

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Citation: Nori W, Hussein ZA. Asymptomatic Thickened Endometrium; Are we Over-Diagnosing it. Libyan Med J. 2022;14(2):38-42.

Received: 08-08-2022
Accepted: 29-08-2022
Published: 30-08-2022

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

Abstract

Endometrial carcinoma ECA is frequently presented as post-menopausal bleeding among symptomatic postmenopausal women (PMW). Fortunately, the prognosis of this malignancy is good once discovered early. The underlying pathology of ECA was closely correlated to thickened endometrium by transvaginal ultrasound, which was set at 4mm for symptomatic PMW. However, that was not the case for asymptomatic cases. The dilemma of incidental thickened endometrium on ultrasound reports of asymptomatic PMW was discussed in this review. We examined the usefulness of mass screening of asymptomatic PMW by transvaginal ultrasound and the recommended normal endometrial thickness and its cutoff value. Endometrial sampling indications, methods, and complications were addressed. The role of biomarkers in screening and their limitation. We aimed to deliver up-to-date evidence of a common problem in medical practice.

Keywords: *Endometrial Cancer, Endometrial Thickness, Transvaginal Ultrasound, Endometrial Sampling, Postmenopausal Women.*

Introduction

The majority of women with endometrial cancer (ECA) are symptomatic, with abnormal uterine bleeding being the predominant presenting symptom. Postmenopausal bleeding is the most frequent presenting symptom of endometrial cancer and should be checked urgently. ECA accounts for 10 percent of postmenopausal bleeding cases [1,2]. Uterine cancer is the sixth most common cancer in women. Its incidence has gone up by about 50%, which is primarily due to:

- Increased obesity (which raises the overall risk of patients by ten folds),
- Higher metabolic diseases, mostly type 2 diabetes mellitus (which raises the overall risk of ECA by two folds),
- Longer life expectancy (women over 54 have a higher overall risk), and the
- Utilization of adjuvant tamoxifen for breast cancer survivors [3].

For symptomatic post-menopausal women (PMW), having post-menopausal bleeding warrants further analysis and exclusion of the risk of ECA. A detailed clinical history and examination are performed to categorize patients' risks accordingly. A transvaginal vaginal ultrasound (TVUS)evaluates the endometrial thickness (ET) and the need for endometrial sampling [4].

The ET is defined as the maximal anterior-posterior diameter of the endometrium echo on a transvaginal image of the uterine wall along the longitudinal axis. What is favorable about TVUS is that it is acceptable by the patient, non-invasive, its cost is comparable to biopsy, and it has a good detection rate for ECA [5].

The American College has set an endometrial thickness ET of more than 4mm as a cutoff value that warrants further endometrial sampling ES [6]; this value was liked with 95% sensitivity in excluding ECA and 99 percent negative predictive value for ECA [7].

The accuracy and precision of TVUS in predicting ECA and the correlation of its cutoff value with the histological finding made it an initial investigation of choice in symptomatic PMW.

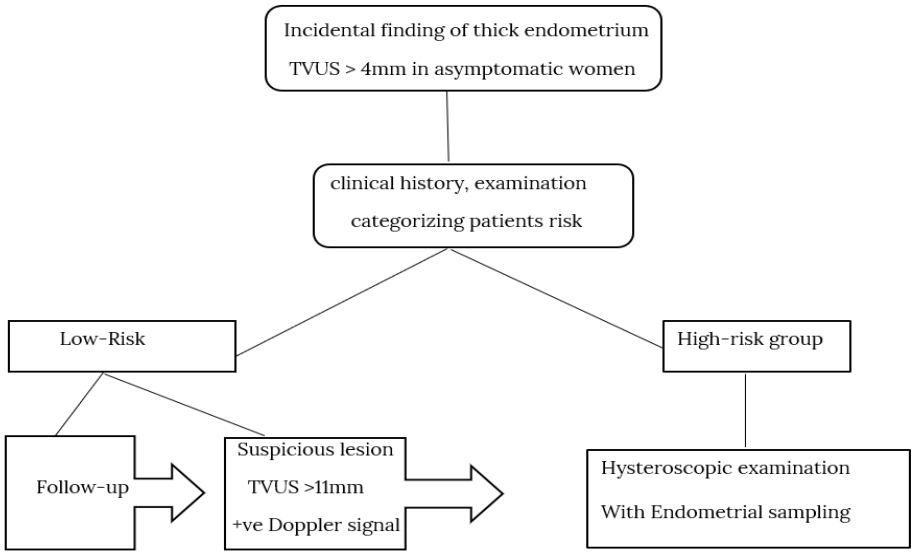
A cutoff value of less than 4 mm in symptomatic women does not necessitate further endometrial sampling unless the bleeding recures or if the woman is categorized as a high-risk group for endometrial cancer [4,6].

Endometrial sampling (ES) by outpatient Pipelle endometrial suction curette or by an office-guided hysteroscopic has largely replaced the old approach of diagnostic curettage that is

considered blind. Pipelle ES does not need general anesthesia; its diagnostic accuracy is about 81%[8].
It has the disadvantage of being painful and has a failure risk due to cervical stenosis, not to mention infection and not having a sufficient tissue sample to perform the histopathological test [9]. A hysteroscopic ES is reserved for cases that failed to obtain a tissue sample on an outpatient basis, women who suffered from recurrent bleeding, and high-risk women for ECA. Hysteroscopy is recommended as the standard investigation to rule out ECA [10].
The majority of ECA, if detected early, has an overall 5-year survival rates of eighty percent. However, the rates of more advanced stages are just fifteen percent, so the importance of early diagnosis cannot be overestimated. Since the prognosis is favorable for early cases, scientists pursued earlier screening methods to catch the disease early. That was the rationale for using trans vaginal ultrasound TVUS as a screening test to unveil EC in asymptomatic women at menopause [11].

Screening of asymptomatic post-menopausal women

Indeed, transvaginal ultrasound has revolutionized many aspects of screening and diagnosis of gynecology diseases, yet its use in asymptomatic women with thickened endometrium creates a dilemma for most physicians [12].
Most global societies have determined that screening for endometrial cancer is not advised in asymptomatic PMW, particularly with TVUS, which has a low predictive value for ECA, in fact, it generated 93 percent false positive results [13]. Some researchers have objected to adding TVUS to screen asymptomatic PMW since the ET cutoff value set earlier for symptomatic PMW cannot be applied for asymptomatic cases [14].
Moreover, there was no reduction in mortality rates for women with ECA with the introduction of population screening by TVUS or ES [15]. One study has argued that evaluating the clinical risk factors for having an ECA would perform better than exposing an asymptomatic patient to TVUS [16]. In 2004 a study reported that with ET ≥11 mm, there was an estimated ECA risk of 7.5 percent, similar to symptomatic PMW women with ET ≥5 mm. They recommended that ES should be done in asymptomatic PMW with ET≥11 mm. Some international society has already endorsed this cutoff value, including the Canadian Society of Obstetrics and Gynecology [17].
The recommendation for endometrial sampling in asymptomatic PMW was extended to include cases with ultrasonic features of high vascularity and non-homogeneous endometrium and women having a clinical risk of ECA as age, late onset menopause, obesity, type 2 DM, increased blood pressure, hormone-replacement therapy, and tamoxifen [18,19].
Li Z, et al. study. Confirmed that endometrial pathology with a positive Doppler flow signals a possible ECA. However, Goldstein discussed that there was no correlation between Doppler flow, resistive index, and pulsatility index with ECA risk; since both studies had different inclusion criteria and were limited by a small sample size that could explain the disparity in their results.
In a recently published meta-analysis, the validity of the cutoff value (> 11mm) was confirmed, with a reported sensitivity and specificity for ECA detection reaching 100 percent and 80 percent, respectively [18]. In a cohort study that examined the performance of ≥10 mm cutoff value for ET among asymptomatic PMW with at least one clinical risk factor included, the study recommended this value for offering ES via Pipelle or hysteroscopy the ECA yielded 1.82 percent of all patients [22]. The decision of endometrial sampling for asymptomatic PMW with an incidental thick endometrium (>4 mm) is not recommended by the American college or the American Cancer Society [23].
For asymptomatic PMW women with ET of more than >4 mm, the ES is not indicated, and follow-up mode for those women by TVUS or by performing ES by an office hysteroscopy relies on the individual case risk for ECA, i.e., family history, metabolic diseases, obesity, and suspicious ultrasonic finding mentioned earlier [4,20], see figure 1.



Figur1. Flow chart for managing asymptomatic thick endometrium in post-menopausal women.

Limitation of TVUS and ES in asymptomatic postmenopausal women

Though the TVUS is a valuable tool in assessing the ECA risk and need for ES, it has its limitations; the presence of uterine pathologies, like fibroid, uterine polyps, adenomyosis, or prior uterine surgery, can limit the accurate measurement of the endometrial thickness.
Other evaluation methods should always follow failure to evaluate the ET accurately. Alternative methods; saline-infused sono-hysterography and/or hysteroscopic examination [24].
PMW on Hormone-Replacement Therapy (HRT) carries unique risks for increased ET. Although there was generally no consensus for ET in those women, some researchers suggested using 8mm as a cutoff value [25]. A recently published review recommended using the same cutoff value of 4 mm to follow them in the lack of evidence-based research [26].
As for tamoxifen users who are breast cancer survivors, American collage declared the lack of benefit from routine surveillance and the need to screen those cases prior to the treatment with TVUS and sono-hysterography; or even have ES office hysteroscopy before initiation of tamoxifen therapy [27].

Role of Ca-125

Ca-125 is a tumor biomarker (cancer antigen 125) that may be increased above 35 U/m in the ovary and endometrium malignancies. However, this marker has a high false positive rate.
An increased level has been noticed in the inflammatory process in the abdomen, benign conditions like pregnancy, menstruation, adenomyosis, and other malignancies like malignant of the gastrointestinal tract [28]. Ca-125 was used to predict the invasion of ECA prior to surgery and was also shown to be valuable in predicting the prognosis [29].
Li Z, et al tested the value of Ca-125 in patients with asymptomatic thickened endometrium, they noticed higher levels among patients with ECA; however, the difference was not statistically significant [20].

Conclusion

Mass Screening for asymptomatic postmenopausal women with TVUS is not recommended; the accidental finding of thickened endometrium in a low-risk group does not warrant endometrial sampling, but follow-up is recommended. Should follow-up show persistent thickened endometrium or positive flow Doppler signals, then ES is warranted. As for the high-risk group, ES should be done.

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